frontiers | Research Topics

Cardiovascular health in children and adolescents: present and future

Edited by
Shikai Yu, Shaun Chen and Zhen-Yu Zhang

Published in
Frontiers in Pediatrics
Frontiers in Cardiovascular Medicine
Frontiers in Public Health

ISSN 1664-8714
ISBN 978-2-8325-5898-0
DOI 10.3389/978-2-8325-5898-0

About Frontiers

Frontiers is more than just an open access publisher of scholarly articles: it is a pioneering approach to the world of academia, radically improving the way scholarly research is managed. The grand vision of Frontiers is a world where all people have an equal opportunity to seek, share and generate knowledge. Frontiers provides immediate and permanent online open access to all its publications, but this alone is not enough to realize our grand goals.

Frontiers journal series

The Frontiers journal series is a multi-tier and interdisciplinary set of open-access, online journals, promising a paradigm shift from the current review, selection and dissemination processes in academic publishing. All Frontiers journals are driven by researchers for researchers; therefore, they constitute a service to the scholarly community. At the same time, the *Frontiers journal series* operates on a revolutionary invention, the tiered publishing system, initially addressing specific communities of scholars, and gradually climbing up to broader public understanding, thus serving the interests of the lay society, too.

Dedication to quality

Each Frontiers article is a landmark of the highest quality, thanks to genuinely collaborative interactions between authors and review editors, who include some of the world's best academicians. Research must be certified by peers before entering a stream of knowledge that may eventually reach the public - and shape society; therefore, Frontiers only applies the most rigorous and unbiased reviews. Frontiers revolutionizes research publishing by freely delivering the most outstanding research, evaluated with no bias from both the academic and social point of view. By applying the most advanced information technologies, Frontiers is catapulting scholarly publishing into a new generation.

What are Frontiers Research Topics?

Frontiers Research Topics are very popular trademarks of the *Frontiers journals series*: they are collections of at least ten articles, all centered on a particular subject. With their unique mix of varied contributions from Original Research to Review Articles, Frontiers Research Topics unify the most influential researchers, the latest key findings and historical advances in a hot research area.

Find out more on how to host your own Frontiers Research Topic or contribute to one as an author by contacting the Frontiers editorial office: frontiersin.org/about/contact

Cardiovascular health in children and adolescents: present and future

Topic editors
Shikai Yu — Tongji University, China
Shaun Chen — University of Cambridge, United Kingdom
Zhen-Yu Zhang — KU Leuven, Belgium

Citation
Yu, S., Chen, S., Zhang, Z.-Y., eds. (2025). *Cardiovascular health in children and adolescents: present and future*. Lausanne: Frontiers Media SA.
doi: 10.3389/978-2-8325-5898-0

Table of contents

frontiers | Frontiers in Pediatrics

TYPE Original Research
PUBLISHED 20 October 2022
DOI 10.3389/fped.2022.1044791

OPEN ACCESS

EDITED BY
Shikai Yu,
Shanghai Tenth People's Hospital, Tongji University, China

REVIEWED BY
Ge Zhu,
Tongji University, China
Elisabetta Lampugnani,
Giannina Gaslini Institute (IRCCS), Italy
Maruti Haranal,
U N Mehta Institute of Cardiology and Research, India

*CORRESPONDENCE
Jijian Zheng
zhengjijian626@sina.com

†These authors have contributed equally to this work and share first authorship

SPECIALTY SECTION
This article was submitted to Pediatric Cardiology, a section of the journal Frontiers in Pediatrics

RECEIVED 15 September 2022
ACCEPTED 30 September 2022
PUBLISHED 20 October 2022

CITATION
Tong C, Liu P, Zhang K, Liu T and Zheng J (2022) A novel nomogram for predicting respiratory adverse events during transport after interventional cardiac catheterization in children.
Front. Pediatr. 10:1044791.
doi: 10.3389/fped.2022.1044791

A novel nomogram for predicting respiratory adverse events during transport after interventional cardiac catheterization in children

Chaoyang Tong†, Peiwen Liu†, Kan Zhang†, Ting Liu and Jijian Zheng*

Department of Anesthesiology, Shanghai Children's Medical Center, School of Medicine and National Children's Medical Center, Shanghai Jiao Tong University, Shanghai, China

Objective: The rate and predictors of respiratory adverse events (RAEs) during transport discharged from operating room after interventional cardiac catheterization in children remain unclear. This study aimed to investigate the incidence and predictors, and to construct a nomogram for predicting RAEs during transport in this pediatric surgical treatment.

Methods: This prospective cohort study enrolled 290 consecutive pediatric patients who underwent ventricular septal defects (VSD), atrial septal defects (ASD), and patent ductus arteriosus (PDA) between February 2019 and December 2020. Independent predictors were used to develop a nomogram, and a bootstrap resampling approach was used to conduct internal validation. Composite RAEs were defined as the occurrence of at least 1 complication regarding laryngospasm, bronchospasm, apnea, severe cough, airway secretions, airway obstruction, and oxygen desaturation.

Results: The rate of RAEs during transport was 23.1% (67 out of 290). Multivariate analysis identified age (vs. ≤3 years, adjusted odds ratio (aOR) = 0.507, 95% confidence interval (CI), 0.268–0.958, $P = 0.036$), preoperative upper respiratory tract infections (URI, aOR = 2.335, 95% CI, 1.223–4.460, $P = 0.01$), type of surgery (vs. VSD, for ASD, aOR = 2.856, 95% CI, 1.272–6.411, $P = 0.011$; for PDA, aOR = 5.518, 95% CI, 2.425–12.553, $P < 0.001$), morphine equivalent (vs. ≤0.153 mg/kg, aOR = 2.904, 95% CI, 1.371–6.150, $P = 0.005$), atropine usage (aOR = 0.463, 95% CI, 0.244–0.879, $P = 0.019$), and RAEs during extubation to transport (aOR = 5.004, 95% CI, 2.633–9.511, $P < 0.001$) as independent predictors of RAEs during transport. These six candidate predictors were used to develop a nomogram, which showed a C-statistic value of 0.809 and good calibration ($P = 0.844$). Internal validation revealed similarly good discrimination (C-statistic, 0.782; 95% CI, 0.726–0.837) and calibration. Decision curve analysis (DCA) also demonstrated the clinical usefulness of the nomogram.

Conclusion: The high rate of RAEs during transport reminds us of the need for more medical care and attention. The proposed nomogram can reliably identify pediatric patients at high risk of RAEs during transport and guide clinicians to make proper transport plans. Our findings have important and

meaningful implications for RAEs risk prediction, clinical intervention and healthcare quality control.

KEYWORDS

respiratory adverse events, children, cardiac catheterization, nomogram, predictors

Introduction

Respiratory adverse events (RAEs) are the most common complication during pediatric anesthesia, characterized by both minor adverse events (oxygen desaturation, airway obstruction or secretions and cough) and major adverse events (laryngospasm, bronchospasm and apnea), with a reported prevalence of up to 50% (1–3). Despite the improvement of existing guidelines for pediatric anesthesia management, RAEs remain one of the leading causes of morbidity and mortality and bring varying levels of physical and psychological trauma to children and parents (4, 5).

Many factors correlated with children's medical history, anesthesia management, and type of surgery contribute to the high rate of this occurrence, and the underlying mechanisms include anatomic and physiological considerations, as well as frequent upper respiratory tract infections (URIs) and inflammation (6–10). Although previous studies have identified several predictors for RAEs during perioperative period, rapid and accurate preoperative assessment of high-risk children by pediatric anesthetists remains a great challenge in clinical practice (11, 12).

Children with congenital heart disease (CHD) are more susceptible to develop viral respiratory tract infections that can cause concomitant cardiac and respiratory compromise, increasing the risk of postoperative respiratory complications (6, 13–15). With the development of interventional technology, CHD is increasingly treated by cardiac catheterization, and the rate of life-threatening events is greatly reduced compared to open heart surgery (16, 17). Nevertheless, the high rate of RAEs remains an unavoidable and intractable problem in this surgical procedure, which may lead to transient damage evolving into unpredictable serious consequences if not treated promptly and effectively (18, 19).

Published studies concerning RAEs mainly focused on the period of anesthesia induction, intraoperative and post-anesthesia care unit (PACU), with relatively abundant medical resources (3, 6–10). However, little attention has been paid to the rate of RAEs during transport discharged from operating room after interventional cardiac catheterization in many pediatric anesthesia practice, which often lacks adequate resources for anesthesia care and monitoring. Further, no prediction model for RAEs during transport after this surgery presenting for anesthesia was established. Thus, this study aimed to investigate the incidence and predictors, and to construct a nomogram for predicting RAEs during transport in this pediatric surgical treatment.

Materials and methods

Study design and ethics

This single-center prospective study was approved by the Institutional Review Board (IRB) of Shanghai Children's Medical Center (SCMCIRB-K20170122) and written informed consent was obtained from parents or the legal guardians of each child before surgery. This trial was registered before patient enrollment at the Chinese Clinical Trial Registry (ChiCTR-RRC-17012519). This study was conducted in accordance with the Guidelines of the International Conference on Harmonization of Clinical Norms and the Declaration of Helsinki, and was adhered to STROBE guidelines.

Patient enrollment

Eligible patients ≤16 years, ASA grade 2 or 3, scheduled for elective interventional cardiac catheterization under general anesthesia (GA) for ventricular septal defects (VSD), atrial septal defects (ASD), and/or patent ductus arteriosus (PDA) from February 2019 to December 2020. Exclusion criteria included parental refusal to sign informed consent, evidence of lower respiratory tract infections (such as pneumonia and bronchitis) within the previous 2 weeks, no medical history (parents or legal guardians could not recall clearly), known hypersensitivity to specific anesthetic agents, history of liver, kidney disease or complex cyanotic heart disease, and recent participation in other studies. 290 children were enrolled in the final analysis (**Figure 1**).

Anesthesia protocols

To minimize other potential bias, all surgical procedures in this study were handled by the same group of surgeons and anesthesiologists. The LMAs were removed by the chief anesthesiologist at the end of surgery when the end-tidal sevoflurane concentration dropped below 1% and the respirations became regular. The Aldrete score was the standard reference for discharging catheterization room. When the scores were ≥6, the chief anesthesiologist will consider transferring the pediatric patients. During transport, all pediatric patients were routinely monitored by electrocardiogram and pulse oximetry, and underwent mask

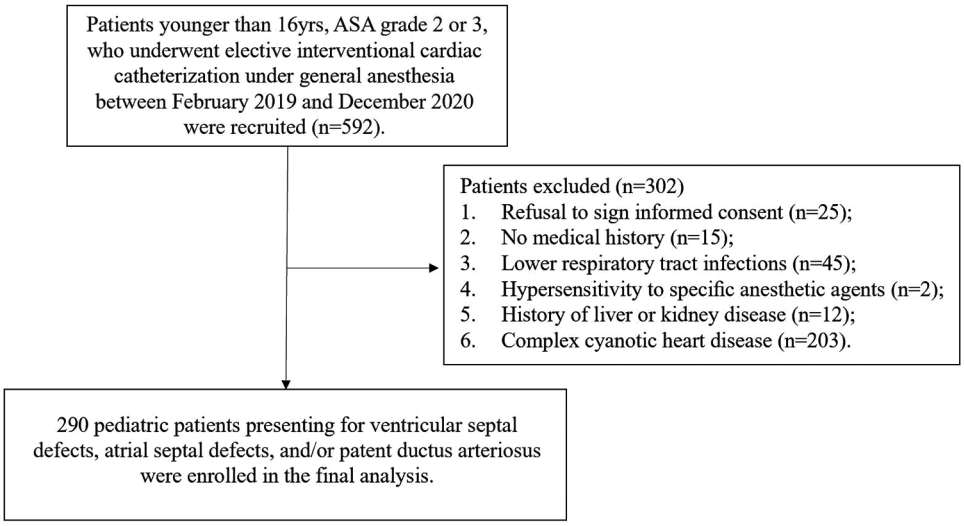


FIGURE 1
Patient flowchart.

ventilation. Additionally, all emergency airway equipment and first aid medicines were fully prepared. Detailed anesthesia protocols were reviewed in our previously published literature (18, 19). Considering the usage for analgesia with fentanyl and sufentanil in all children, we standardized the doses with following method: the total dose in milligrams for each opioid was multiplied by its standard equianalgesic conversion ratio and divided by lean body weight (20–22).

Data collection, outcomes and definition

Before surgical procedure, the questionnaire form concerning children's demographic information was completed by parents or legal guardians. Intraoperative clinical data and outcomes including emergence agitation, vomiting, fever, and respiratory adverse events (RAEs) were recorded by senior resident anesthetists. Children with any two of the following URI symptoms confirmed by parents or legal guardians within the past 8 weeks were considered to have a history of URI: nasal congestion, runny nose, dry or wet cough, sore throat, sneezing, or fever >38°C (6, 7). Composite RAEs were defined as the occurrence of at least 1 complication including laryngospasm, bronchospasm, apnea, severe cough, airway secretions or obstruction, and oxygen desaturation (6, 7, 23). In this study, the perioperative period was further divided into the following 6 parts, namely, anesthesia induction, intraoperative period, after surgery to extubation, extubation to transport, during transport, and in ward, so as to more accurately study the occurrence of RAEs in different periods.

Statistical analysis

Statistical power calculations were not performed prior to this study since the sample size was based on available data. Statistics and data analysis plans were defined before accessing the data and were completed after the data were accessed. Continuous variables were compared using Two independent sample *t*-test or Mann-Whitney *U* test based on the rate of RAEs during transport. Categorical variables were compared with Chi-square test or Fisher exact test, depending on the sample size. Univariate analysis showed that all factors significantly correlated with RAEs during transport ($P < 0.2$) were inserted into the multivariate logistic regression model using the forward selection strategy.

The predictive model was presented with a nomogram to provide a visual point system to estimate the probability of RAEs during transport. Hosmer-Lemeshow (H-L) goodness-of-fit test was used to evaluate the model's fit. Discrimination (C-statistic) and calibration (calibration curve) were used to assess the performance of the prediction model. The area under the receiver operating characteristic curve (AUROC) was calculated to reflect model's discrimination. To reduce overfitting and quantify optimism, the nomogram was internally validated with an approach to 1,000 bootstrapped resampling and calculating an optimism-corrected C-statistic. Decision curve analysis (DCA) was used to describe the clinical validity and net benefit of the nomogram (24). Statistical analysis was performed using the SPSS 26.0 software (IBM Corp., Armonk, NY, USA). R version 4.1.2 was used with the packages of rms, tidyr, dplyr, rmda, forestplot, pROC. *P*-value <0.05 was considered statistically significant.

Results

Study cohort

From February 2019 to December 2020, 290 pediatric patients underwent this surgical procedure, of which 33.1% (96 out of 290) received ASD, 37.6% (109 out of 290) received VSD, and 29.3% (85 out of 290) received PDA. Also, among all enrolled patients, 34.1% (99 out of 290) and 23.1% (67 out of 290) patients occurred RAEs during extubation to transport and transport discharged from operating room, respectively (**Supplementary Figure S1**). The most common RAEs was desaturation, found in 127 times (51.0%), followed by airway obstruction in 97 (39.0%), airway secretion in 12 (4.8%) and laryngospasm in 10 (4.0%), and other RAEs including laryngospasm, apnea, and severe cough was uncommon (**Supplementary Figure S2**).

Model development

Univariate analysis found that seven variables were significantly associated with RAEs during transport (**Table 1**). Multivariate analysis identified age (vs. ≤3 years, adjusted odds ratio (aOR) = 0.507, 95% confidence interval (CI), 0.268–0.958, $P = 0.036$), preoperative URI (aOR = 2.335, 95% CI, 1.223–4.460, $P = 0.01$), type of surgery (vs. VSD, for ASD, aOR = 2.856, 95% CI, 1.272–6.411, $P = 0.011$; for PDA, aOR = 5.518, 95% CI, 2.425–12.553, $P < 0.001$), morphine equivalent (vs. ≤0.153 mg/kg, aOR = 2.904, 95% CI, 1.371–6.150, $P = 0.005$), atropine usage (aOR = 0.463, 95% CI, 0.244–0.879, $P = 0.019$), and RAEs during extubation to transport (aOR = 5.004, 95% CI, 2.633–9.511, $P < 0.001$) as independent predictors of RAEs during transport (**Figure 2**). To determine the threshold for morphine equivalent, ROC analysis was performed, which showed the optimal cutoff value was 0.153. Using these six parameters, this study developed a nomogram to predict the probability of RAEs during transport (**Figure 3**).

Model performance and internal validation

H-L goodness-of-fit test value was 0.844. The C- statistic value of the prediction model was 0.809 (95% CI, 0.755–0.862, $P < 0.001$), which showed good discrimination. The sensitivity and specificity based on AUROC curve were 73.1% and 74.9%, respectively (**Figure 4A**). The apparent calibration curve was close to the 45° ideal line, indicating that the observed probability was consistent with predicted probability in the development cohort (**Figure 4B**). To lessen the optimism of the model, internal validation with 1,000 bootstrap approach was conducted, which reflect good discrimination with optimism-corrected C- statistic of 0.782 (95% CI, 0.726–0.837). And the bias-corrected calibration

TABLE 1 Perioperative characteristics stratified by RAEs during transport.

Variables[a]	RAEs ($n = 67$)	No-RAEs ($n = 223$)	*P* value
Age, years	3.2 ± 2.3	3.8 ± 2.3	0.091
Age >3 years	26 (38.8)	121 (54.3)	0.027*
Sex			0.464
Male	24 (35.8)	91 (40.8)	
Female	43 (64.2)	132 (59.2)	
ASA grade			0.907
II	57 (85.1)	191 (85.7)	
III	10 (14.9)	32 (14.3)	
Height, cm	94.6 ± 17.6	101.2 ± 17.7	0.026*
Weight, kg	14.8 ± 6.1	16.5 ± 7.4	0.080
BMI, kg/m^2	16.0 ± 1.8	15.8 ± 2.0	0.596
History of allergy	14 (20.9)	30 (13.5)	0.136
History of asthma	1 (1.5)	3 (1.3)	>0.999
History of hay fever	5 (7.5)	22 (9.9)	0.553
Bronchial hyperreactivity	2 (3.0)	4 (1.8)	0.625
Osas	24 (35.8)	70 (31.4)	0.497
Passive smoking	23 (34.3)	65 (29.1)	0.419
Type of surgery			0.006*
VSD	16 (23.9)	93 (41.7)	
ASD	22 (32.8)	74 (33.2)	
PDA	29 (43.3)	56 (25.1)	
Preoperative URI	41 (61.2)	92 (41.3)	0.004*
Propofol, mg	56.3 ± 26.5	61.1 ± 25.8	0.194
Morphine equivalent, mg	0.18 ± 0.04	0.17 ± 0.04	0.189
Morphine equivalent >0.153 mg/kg	53 (79.1)	147 (65.0)	0.041*
Muscle relaxant	1 (1.5)	5 (2.2)	>0.999
Atropine usage	28 (41.8)	139 (62.3)	0.003*
Dexmedetomidine	49 (73.1)	139 (62.3)	0.104
Operative time, min	36.9 ± 18.2	36.8 ± 20.3	0.969
Anesthesia time, min	41.5 ± 18.4	41.8 ± 20.0	0.921
Extubation time, min	3.5 ± 2.7	3.5 ± 2.9	0.891
Deep extubation	61 (91.0)	196 (87.9)	0.476
Emergence agitation	5 (7.5)	25 (11.2)	0.377
Vomiting	3 (4.5)	16 (7.2)	0.579
Fever	1 (1.5)	5 (2.2)	>0.999
RAEs during extubation to transport	41 (61.2)	58 (26.0)	<0.001*

RAEs, respiratory adverse events; ASA, American society of anesthesiology; BMI, body mass index; VSD, ventricular septal defects; ASD, atrial septal defects; PDA, patent ductus arteriosus; URI, upper respiratory tract infection.
[a]Continuous data are shown as mean ± standard deviation and categoric data as number (%).
*Statistically significant ($P < 0.05$).

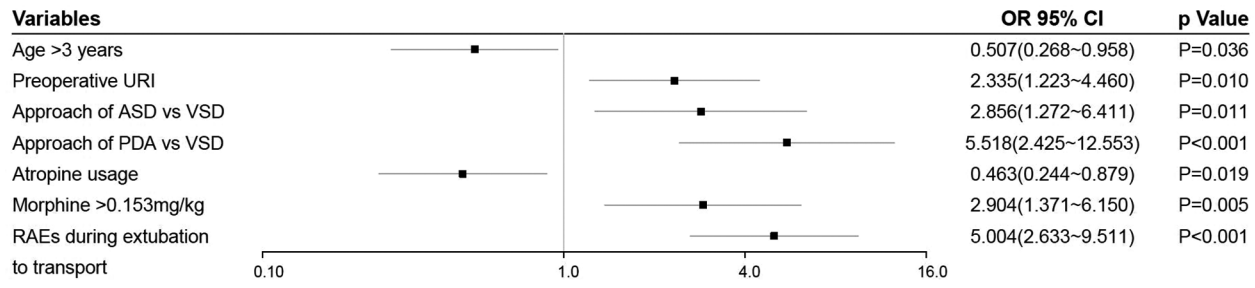


FIGURE 2
Forest plot of independent predictors of RAEs during transport. URI, upper respiratory tract infection; ASD, atrial septal defects; VSD, ventricular septal defects; PDA, patent ductus arteriosus; RAEs, respiratory adverse events.

curve also demonstrated that the prediction model was well calibrated when the actual observed probability of RAEs during transport was less than 40% (Figure 4B).

DCA for the development prediction model

The depicted DCA was used to determine whether decisions based on the predictive model had clinical applicability compared to the default strategy. Such analyses provide insight into the range of predicted risk for which the model has a high net benefit than simply either treating all (slope line) patients versus treating no (horizontal line) patient, that is to say, a prediction model is only useful at the threshold risk. The depicted DCA indicated the expected net benefit (red curve) per patient for predicting the risk of RAEs during transport. Within the threshold risk range of 0%–74%, intervention decisions based on the predictive model are clearly beneficial (Figure 5).

Discussion

The incidence of RAEs during transport after interventional cardiac catheterization in pediatric patients was 23.1%. This study identified six independent predictors for RAEs during transport, of which morphine equivalent and atropine usage

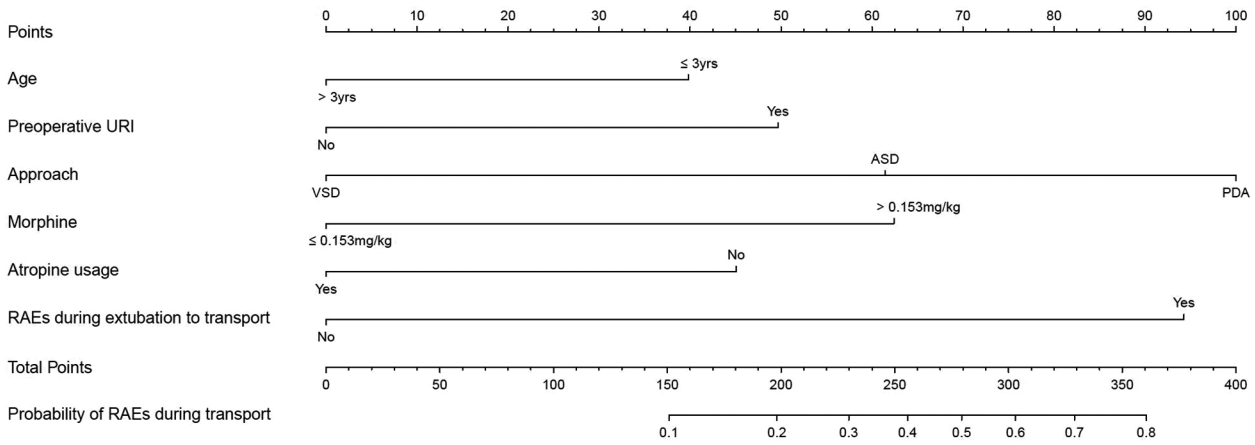


FIGURE 3
A novel nomogram to predict RAEs during transport. The nomogram provides a visual point system based on the combination of patient characteristics (age, preoperative URI, type of surgery, morphine equivalent, atropine usage, and RAEs during extubation to transport) to estimate the probability of RAEs during transport. To calculate the probability of RAEs during transport, the points of six variables determined on the scale were added to obtain the total points. Draw a vertical line from the total points scale to the last axis to obtain the corresponding probability of RAEs during transport. For example, if a pediatric patient ≤3 years (40 scores), combined with preoperative URIs (50 scores), presenting for ASD (60 scores), accompanied with morphine equivalent >0.153 mg/kg (60 scores) and atropine usage (45 scores), and developed RAEs during extubation to transport (95 scores), the total points were 350 scores, and the corresponding occurrence of RAEs during transport were nearly 80%. URI, upper respiratory tract infection; ASD, atrial septal defects; VSD, ventricular septal defects; PDA, patent ductus arteriosus; RAEs, respiratory adverse events.

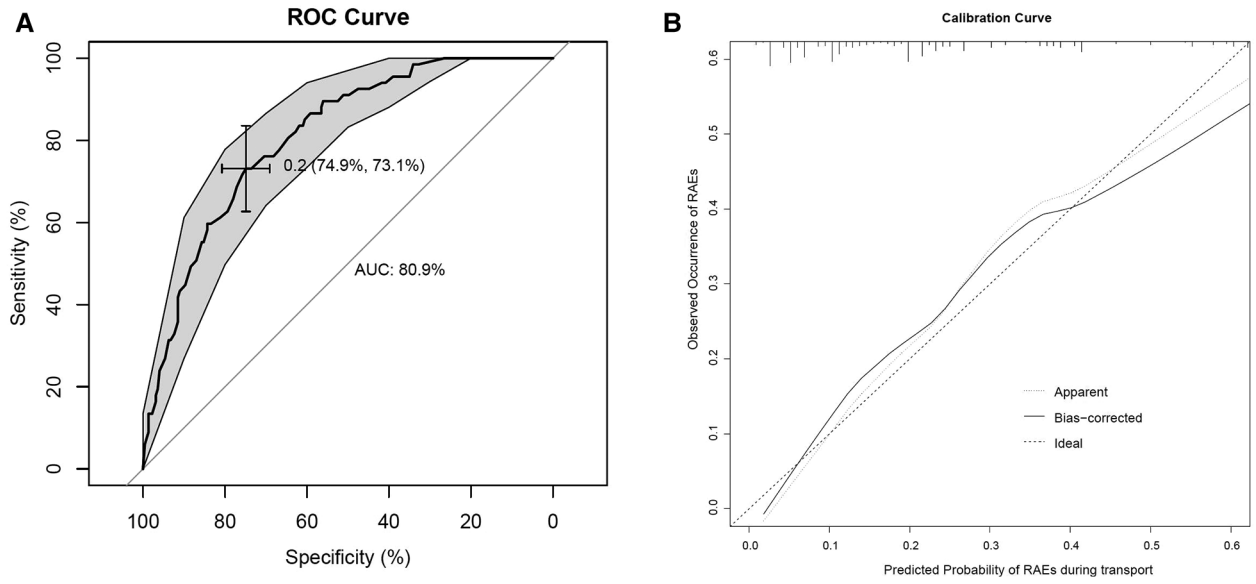


FIGURE 4
(A) AUROC curve for RAEs prediction model. (B) Internal calibration curves. A completely accurate prediction model will generate a plot where the probability of the actual observed and predicted corresponding completely, and fall along the 45° line (dashed line). The apparent calibration curve (dotted line) represents the calibration of the model in the development data set, while the bias-corrected curve (solid line) is the calibration result after correcting the optimism with the 1,000 bootstrap-resampling.

were modifiable factors that could be optimized to reduce the occurrence of RAEs. Using these six parameters, this study constructed a nomogram to estimate the risk of RAEs during transport, with good C-statistic and calibration in internal validation. The DCA also indicated the clinical usefulness of the nomogram, namely, intervention decisions based on the predictive model were clearly beneficial when the threshold risk range of 0%–74%.

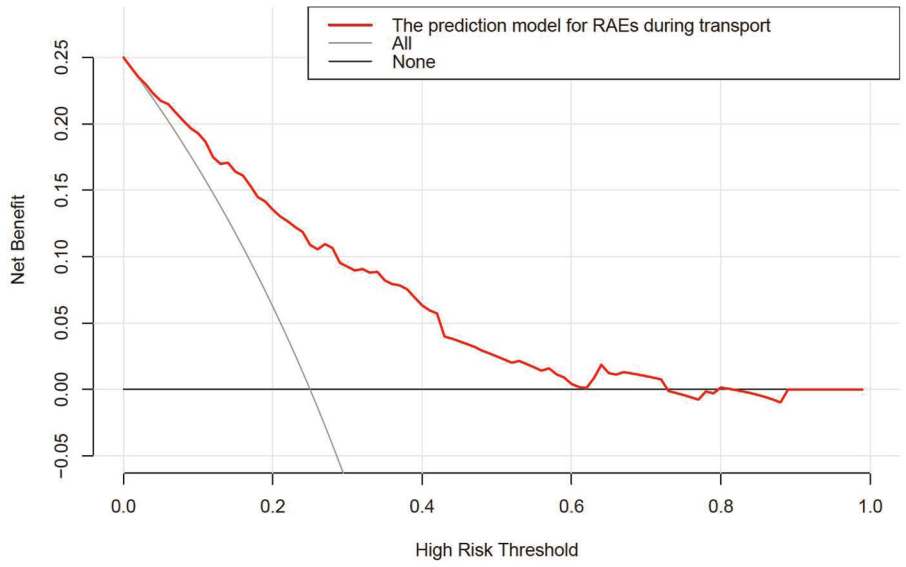


FIGURE 5
The DCA shows the clinical usefulness of the nomogram. The *Y*-axis represents net benefit. The solid red line is a nomogram predicting the risk of RAEs during transport. The solid gray line indicates that all patients occurred RAEs during transport, while the fine solid black line indicates that no patient occurred RAEs during transport. This DCA could provide a larger net benefit, with ranges of 0%–74%. DCA, decision curve analysis; RAEs, respiratory adverse events.

Our study addresses an important knowledge gap in the medical literature regarding the incidence and predictors of RAEs during transport after this surgical procedure in pediatric patients. Previous scholars mainly focused on the construction of different prediction models for RAEs in the period of anesthesia induction, PACU or perioperative, and most of them were retrospective nature with insufficient efficacy (3, 6–10). Our findings suggest that high rate of RAEs during transport deserves our sufficient attention and medical care in the context of the relative lack of medical resources. The prediction model constructed based on a prospectively collected data can effectively predict the risk of RAEs during transport, which is helpful for the identification of high-risk groups and the adjustment of transport plans. Importantly, as two adjustable factors, morphine equivalent and atropine usage have important clinical implications for guiding clinicians to formulate feasible schemes to further reduce the occurrence of RAEs.

Previous documents have identified several underlying predictors for RAEs in pediatric patients during perioperative period, including younger age, ASA grade, race, obesity, obstructive sleep apnea, preexisting pulmonary disorder, URI, premedication, passive smoking, anesthetic technique, anesthetic care without a pediatric anesthetist, type of surgery, and operative time (6–10, 19, 23). By comparison, this study also demonstrated that age ≤3 years, preoperative URI, type of surgery, morphine equivalent and atropine usage, and RAEs during extubation to transport were independent predictors for RAEs during transport. Among these factors, morphine equivalent and atropine usage were rarely reported in the literature.

An important finding of this study is that morphine equivalent and atropine usage are two important modifiable factors that can reduce the risk of RAEs during transport. Opioid dose is significantly positively correlated with perioperative adverse outcomes and long-term prognosis (22, 25). However, there is no literature reporting the effect of opioid dosage on RAEs during pediatric anesthesia. In order to more accurately assess this potential effect, we standardized opioids commonly used in clinical practice, such as fentanyl and sufentanil, according to the analgesic conversion ratio and calculated the dosage under normalized lean body weight, which has clinical practicality (20–22). Our findings echoed the understanding of previous studies that high doses of opioid usage per kg were associated with an increased risk of RAEs during transport. Due to its unique pharmacokinetics and association with postoperative hyperalgesia, remifentanil dose was not included in the opioid calculations but was adjusted as *a priori* defined covariate in the regression models.

Atropine usage, the other of the two adjustable variables, was associated with a lower incidence of RAEs during transport, providing a new insight into medication usage. The underlying biological mechanism is that atropine usage can reduce the production of airway secretions, thereby reducing the risk of RAEs. In the previous literature, the premedication used to prevent or minimize RAEs mainly includes sedative drugs and local anesthetics, such as dexmedetomidine, midazolam, and lidocaine topicalization of the airway (3, 7, 26–28). In our published study, we have confirmed that premedication with intranasal dexmedetomidine was an effective method to decrease the occurrence of RAEs in children with CHD (28). It has also been proven to be beneficial in pediatric patients receiving tonsillectomy and adenoidectomy (3). However, there are conflicting studies of midazolam and RAEs. A national cohort study showed that midazolam usage has a preventive effect on RAEs (29), whereas several studies found that premedication with midazolam appears to increase the incidence of RAEs (3, 7).

In terms of model construction, this study was the first to predict RAEs during transport after this pediatric surgery, and all variables inserted in the predictive model were quantifiable predictors readily available to the clinicians. Besides, the nomogram can provide a visual point system to estimate the probability of RAEs during transport with good discrimination after internal validation. Bias-corrected calibration curve showed that the model could accurately predict the occurrence of RAEs during transport when the observed probability of RAEs during transport was less than 40%. Inversely, a few existing models that cannot accurately and objectively predict RAEs during anesthesia induction or perioperative period, and do not include a special type of surgery such as interventional cardiac catheterization (8, 30–32). Based on the clinical data of 19,095 pediatric patients undergoing elective ambulatory anesthesia for surgery and radiology, Subramanyam et al. developed and validated a risk prediction model for the occurrence of RAEs from the onset of anesthesia induction until discharge from the PACU, with a C-statistic of 0.64 (8).

Strengths and limitations

Our study has several important strengths. This was an observational study based on a prospectively collected database, and the statistical methods and main outcomes were developed and completed before the start of this trial. To the best of our knowledge, this study was the first to investigate the incidence and predictors, and to construct a nomogram for accurately predicting the occurrence of RAEs during transport after this pediatric surgical treatment. Likewise, several limitations are among our research. First, as a monocentric cohort study, it has the inherent design biases. Second, for the specific surgical type of interventional cardiac catheterization, the pace and the limited time available for postoperative recovery and transport in pediatric patients may slightly increase the occurrence of RAEs during transport.

Third, although the prediction model had good performance in internal validation, external validation in a multicenter setting was still required. Finally, randomized controlled trials are needed to confirm whether the two newly reported modifiable factors, morphine equivalents and atropine usage, have an effect on RAEs during transport or even during perioperative period.

Conclusion

This prospective study explored the incidence and predictors, and constructed a novel nomogram for predicting the occurrence of RAEs during transport. The high rate of RAEs during transport after this pediatric surgical procedure reminds us of the need for more medical care and attention. Six independent predictors for RAEs during transport were identified, of which morphine equivalents and atropine usage were newly reported. Using these six parameters, this study established a novel nomogram, which can reliably identify pediatric patients at high risk of RAEs during transport and guide clinicians to make proper transport plans. Our findings have important and meaningful implications for RAEs risk prediction, clinical intervention and healthcare quality control.

Data availability statement

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

Ethics statement

The studies involving human participants were reviewed and approved by the Institutional Review Board of Shanghai Children's Medical Centre (SCMCIRB-K20170122) and written informed consent was obtained from parents or the legal guardians of each child before surgery. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

Study conception, design, statistic analysis and drafting of the manuscript: CT, PL and KZ. Acquisition of data: CT, KZ and TL. Analysis and interpretation of data: JZ and CT. Critical revision: JZ, CT and KZ. All authors contributed to the article and approved the submitted version.

Funding

This work was supported by the Natural Science Foundation of Shanghai (21ZR1441100), Pudong New District Science and Technology Development Innovation Foundation (PKJ2016-Y34) and the Young Scholar Research grant from the Shanghai Municipal Health Committee (20194Y0094).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2022.1044791/full#supplementary-material.

References

1. Murat I, Constant I, Maud'huy H. Perioperative anesthetic morbidity in children: a database of 24,165 anesthetics over a 30-month period. *Paediatr Anaesth.* (2004) 14(2):158–66. doi: 10.1111/j.1460-9592.2004.01167.x

2. von Ungern-Sternberg BS, Sommerfield D, Slevin L, Drake-Brockman TFE, Zhang G, Hall GL. Effect of albuterol premedication vs placebo on the occurrence of respiratory adverse events in children undergoing tonsillectomies: the REACT randomized clinical trial. *JAMA Pediatr.* (2019) 173(6):527–33. doi: 10.1001/jamapediatrics.2019.0788

3. Shen F, Zhang Q, Xu Y, Wang X, Xia J, Chen C, et al. Effect of intranasal dexmedetomidine or midazolam for premedication on the occurrence of respiratory adverse events in children undergoing tonsillectomy and adenoidectomy: a randomized clinical trial. *JAMA Netw Open.* (2022) 5(8): e2225473. doi: 10.1001/jamanetworkopen.2022.25473

4. Tay CL, Tan GM, Ng SB. Critical incidents in pediatric anesthesia: an audit of 10 000 anesthetics in Singapore. *Pediatr Anaesth.* (2001) 11(6):711–8. doi: 10.1046/j.1460-9592.2001.00767.x

5. Oofuvong M, Geater AF, Chongsuvivatwong V, Chanchayanon T, Sriyanaluk B, Saefung B, et al. Excess costs and length of hospital stay attributable to perioperative respiratory events in children. *Anesth Analg*. (2015) 120(2):411–9. doi: 10.1213/ANE.0000000000000557

6. Malviya S, Voepel-Lewis T, Siewert M, Pandit UA, Riegger LQ, Tait AR. Risk factors for adverse postoperative outcomes in children presenting for cardiac surgery with upper respiratory tract infections. *Anesthesiology*. (2003) 98 (3):628–32. doi: 10.1097/00000542-200303000-00009

7. von Ungern-Sternberg BS, Boda K, Chambers NA, Rebmann C, Johnson C, Sly PD, et al. Risk assessment for respiratory complications in pediatric anesthesia: a prospective cohort study. *Lancet*. (2010) 376(9743):773–83. doi: 10.1016/S0140-6736(10)61193-2

8. Subramanyam R, Yeramaneni S, Hossain MM, Anneken AM, Varughese AM. Perioperative respiratory adverse events in pediatric ambulatory anesthesia: development and validation of a risk prediction tool. *Anesth Analg*. (2016) 122(5):1578–85. doi: 10.1213/ANE.0000000000001216

9. Tariq S, Syed M, Martin T, Zhang X, Schmitz M. Rates of perioperative respiratory adverse events among Caucasian and African American children undergoing general anesthesia. *Anesth Analg*. (2018) 127(1):181–7. doi: 10.1213/ANE.0000000000003430

10. Wudineh DM, Berhe YW, Chekol WB, Adane H, Workie MM. Perioperative respiratory adverse events among pediatric surgical patients in university hospitals in northwest Ethiopia; A prospective observational study. *Front Pediatr*. (2022) 10:827663. doi: 10.3389/fped.2022.827663

11. Lerman J. Perioperative respiratory complications in children. *Lancet*. (2010) 376(9743):745–6. doi: 10.1016/S0140-6736(10)61199-3

12. Tait AR, Voepel-Lewis T, Christensen R, O'Brien LM. The STBUR questionnaire for predicting perioperative respiratory adverse events in children at risk for sleep-disordered breathing. *Paediatr Anaesth*. (2013) 23(6):510–6. doi: 10.1111/pan.12155

13. Welliver Sr RC, Checchia PA, Bauman JH, Fernandes AW, Mahadevia PJ, Hall CB. Fatality rates in published reports of RSV hospitalizations among high-risk and otherwise healthy children. *Curr Med Res Opin*. (2010) 26 (9):2175–81. doi: 10.1185/03007995.2010.505126

14. Delgado-Corcoran C, Witte MK, Ampofo K, Castillo R, Bodily S, Bratton SL. The impact of human rhinovirus infection in pediatric patients undergoing heart surgery. *Pediatr Cardiol*. (2014) 35(8):1387–94. doi: 10.1007/s00246-014-0941-3

15. Moynihan K, Barlow A, Alphonso N, Anderson B, Johnson J, Nourse C, et al. Impact of viral respiratory pathogens on outcomes after pediatric cardiac surgery. *Pediatr Crit Care Med*. (2017) 18(3):219–27. doi: 10.1097/PCC.0000000000001083

16. Promphan W, Qureshi SA. What interventional cardiologists are still leaving to the surgeons? *Front Pediatr*. (2016) 4:59. doi: 10.3389/fped.2016.00059

17. Lin CH, Hegde S, Marshall AC, Porras D, Gauvreau K, Balzer DT, et al. Incidence and management of life-threatening adverse events during cardiac catheterization for congenital heart disease. *Pediatr Cardiol*. (2014) 35(1):140–8. doi: 10.1007/s00246-013-0752-y

18. Zhang S, Ding S, Cai M, Bai J, Zhang M, Huang Y, et al. Impact of upper respiratory tract infections on perioperative outcomes of children undergoing therapeutic cardiac catheterisation. *Acta Anaesthesiol Scand*. (2018) 62 (7):915–23. doi: 10.1111/aas.13113

19. Zhang K, Wang S, Li M, Wu C, Sun L, Zhang S, et al. Anesthesia timing for children undergoing therapeutic cardiac catheterization after upper respiratory infection: a prospective observational study. *Minerva Anestesiol*. (2020) 86 (8):835–43. doi: 10.23736/S0375-9393.20.14293-7

20. Gordon DB, Stevenson KK, Griffie J, Muchka S, Rapp C, Ford-Roberts K. Opioid equianalgesic calculations. *J Palliat Med*. (1999) 2(2):209–18. doi: 10.1089/jpm.1999.2.209

21. Ingrande J, Lemmens HJ. Dose adjustment of anaesthetics in the morbidly obese. *Br J Anaesth*. (2010) 105(Suppl 1):i16–23. doi: 10.1093/bja/aeq312

22. Long DR, Lihn AL, Friedrich S, Scheffenbichler FT, Safavi KC, Burns SM, et al. Association between intraoperative opioid administration and 30-day readmission: a pre-specified analysis of registry data from a healthcare network in new England. *Br J Anaesth*. (2018) 120(5):1090–102. doi: 10.1016/j.bja.2017.12.044

23. Tait AR, Malviya S, Voepel-Lewis T, Munro HM, Seiwert M, Pandit UA. Risk factors for perioperative adverse respiratory events in children with upper respiratory tract infections. *Anesthesiology*. (2001) 95(2):299–306. doi: 10.1097/00000542-200108000-00008

24. Van Calster B, Wynants L, Verbeek JFM, Verbakel JY, Christodoulou E, Vickers AJ, et al. Reporting and interpreting decision curve analysis: a guide for investigators. *Eur Urol*. (2018) 74(6): 796–804. doi: 10.1016/j.eururo.2018.08.038

25. Cron DC, Englesbe MJ, Bolton CJ, Joseph MT, Carrier KL, Moser SE, et al. Preoperative opioid use is independently associated with increased costs and worse outcomes after major abdominal surgery. *Ann Surg*. (2017) 265 (4):695–701. doi: 10.1097/SLA.0000000000001901

26. Li LW, He L, Ai Y, Chu Q, Zhang W. Site-directed topical lidocaine spray attenuates perioperative respiratory adverse events in children undergoing elective surgery. *J Surg Res*. (2016) 203(1):206–10. doi: 10.1016/j.jss.2016.03.011

27. Poonai N, Spohn J, Vandermeer B, Ali S, Bhatt M, Hendrikx S, et al. Intranasal dexmedetomidine for procedural distress in children: a systematic review. *Pediatrics*. (2020) 145(1):e20191623. doi: 10.1542/peds.2019-1623

28. Zhang S, Zhang R, Cai M, Zhang K, Zhang M, Zheng J. Intranasal dexmedetomidine premedication in children with recent upper respiratory tract infection undergoing interventional cardiac catheterisation: a randomised controlled trial. *Eur J Anaesthesiol*. (2020) 37(2):85–90. doi: 10.1097/EJA.0000000000001097

29. Michel F, Vacher T, Julien-Marsollier F, Dadure C, Aubineau JV, Lejus C, et al. Peri-operative respiratory adverse events in children with upper respiratory tract infections allowed to proceed with anaesthesia: a French national cohort study. *Eur J Anaesthesiol*. (2018) 35(12):919–28. doi: 10.1097/EJA.0000000000000875

30. Lee LK, Bernardo MKL, Grogan TR, Elashoff DA, Ren WHP. Perioperative respiratory adverse event risk assessment in children with upper respiratory tract infection: validation of the COLDS score. *Paediatr Anaesth*. (2018) 28(11): 1007–14. doi: 10.1111/pan.13491

31. Tao S, Zhang T, Wang K, Xie F, Ni L, Mei Z, et al. Identification of the risk factors in perioperative respiratory adverse events in children under general anesthesia and the development of a predictive model. *Transl Pediatr*. (2021) 10 (7):1877–82. doi: 10.21037/tp-21-257

32. Zhang Q, Shen F, Wei Q, Liu H, Li B, Zhang Q, et al. Development and validation of a risk nomogram model for perioperative respiratory adverse events in children undergoing airway surgery: an observational prospective cohort study. *Risk Manag Healthc Policy*. (2022) 15:1–12. doi: 10.2147/RMHP.S347401

frontiers | Frontiers in Public Health

TYPE Original Research
PUBLISHED 22 December 2022
DOI 10.3389/fpubh.2022.1071304

OPEN ACCESS

EDITED BY
Zhen-Yu Zhang,
KU Leuven, Belgium

REVIEWED BY
Dongmei Wei,
KU Leuven, Belgium
Michel Boulvain,
Université de Genève, Switzerland

*CORRESPONDENCE
Megan L. Gow
✉ megan.gow@health.nsw.gov.au

SPECIALTY SECTION
This article was submitted to Children and Health, a section of the journal Frontiers in Public Health

RECEIVED 16 October 2022
ACCEPTED 05 December 2022
PUBLISHED 22 December 2022

CITATION
Varley BJ, Henry A, Roberts L, Davis G, Skilton MR, Craig ME and Gow ML (2022) Intrauterine exposure to preeclampsia does not impair vascular health in children.
Front. Public Health 10:1071304.
doi: 10.3389/fpubh.2022.1071304

Intrauterine exposure to preeclampsia does not impair vascular health in children

Benjamin J. Varley[1,2], Amanda Henry[3,4,5,6], Lynne Roberts[5,7], Gregory Davis[5,7], Michael R. Skilton[8,9,10], Maria E. Craig[1,2,4,5] and Megan L. Gow[1,3,5]*

[1]The University of Sydney, Children's Hospital Westmead Clinical School, Sydney, NSW, Australia, [2]Department of Paediatrics and Child Health, St George Hospital, Kogarah, NSW, Australia, [3]Discipline of Paediatrics and Child Health, School of Clinical Medicine, UNSW Medicine and Health, University of New South Wales, Sydney, NSW, Australia, [4]Discipline of Women's Health, School of Clinical Medicine, UNSW Medicine and Health, University of New South Wales, Sydney, NSW, Australia, [5]Department of Women's Health, St George Hospital, Kogarah, NSW, Australia, [6]The George Institute for Global Health, Sydney, NSW, Australia, [7]School of Clinical Medicine, UNSW Medicine and Health, University of New South Wales, Sydney, NSW, Australia, [8]Boden Initiative, Charles Perkins Centre, University of Sydney, Sydney, NSW, Australia, [9]Sydney Medical School, University of Sydney, Sydney, NSW, Australia, [10]Sydney Institute for Women, Children and their Families, Sydney Local Health District, Sydney, NSW, Australia

Background and objectives: Preeclampsia is a serious multisystem blood pressure disorder during pregnancy that is associated with increased long-term risk of cardiovascular disease to the mother and offspring. We investigated the vascular health of children exposed to intrauterine preeclampsia.

Materials and methods: This was a cross-sectional study of offspring in a prospective cohort of women with complications during pregnancy. Children aged between 2 and 5 years [median age 4.7 (2.8, 5.1) years] exposed to intrauterine preeclampsia ($n = 26$) or normotensive controls ($n = 34$), were recruited between July 2020 and April 2021. Vascular health was assessed by measuring aortic intima-media thickness and pulse wave velocity. Univariate generalized linear regression models were used to explore associations between vascular measurements and explanatory variables.

Results: Children exposed to preeclampsia had a lower body mass index at assessment (15.5 vs. 16.2 kg/m^2, $p = 0.04$), birth weight (2.90 vs. 3.34 kg, $p = 0.004$), gestational age at birth (37.5 vs. 39.4 weeks, $p < 0.001$) and higher frequency of preterm birth (27% vs. 6%, $p = 0.02$). There were no differences in vascular health between children exposed to preeclampsia vs. controls (mean aortic intima-media thickness 0.575 mm vs. 0.563 mm, $p = 0.51$, pulse wave velocity 4.09 vs. 4.18 m/s, $p = 0.54$) and there were no significant associations in univariate analyses.

Conclusions: There were no major adverse differences in vascular health which contrasts with existing studies. This suggests exposure to intrauterine preeclampsia may result in a less severe cardiovascular phenotype in young children. While reassuring, longitudinal studies are required to determine if and when exposure to intrauterine preeclampsia affects vascular health in children.

KEYWORDS

preeclampsia, aortic intima-media thickness, pulse wave velocity, children, early arterial injury

Introduction

Preeclampsia is a multisystem disorder in pregnancy, characterized by pregnancy hypertension after 20 weeks' gestation and maternal and/or fetal organ dysfunction. Preeclampsia affects 3–5% of all pregnancies and is associated with increased maternal and infant mortality as well as adverse pregnancy outcomes including preterm birth and fetal growth restriction (1, 2). There is an increased long-term risk of cardiovascular disease (CVD) in these mothers as a result of preeclampsia (1), and there is growing evidence of increased long-term cardiovascular risk in children exposed to intrauterine preeclampsia (3, 4). Historically, research investigating the effects of preeclampsia exposure on children has primarily focused on identifying traditional risk factors such as increased body mass index (BMI) and blood pressure (BP).

Atherosclerosis and arteriosclerosis are key pathophysiological processes that result in the structural and degenerative changes of large arteries which underlie CVD. Measurements of intima-media thickness and pulse wave velocity (PWV) can assess such arterial wall changes and are recognized as acceptable, non-invasive measurements of early arterial injury in children (5–7), and can be used to predict potential risk of future CVD (8–10). Measurement of carotid intima-media thickness is widely used in adults for future CVD risk assessment (11). However, abdominal aorta intima-media thickness (aIMT) may be a more appropriate measure in children (6, 12, 13), as it is more sensitive to childhood risk factors including familial hypercholesterolemia, type 1 diabetes (13), and adverse outcomes during pregnancy such as fetal growth restriction (14, 15) and large for gestational age (16, 17). Preliminary evidence has shown greater aIMT in neonates exposed to preeclampsia compared to those unexposed (18–20), whereas effects on PWV during childhood are conflicting (21, 22).

The purpose of this study was to investigate whether vascular health in children aged 2–5 years of age is affected by exposure to intrauterine preeclampsia. The primary hypothesis was that children exposed to preeclampsia have signs of early arterial injury including increased aIMT and PWV, compared to the children of uncomplicated pregnancies.

Materials and methods

This was a cross-sectional sub-study of offspring from participants in the Postpartum Physiology, Psychology and Pediatric follow up study (P4 study), a prospective, observational study of postpartum women with either normal BP or preeclampsia in their preceding pregnancy, conducted at St George Hospital, Sydney, Australia. A study protocol for the P4 cohort has been published (23).

Women were eligible for the P4 study if they gave birth to a singleton live baby within the previous 6 months and had a good understanding of written and spoken English. Women were excluded if they had chronic hypertension, diabetes, renal or other serious disease prior to pregnancy, were pregnant again at the time of first (6 months postpartum) assessment, or if their baby was born with a congenital anomaly.

The recruited cohort consisted of 90 women who had preeclampsia during pregnancy and 402 control women who had a normotensive pregnancy. Preeclampsia was defined as persistent *de novo* hypertension (systolic BP $\geq$ 140 mmHg and/or diastolic BP $\geq$ 90 mmHg) that developed at or after 20 weeks' gestation accompanied with one or more of the following new-onset conditions: proteinuria, other maternal organ dysfunction including liver or kidney involvement, neurological complications, low platelets or uteroplacental dysfunction, according to the guidelines of the International Society for the Study of Hypertension in Pregnancy (24, 25). Preeclampsia with severe hypertension was defined as systolic BP $\geq$ 160 mmHg and/or diastolic BP $\geq$ 110 mmHg (25) and onset was considered early if occurring before 34 weeks gestation (26).

All children born to mothers in the P4 cohort study were eligible for recruitment into this cross-sectional sub-study. Children between 2 and 5 years of age were recruited between July 2020 to April 2021. Children were excluded from analysis if neither aIMT nor PWV could be obtained. Previous study data examining aortic-IMT in growth-restricted neonates vs. controls [MD (SD), 0.07 (0.08)] (27) indicated a minimum required sample size of 22 children exposed to preeclampsia and 22 normotensive controls to detect a significant difference between groups (power = 0.8, $\alpha = 0.5$). This sub-study was approved by the South Eastern Sydney Local Health District Human Research Ethics Committee (2019/ETH11984).

Pediatric assessments

Height was measured using a stadiometer and weight with electronic scales. Height, weight and BMI z-scores were calculated according to WHO Child Growth Standards (28). Gestational age at birth, birth weight and length were collected from the mother's maternity medical records. Z-scores for birth weight and length according to gestational age were calculated for preterm (<37 weeks) and term infants using the INTERGROWTH-21st (29) and WHO Child Growth Standards, respectively (28). Small for gestational age was defined as a birth weight z-score below −1.28 for gestational age and sex, corresponding to the 10th percentile.

Vascular structure was assessed by aIMT which was measured using a GE Voluson S6 system with a linear array transducer (GE 9L-RS) and a frequency of 3–10 MHz, as previously described (13). High-resolution images of the far

wall of a non-branched, 1 cm longitudinal segment of the abdominal aorta near the aortic bifurcation were captured. Gain was adjusted to optimize image quality. A minimum of two loops were captured for blinded offline analysis. Mean and maximum aIMT were calculated with validated edge detection software during end-diastole (Carotid Analyzer, Medical Imaging Applications LLC; Coralville, IA). AIMT was defined as the distance from the edge of the lumen intima to the media-adventitia border of the far wall. Aortic diameter was defined as the media-adventitia borders between near and far walls and was captured during end diastole. All scans and analyses were performed by one technician (BJV) after training from an experienced technician and followed a standardized protocol. AIMT scans were excluded if they lacked sufficient quality for analysis, including too much movement, poor image quality or presence of sonographic artifacts.

Vascular function was assessed by measuring PWV and central BP using the SphygmoCor XCEL (AtCor Medical, West Ryde, NSW, Australia) as described (30). Simultaneous recordings of pulse waveforms were obtained by placing an applanation tonometer on the right common carotid, whereas the femoral waveform was measured by volume displacement produced by a cuff placed around the upper thigh. The arterial path was measured directly using non-stretchable tape between the right common carotid and femoral arteries multiplied by 0.8. PWV was automatically calculated by the XCEL software system (Version 1.3) by dividing the arterial path distance by the transit time between the pulse waveforms. A standard brachial cuff was used to capture brachial and diastolic pressures and provide central BP. An average of three measurements was used for each assessment. PWV measurements were excluded if they did not meet quality control of the Sphygmocor device (31). Under optimal conditions, children rested for a minimum of 10 mins in a supine position before vascular measurements.

Maternal assessments

Pregnancy data including antihypertensive medication, pregnancy outcome, dating scan, weight and BMI were obtained from the mother's maternity medical records. Demographic data including age, ethnicity, highest education level, previous diabetes and smoking status, alcohol intake, exercise and drug use were obtained from a questionnaire that the mother completed 6 months after birth.

Data analysis

Descriptive statistical analyses are reported as mean ± SD or median (IQR). The primary outcome measures were aIMT and PWV. Secondary outcome measurements included aortic lumen diameter and central BP. Between group differences for continuous outcome measures were assessed using independent sample *t*-tests (normal distribution) or Mann-Whitney *U* Tests (non-normal distribution) and for categorical outcomes using Chi-square or Fisher's exact tests. Univariate generalized linear models were used to compare means, with adjustment for age and gender, and in a separate model, BMI and birthweight. Non-parametric variables were log transformed for univariate linear models.

Univariate generalized linear regression models were also used to explore the association between outcome measures and explanatory variables, including gestational age at birth, birth weight, birthweight Z-score, birth length, birth length z-score, gender, height, height Z-score, weight, weight Z-score, BMI, BMI Z-score, preterm, small for gestational age, maternal age, maternal dating scan BMI, maternal dating scan weight, maternal smoking ever, maternal moderate exercise at 6 months, maternal alcoholic drinks at 6 months, parity, antihypertensive medication in pregnancy, months breastfed, drug use ever, preeclampsia severity of hypertension, preeclampsia onset, highest maternal BP during pregnancy and preeclampsia exposure. Sub-group analysis of aIMT and PWV by preeclampsia severity of hypertension, onset, and gestational age were also performed. All statistical analyses were performed using SPSS (version 26; SPSS Inc., Chicago, IL, USA).

Results

Participant characteristics

Sixty-nine children from the P4 study were consented to participate in this sub-study and underwent assessment. Five participants were excluded as they were unable to complete the vascular assessments at the study visit and a further four were excluded in quality control because neither aIMT nor PWV could be obtained (Figure 1). A total of 26 children exposed to intrauterine preeclampsia and 34 controls were included in the final analysis.

The characteristics of participants are shown in Table 1. Children exposed to preeclampsia had a lower BMI at time of assessment (15.5 kg/m^2 vs. 16.2 kg/m^2), birth weight (2.90 kg vs. 3.34 kg), gestational age at birth (37.5 weeks vs. 39.4 weeks) and higher frequency of preterm birth (27% vs. 6%). There were no other differences between groups. Vascular measurements are presented in Table 2 and individual participant data are presented in Figure 2. Central systolic BP was higher in children exposed to preeclampsia when adjusted by BMI and birthweight. There were no differences in aIMT or PWV between groups.

Maternal characteristics are described in Table 3. Mothers with preeclampsia had a higher BMI at dating scan (24.0 vs. 22.4), higher rates of cesarean section (58% vs. 5%),

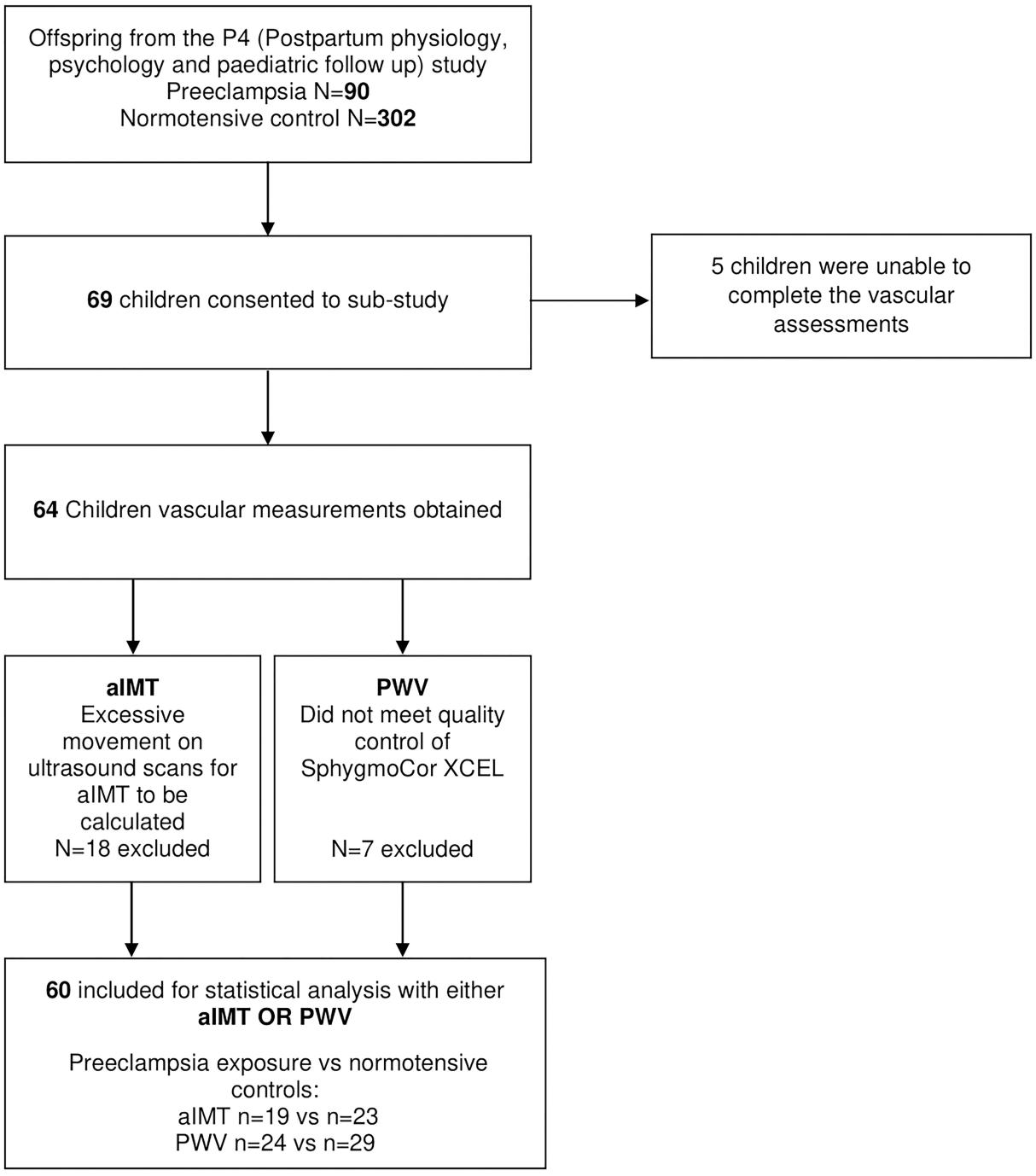


FIGURE 1
Participant recruitment and analysis flow diagram.

antihypertensive medication (60% vs. 0%) and exercised more at 6 months (2 vs. 1 days). Otherwise, characteristics of mothers were not different. Mothers with preeclampsia were classified as early vs. late onset (19% vs. 81%) and severe hypertension preeclampsia vs. non severe (58% vs. 42%).

There were no significant associations between vascular measurements and explanatory variables in univariate analysis. Moreover, there were also no differences in aIMT or PWV in sub-group analysis by preeclampsia onset, BP severity and gestational age (results not shown).

10.3389/fpubh.2022.1071304

TABLE 1 Offspring characteristics stratified by exposure to preeclampsia vs. normotensive pregnancy.

	Preeclampsia $n = 26$	Control $n = 34$	p value
Male	15 (58)	19 (56)	0.89
Age at assessment (years)	4.3 (3.2, 5.1)	5.0 (2.2, 5.3)	0.92
Height (cm)	107 (97.3, 112)	107 (89.4, 111)	0.46
Height Z-score	0.46 (−0.54, 0.87)	−0.18 (−0.71, 0.43)	0.15
Weight (kg)	17.2 (15.2, 19.4)	18.2 (13.4, 19.9)	0.99
Weight Z-score*	0.21 ± 1.00	0.30 ± 0.79	0.69
BMI (kg/m^2)	15.5 ± 1.2	16.2 ± 1.2	**0.04**
BMI Z-score	0.05 ± 0.83	0.47 ± 0.80	0.05
Birth weight (kg)	2.90 ± 0.66	3.34 ± 0.46	**0.004**
Birth weight Z-score*	−0.33 ± 0.83	−0.07 ± 0.99	0.28
Birth length (cm)	48.5 ± 3.7	50.0 ± 2.4	0.06
Birth length Z-score*	−0.20 ± 1.01	−0.13 ± 1.12	0.81
Gestational age (weeks)	37.5 ± 2.3	39.4 ± 1.4	**<0.001**
Preterm birth	7 (27)	2 (6)	**0.02**
Months breastfed	11.1 ± 8.3	12.7 ± 6.8	0.41

Data presented as n (%), mean ± SD or median (IQR).
*Corrected for gestational age.
BMI, Body mass index.
The bold values indicate the statistical significance ($p < 0.05$).

Discussion

In this cohort of children exposed to preeclampsia and controls, there were no major adverse differences in vascular structure or function. This contrasts with our hypothesis but reassuringly suggests that exposure to preeclampsia does not lead to vascular structure and function aberrations consistent with signs of early CVD in young children.

In our study, PWV was not different between participants exposed to intrauterine preeclampsia compared with controls. To the best of our knowledge, only two other studies have measured PWV in children exposed to intrauterine preeclampsia. One study from Pakistan with children aged 2–10 years (mean age 5 ± 2.2 years) reported a significant, albeit small, difference compared with controls (0.42 vs. 0.39 m/s) (21). However, participants exposed to preeclampsia had a lower gestational age, lower birthweight and higher rates of preterm birth compared to children in our study. Similarly to our study, the Avon Longitudinal Study of Parents and Children found no difference in carotid-radial PWV between groups in children and early adolescents (22). Our recent systematic review of exposures during the first 1,000 days of life suggest that changes to PWV may not manifest until adolescence (32).

Two other studies (18, 19) have investigated the association between intrauterine preeclampsia exposure and aIMT in childhood. Both reported a greater difference in aIMT compared with controls which contrasts with our findings. However, these studies may not be representative globally. In the study from Greece by Oikonomou (19), aIMT was measured in neonates during the first 5 days of life. This study included only neonates exposed to early onset preeclampsia, which is often associated with fetal complications including growth restriction compared to late-onset (33) and may have influenced aIMT. In our study, preeclampsia was predominately late onset which is reflective of the overall population distribution of early vs. late-onset preeclampsia (34) and therefore our results may be more generalizable. The rate of gestational diabetes was also higher in Oikonomou's preeclampsia group compared to controls (31% vs. 8%) (19) and may have also influenced the findings as maternal diabetes is known to influence aIMT (16, 35).

The presence of other CVD risk factors may explain differences between our results and previous studies. Neonates in a cohort from Turkey exposed to intrauterine preeclampsia had significantly higher triglycerides (2.2 vs. 0.3 mmol/L) and lower high density lipoprotein (1.0 vs. 1.5 mmol/L) compared to controls (18). Triglycerides were also significantly higher in mothers of exposed neonates compared to controls (12.4 vs. 7.2 mmol/L). Although lipids are elevated in women with preeclampsia compared to controls (36, 37), chronic and transient maternal hypercholesterolaemia are associated with increased fatty streak formation in the fetal aorta compared to the aortas of fetuses from mothers with normal cholesterol (38). In neonates, evidence of elevation of lipids following preeclampsia exposure is conflicting. A systematic review of the effect of preeclampsia exposure on the lipid concentration of cord blood found that three of six studies reported a significant increase in triglycerides compared to controls (3). Additional studies have reported a significant increase in lipids in children exposed to preeclampsia compared with controls (39) and another found no differences between groups (40) however, it is not known how long triglycerides persist as longitudinal studies have not been performed. As elevated triglyceride levels are associated with greater aIMT of neonates exposed to other adverse pregnancy complications such as growth restriction (35) or born large for gestational age (16), we speculate that elevated neonate lipids levels may have influenced the aIMT in the study by Akcakus et al. (18). Meta-analysis have reported that LDL is greater and HDL is lower in the cord blood of offspring exposed to intrauterine preeclampsia, however there were no differences in the lipids of children, adolescents and young children exposed to preeclampsia (3). While we did not assess lipids in this study, they should be investigated in future research.

There are challenges in assessing PWV and aIMT in young children. While feasible (41), we had to exclude five participants as they were unable to cooperate or keep still during the vascular assessments. Moreover, distractions were required in 40% of

TABLE 2 All vascular outcomes stratified by exposure to preeclampsia vs. normotensive pregnancy.

	Preeclampsia	Control	*p*	Adjusted *p* value[a]	Adjusted *p* value[b]
aIMT	$N = 19$	$N = 23$			
Mean aortic intima-media thickness (mm)	0.575 ± 0.06	0.563 ± 0.05	0.51	0.48	0.49
Max aortic intima-media thickness (mm)	0.644 ± 0.07	0.628 ± 0.06	0.42	0.45	0.62
Aortic lumen diameter (mm)	8.04 (7.62, 8.60)	7.55 (7.01, 8.25)	0.06	0.11	0.05
Weight adjusted mean aIMT (mm/kg)	0.033 (0.030, 0.041)	0.037 (0.029, 0.044)	0.71	0.97	0.25
Mean aIMT/aortic lumen diameter	0.071 ± 0.01	0.075 ± 0.01	0.32	0.47	0.20
Weight adjusted max aIMT (mm/kg)	0.036 (0.033, 0.044)	0.041 (0.032, 0.049)	0.71	0.89	0.23
Max aIMT/aortic lumen diameter	0.077 (0.071, 0.090)	0.079 (0.075, 0.088)	0.33	0.43	0.14
Arterial stiffness	$N = 24$	$N = 29$			
PWV (m/s)	4.09 ± 0.51	4.18 ± 0.53	0.54	0.51	0.34
Central blood pressure	$N = 26$	$N = 32$			
Central systolic blood pressure (mmHg)	93.7 ±5.4	91.4 ± 7.1	0.17	0.18	**0.04**
Central diastolic blood pressure (mmHg)	67.0 ± 4.4	66.3 ± 6.9	0.67	0.60	0.15
Central pulse pressure (mmHg)	26.5 (24.3, 29.3)	25.2 (22.1, 27.6)	0.05	0.06	0.09

Data presented as mean ± SD or median (IQR).
[a]Adjusted for age and gender.
[b]Adjusted for BMI and birth weight.
aIMT, aortic intima-media thickness; PWV, carotid-femoral pulse wave velocity.
The bold values indicate the statistical significance ($p < 0.05$).

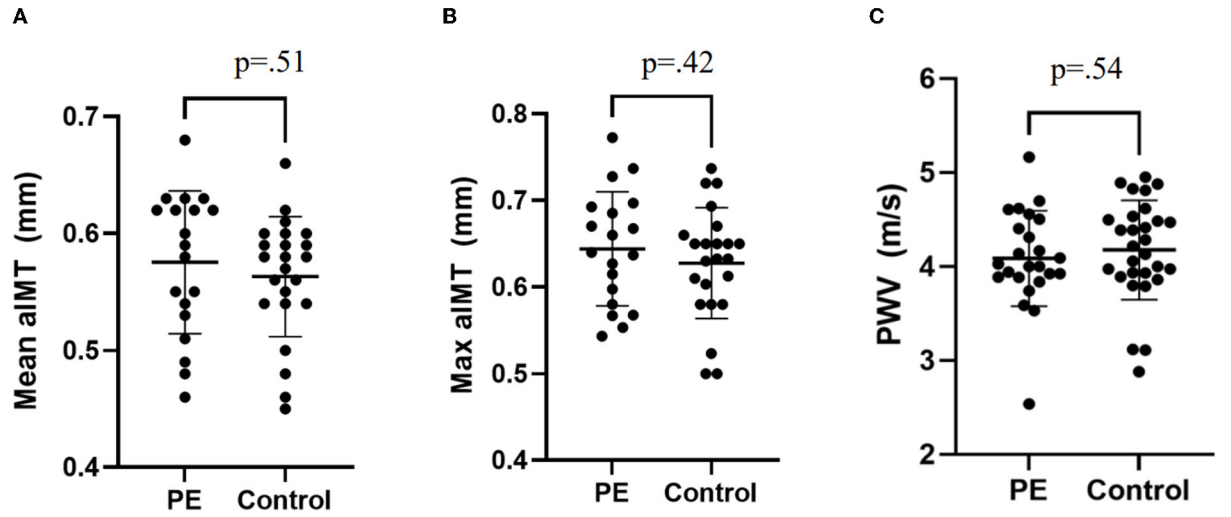


FIGURE 2
Individual patient data for vascular measures. **(A)** Mean aIMT, **(B)** Maximum aIMT, and **(C)** Pulse wave velocity. Plots presented as mean ± SD. PE, Preeclampsia.

participants in order to sufficiently perform the assessments. A further four participants were excluded as they did not meet quality control. Despite this, we obtained more successful measurements than other studies which measured aIMT (41) or PWV (41, 42) in early childhood populations.

The effects of exposure to intrauterine preeclampsia may vary throughout childhood. As our study was conducted in children aged two to five, we cannot rule out the possibility of a regression in intimal thickening after birth. This is supported by a series of post mortem studies by Stary (43), where the frequency of fatty streaks located in the coronary arteries decreased after infancy and during early childhood before increasing in late childhood. This suggests that early lesions found in infancy were formed *in-utero* and are reflective of maternal risk factors. Accordingly, vascular health markers assessed in childhood may be more indicative of exposure

TABLE 3 Maternal characteristics stratified by preeclampsia vs. normotensive pregnancy.

	Preeclampsia $n = 26$	Control $n = 34$	*p* value
Age at birth (years)	32.5 ± 4.8	32.6 ± 3.9	0.91
Smoking ever at 6 months	9 (35)	9 (27)	0.49
Alcoholic drinks/week at 6 months (drinks)	1 (0, 2)	0 (0, 2)	0.44
Moderate exercise/week at 6 months (days)	2 (1,3)	1 (0, 2.25)	0.05
Illicit drug use ever at 6 months	7 (27)	16 (47)	0.11
Antihypertensive medication during pregnancy	15 (60)	0 (0)	**<0.001**
Parity			0.36
1	19 (73)	21 (62)	
2	7 (27)	13 (38)	
Ethnicity: Oceanian	14 (54)	18 (53)	0.94
Pre-pregnancy BMI (kg/m^2)*	24.0(22.6, 27.0)	22.4 (20.9, 24.0)	**0.02**
Dating scan weight (kg)	64 (58.8, 69.0)	58.5 (54.5, 66.3)	0.06
Cesarean section	15 (58)	5 (15)	**<0.001**
Education			0.07
Tertiary	8 (31)	4 (12)	
University	18 (69)	30 (88)	
GDM/GDM in previous pregnancy	4 (15)	2 (6)	0.22
Preeclampsia onset			
Early	5 (19)	–	–
Late	21 (81)	–	
Preeclampsia blood pressure severity			
Hypertension[a]	11 (42)	–	–
Severe hypertension[b]	15 (58)	–	

Data presented as n (%), mean ± SD or median (IQR).
Categorical data calculates with Chi square or Fisher's exact.
BMI, body mass index; DBP, diastolic blood pressure; GDM, gestational diabetes mellitus; SBP, systolic blood pressure.
*Based on self-reported weight.
[a]Defined as Systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg.
[b]Defined as Systolic blood pressure ≥160 mmHg and/or diastolic blood pressure ≥110 mmHg.
The bold values indicate the statistical significance ($p < 0.05$).

to childhood risk factors. Longitudinal studies should seek to establish whether vascular health changes seen in newborn offspring exposed to preeclampsia regress during infancy. On the other hand, the time point of our study may be too early to detect clinically significant changes. A systematic review of 53,029 individuals investigated the association between exposure to intrauterine preeclampsia with cardiovascular risk factors and reported elevated BP and a mild increase in BMI from childhood and in early adulthood (3) however, there was considerable heterogeneity. We also found a mild increase in central systolic BP in children exposed to preeclampsia, after adjusting for BMI and birth weight. This is an important finding because elevated BP tracks from childhood to adulthood and is likely to predict hypertension in adulthood (44), highlighting the potential for early intervention in high-risk children. Although limited, evidence from the aforementioned systematic review (3) also indicated that vascular function is altered, with changes to endothelial function and cardiac morphometry reported in children exposed to preeclampsia compared to controls. PWV or IMT were not reported in this systematic review.

Although preeclampsia exposure was not associated with adverse cardiovascular markers in our cohort, there is growing evidence of the long term effects of offspring exposed to intrauterine preeclampsia including increased cardiovascular morbidity, elevated BMI and BP (4). Therefore those exposed to intrauterine preeclampsia may benefit from routine screening and monitoring of cardiovascular risk factors, particularly BP, to identify individuals at the greatest risk and to target intervention strategies. Routine screening may also be important as preeclampsia exposure often overlaps with other adverse outcomes in pregnancy such as low birth weight and preterm birth, which are both independently associated with increased CVD risk in later life (45, 46). However, the results of our study provide reassurance to parents of young children exposed to in intrauterine preeclampsia, as signs of increased CVD risk were not present in this cohort of children aged 2–5 years.

Strengths of the study include recruitment of participants in this sub-study from an established prospective cohort study of ethnically diverse women and their children as well as a large parallel control group (23). The participants are well characterized from a cohort that is broadly reflective of the overall preeclampsia population i.e., mostly late onset and without severe fetal growth restriction, and were assessed over a narrow age range. However, future studies which include a mix of exposure to early and late onset may be helpful in determining the impact of intrauterine preeclampsia exposure on vascular health. We followed best practice procedures for data collection (6, 47), using validated and acceptable methods for assessing early arterial injury in children (42, 48, 49), which contrasts other published studies (20, 32). Other adverse complications such as low birth weight and preterm birth increase CVD risk in later life (45, 46), however, we found no associations between aIMT or PWV and confounders in univariate or sub-group analysis. Due to slow recruitment and smaller than expected enrolment in to the study, we were unable to match

cases vs. controls as initially planned. Whilst we recognize the study was potentially underpowered, none of the findings approached statistical or clinical significance. Further research, including longitudinal follow-up, is required to determine if alterations to vascular structure and function are apparent later in life.

We found no differences in vascular structure or function in 2–5 year old children as a result of intrauterine preeclampsia exposure. While this finding is reassuring, more research is required in larger cohorts with longitudinal follow up to determine if, and when, exposure to intrauterine preeclampsia affects the vascular health of children.

Data availability statement

Data from this study will not be made available because accessing patient level data requires an application and permissions. Requests to access the datasets should be directed to megan.gow@health.nsw.gov.au.

Ethics statement

The studies involving human participants were reviewed and approved by South Eastern Sydney Local Health District Human Research Ethics Committee (2019/ETH11984). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

BV collected the data, carried out data analysis, interpreted the results, drafted the initial draft of the manuscript, and revised the manuscript. AH and GD conceived the study and design (P4 study) and critically reviewed the manuscript. LR collected the data (P4 study) and critically reviewed the manuscript. MS critically reviewed the manuscript and contributed to the study design. MC and MG conceived the study, were involved in interpretation of results and critically reviewed the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Funding

This work was supported by Australian Government Research Training Program PhD scholarship (BV), NHMRC Early Career Fellowships [APP1158876 (MG)], and NHMRC practitioner fellowship [APP1136735 (MC)].

Acknowledgments

The authors acknowledge all families for their participation in this study.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Chappell LC, Cluver CA, Kingdom J, Tong S. Pre-eclampsia. *Lancet.* (2021) 398:341–54. doi: 10.1016/S0140-6736(20)32335-7

2. Mol BWJ, Roberts CT, Thangaratinam S, Magee LA, de Groot CJM, Hofmeyr GJ. Pre-eclampsia. *Lancet.* (2016) 387:999–1011. doi: 10.1016/S0140-6736(15)00070-7

3. Andraweera PH, Lassi ZS. Cardiovascular risk factors in offspring of preeclamptic pregnancies—systematic review and meta-analysis. *J Pediatr.* (2019) 208:104–13.e6. doi: 10.1016/j.jpeds.2018.12.008

4. Wojczakowski W, Kimber-Trojnar Z, Dziwisz F, Słodzińska M, Słodziński H, Leszczyńska-Gorzelak B. Preeclampsia and cardiovascular risk for offspring. *J Clin Med.* (2021) 10:3154. doi: 10.3390/jcm10143154

5. Urbina EM, Williams RV, Alpert BS, Collins RT, Daniels SR, Hayman L, et al. Noninvasive assessment of subclinical atherosclerosis in children and adolescents. *Hypertension.* (2009) 54:919–50. doi: 10.1161/HYPERTENSIONAHA.109.192639

6. Skilton RM, Celermajer SD, Cosmi E, Crispi F, Gidding SS, Raitakari TO, et al. Natural history of atherosclerosis and abdominal aortic intima-media thickness: rationale, evidence, and best practice for detection of atherosclerosis in the young. *J Clin Med.* (2019) 8:1201. doi: 10.3390/jcm8081201

7. Dalla Pozza R, Ehringer-Schetitska D, Fritsch P, Jokinen E, Petropoulos A, Oberhoffer R. Intima media thickness measurement in children: a statement from the Association for European Paediatric Cardiology (AEPC) Working Group on Cardiovascular Prevention Endorsed by the Association for European Paediatric Cardiology. *Atherosclerosis.* (2015) 238:380–7. doi: 10.1016/j.atherosclerosis.2014.12.029

8. van den Oord SCH, Sijbrands EJG, ten Kate GL, van Klaveren D, van Domburg RT, van der Steen AFW, et al. Carotid intima-media thickness for cardiovascular risk assessment: systematic review and meta-analysis. *Atherosclerosis.* (2013) 228:1–11. doi: 10.1016/j.atherosclerosis.2013.01.025

9. Lorenz MW, Markus HS, Bots ML, Rosvall M, Sitzer M. Prediction of clinical cardiovascular events with carotid intima-media thickness. *Circulation.* (2007) 115:459–67. doi: 10.1161/CIRCULATIONAHA.106.628875

10. Ben-Shlomo Y, Spears M, Boustred C, May M, Anderson SG, Benjamin EJ, et al. Aortic pulse wave velocity improves cardiovascular event prediction: an individual participant meta-analysis of prospective observational data from 17,635 subjects. *J Am Coll Cardiol.* (2014) 63:636–46. doi: 10.1016/j.jacc.2013.09.063

11. Epure AM, Rios-Leyvraz M, Anker D, Di Bernardo S, da Costa BR, Chiolero A, et al. Risk factors during first 1,000 days of life for carotid intima-media thickness in infants, children, and adolescents: a systematic review with meta-analyses. *PLoS Med.* (2020) 17:e1003414. doi: 10.1371/journal.pmed.1003414

12. Dawson JD, Sonka M, Blecha MB, Lin W, Davis PH. Risk factors associated with aortic and carotid intima-media thickness in adolescents and young adults: the muscatine offspring study. *J Am Coll Cardiol.* (2009) 53:2273–9. doi: 10.1016/j.jacc.2009.03.026

13. Järvisalo MJ, Jartti L, Näntö-Salonen K, Irjala K, Rönnemaa T, Hartiala Jaakko J, et al. Increased aortic intima-media thickness: a marker of preclinical atherosclerosis in high-risk children. *Circulation.* (2001) 104:2943–7. doi: 10.1161/hc4901.100522

14. Gomez-Roig MD, Mazarico E, Valladares E, Guirado L, Fernandez-Arias M, Vela A. Aortic intima-media thickness and aortic diameter in small for gestational age and growth restricted fetuses. *PLoS ONE.* (2015) 10:e0126842. doi: 10.1371/journal.pone.0126842

15. Akazawa Y, Hachiya A, Yamazaki S, Kawasaki Y, Nakamura C, Takeuchi Y, et al. Cardiovascular remodeling and dysfunction across a range of growth restriction severity in small for gestational age infants—implications for fetal programming. *Circ J.* (2016) 80:2212–20. doi: 10.1253/circj.CJ-16-0352

16. Akcakus M, Koklu E, Baykan A, Yikilmaz A, Coskun A, Gunes T, et al. Macrosomic newborns of diabetic mothers are associated with increased aortic intima-media thickness and lipid concentrations. *Horm Res Paediatr.* (2007) 67:277–83. doi: 10.1159/000098157

17. Koklu E, Kurtoglu S, Akcakus M, Yikilmaz A, Gunes T. Serum insulin-like growth factor-I (Igf-I) Igf binding protein-3 (Igfbp-3) and leptin levels are related to abdominal aortic intima-media thickness in macrosomic newborns. *Growth Horm IGF Res.* (2007) 17:26–32. doi: 10.1016/j.ghir.2006.10.002

18. Akcakus M, Altunay L, Yikilmaz A, Yazici C, Koklu E. The relationship between abdominal aortic intima-media thickness and lipid profile in neonates born to mothers with preeclampsia. *J Pediatr Endocrinol Metab.* (2010) 23:1143. doi: 10.1515/jpem.2010.179

19. Oikonomou N, Fouzas S, Gkentzi D, Dimitriou G, Karatza AA. Aortic intima-media thickness in neonates exposed to early-onset preeclampsia. *Early Hum Dev.* (2020) 151:105166. doi: 10.1016/j.earlhumdev.2020.105166

20. Varley BJ, Nasir RF, Skilton MR, Craig ME, Gow ML. Early life determinants of vascular structure in fetuses, infants, children, and adolescents: a systematic review and meta-analysis. *J Pediatr.* (2022) 2022:1–10. doi: 10.1016/j.jpeds.2022.08.033

21. Hoodbhoy Z, Aslam N, Mohsin S, Ashiqali S, Ali H, Sattar S, et al. Cardiovascular dysfunction in children exposed to preeclampsia during fetal life. *J Am Soc Echocardiogr.* (2021). doi: 10.1016/j.echo.2021.01.008

22. Lawlor DA, Macdonald-Wallis C, Fraser A, Nelson SM, Hingorani A, Davey Smith G, et al. Cardiovascular biomarkers and vascular function during childhood in the offspring of mothers with hypertensive disorders of pregnancy: findings from the avon longitudinal study of parents and children. *Eur Heart J.* (2012) 33:335–45. doi: 10.1093/eurheartj/ehr300

23. Davis GK, Roberts L, Mangos G, Henry A, Pettit F, O'Sullivan A, et al. Postpartum physiology, psychology and paediatric follow up study (p4 study)—study protocol. *Pregnancy Hypertens.* (2016) 6:374–9. doi: 10.1016/j.preghy.2016.08.241

24. Brown MA, Magee LA, Kenny LC, Karumanchi SA, McCarthy FP, Saito S, et al. The hypertensive disorders of pregnancy: ISSHP classification, diagnosis and management recommendations for international practice. *Pregnancy Hypertens.* (2018) 13:291–310. doi: 10.1016/j.preghy.2018.05.004

25. Magee LA, Brown MA, Hall DR, Gupte S, Hennessy A, Karumanchi SA, et al. The 2021 international society for the study of hypertension in pregnancy classification, diagnosis and management recommendations for international practice. *Pregnancy Hypertens.* (2022) 27:148–69. doi: 10.1016/j.preghy.2021.09.008

26. Tranquilli AL, Brown MA, Zeeman GG, Dekker G, Sibai BM. The definition of severe and early-onset preeclampsia. Statements from the International Society for the Study of Hypertension in Pregnancy (ISSHP). *Pregnancy Hypertens.* (2013) 3:44–7. doi: 10.1016/j.preghy.2012.11.001

27. Skilton MR, Evans N, Griffiths KA, Harmer JA, Celermajer DS. Aortic Wall Thickness in newborns with intrauterine growth restriction. *Lancet.* (2005) 365:1484–6. doi: 10.1016/S0140-6736(05)66419-7

28. World Health Organization. *Child Growth Standards.* (2022). Available online at: https://www.who.int/tools/child-growth-standards/software (accessed March 30, 2022).

29. Villar J, Giuliani F, Bhutta ZA, Bertino E, Ohuma EO, Ismail LC, et al. Postnatal growth standards for preterm infants: the preterm postnatal follow-up study of the intergrowth-21st project. *Lancet Glob Health.* (2015) 3:e681–e91. doi: 10.1016/S2214-109X(15)00163-1

30. Cai TY, Meroni A, Dissanayake H, Phang M, Avolio A, Celermajer DS, et al. Validation of a cuff-based device for measuring carotid-femoral pulse wave velocity in children and adolescents. *J Hum Hypertens.* (2019) 34:311–8. doi: 10.1038/s41371-019-0191-1

31. AtCorMedical Pty Ltd. *Operator's Manual Sphygmocor Xcel System V1.* Sydney, NSW: AtCor Medical Pty Ltd (2020).

32. Varley BJ, Nasir RF, Craig ME, Gow ML. Early life determinants of arterial stiffness in neonates, infants, children and adolescents: a systematic review and meta-analysis. *Atherosclerosis.* (2022) 355:1–7. doi: 10.1016/j.atherosclerosis.2022.07.006

33. Raymond D, Peterson E. A critical review of early-onset and late-onset preeclampsia. *Obstet Gynecol Surv.* (2011) 66:97–506. doi: 10.1097/OGX.0b013e3182331028

34. Lisonkova S, Joseph KS. Incidence of preeclampsia: risk factors and outcomes associated with early- versus late-onset disease. *Am J Obstet Gynecol.* (2013) 209:544.e1–e12. doi: 10.1016/j.ajog.2013.08.019

35. Koklu E, Kurtoglu S, Akcakus M, Koklu S, Buyukkayhan D, Gumus H, et al. Increased aortic intima-media thickness is related to lipid profile in newborns with intrauterine growth restriction. *Horm Res.* (2006) 65:269–75. doi: 10.1159/000092536

36. Gallos ID, Sivakumar K, Kilby MD, Coomarasamy A, Thangaratinam S, Vatish M. Pre-eclampsia is associated with, and preceded by, hypertriglyceridaemia: a meta-analysis. *BJOG.* (2013) 120:1321–32. doi: 10.1111/1471-0528.12375

37. Spracklen CN, Smith CJ, Saftlas AF, Robinson JG, Ryckman KK. Maternal hyperlipidemia and the risk of preeclampsia: a meta-analysis. *Am J Epidemiol.* (2014) 180:346–58. doi: 10.1093/aje/kwu145

38. Napoli C, D'Armiento FP, Mancini FP, Postiglione A, Witztum JL, Palumbo G, et al. Fatty streak formation occurs in human fetal aortas and is greatly enhanced by maternal hypercholesterolemia. Intimal accumulation of low density lipoprotein and its oxidation precede monocyte recruitment into early atherosclerotic lesions. *J Clin Invest.* (1997) 100:2680–90. doi: 10.1172/JCI119813

39. Kharb S, Nanda S. Patterns of biomarkers in cord blood during pregnancy and preeclampsia. *Curr Hypertens Rev.* (2017) 13:57–64. doi: 10.2174/1573402113666170126101914

40. Alahakoon TI, Medbury HJ, Williams H, Lee VW. Lipid profiling in maternal and fetal circulations in preeclampsia and fetal growth restriction-a prospective case control observational study. *BMC Preg Childbirth.* (2020) 20:61. doi: 10.1186/s12884-020-2753-1

41. Zhao B, Johnston FH, Dalton M, Negishi K. Feasibility and normal ranges of arterial intima-media thickness and stiffness in 2-year-old children: a pilot study. *Pediatr Cardiol.* (2019) 40:914–20. doi: 10.1007/s00246-019-02088-1

42. Keehn L, Milne L, McNeill K, Chowienczyk P, Sinha MD. Measurement of pulse wave velocity in children: comparison of volumetric and tonometric sensors, brachial-femoral and carotid-femoral pathways. *J Hypertens.* (2014) 32:1464–9. doi: 10.1097/HJH.0000000000000203

43. Stary HC. Lipid and macrophage accumulations in arteries of children and the development of atherosclerosis. *Am J Clin Nutr.* (2000) 72:1297s—306s. doi: 10.1093/ajcn/72.5.1297s

44. Chen X, Wang Y. Tracking of blood pressure from childhood to adulthood. *Circulation.* (2008) 117:3171–80. doi: 10.1161/CIRCULATIONAHA.107.730366

45. Belbasis L, Savvidou MD, Kanu C, Evangelou E, Tzoulaki I. Birth weight in relation to health and disease in later life: an umbrella review of systematic reviews and meta-analyses. *BMC Med.* (2016) 14:147. doi: 10.1186/s12916-016-0692-5

46. Markopoulou P, Papanikolaou E, Analytis A, Zoumakis E, Siahanidou T. Preterm birth as a risk factor for metabolic syndrome and cardiovascular disease in adult life: a systematic review and meta-analysis. *J Pediatr*. (2019) 210:69–80.e5. doi: 10.1016/j.jpeds.2019.02.041

47. Van Bortel LM, Laurent S, Boutouyrie P, Chowienczyk P, Cruickshank JK, De Backer T, et al. Expert consensus document on the measurement of aortic stiffness in daily practice using carotid-femoral pulse wave velocity. *J Hypertens.* (2012) 30:445–8. doi: 10.1097/HJH.0b013e32834fa8b0

48. Stabouli S, Printza N, Zervas C, Dotis J, Chrysaidou K, Maliahova O, et al. Comparison of the sphygmocor xcel device with applanation tonometry for pulse wave velocity and central blood pressure assessment in youth. *J Hypertens.* (2019) 37:30–6. doi: 10.1097/HJH.0000000000001819

49. McCloskey K, Ponsonby A-L, Carlin JB, Jachno K, Cheung M, Skilton MR, et al. Reproducibility of aortic intima-media thickness in infants using edge-detection software and manual caliper measurements. *Cardiovasc Ultrasound.* (2014) 12:18. doi: 10.1186/1476-7120-12-18

frontiers | Frontiers in Public Health

TYPE Original Research
PUBLISHED 05 January 2023
DOI 10.3389/fpubh.2022.1056484

OPEN ACCESS

EDITED BY
Zhen-Yu Zhang,
KU Leuven, Belgium

REVIEWED BY
Malgorzata Wojcik,
Jagiellonian University Medical College, Poland
Andrea Lukács,
University of Miskolc, Hungary

*CORRESPONDENCE
Mario Leone
✉ mario.leone@uqac.ca

SPECIALTY SECTION
This article was submitted to Children and Health, a section of the journal Frontiers in Public Health

RECEIVED 28 September 2022
ACCEPTED 05 December 2022
PUBLISHED 05 January 2023

CITATION
Leone M, Levesque P, Bourget-Gaudreault S, Lemoyne J, Kalinova E, Comtois AS, Bui HT, Léger L, Frémont P and Allisse M (2023) Secular trends of cardiorespiratory fitness in children and adolescents over a 35-year period: Chronicle of a predicted foretold. *Front. Public Health* 10:1056484. doi: 10.3389/fpubh.2022.1056484

Secular trends of cardiorespiratory fitness in children and adolescents over a 35-year period: Chronicle of a predicted foretold

Mario Leone[1,2]*, Patrick Levesque[1], Sabrina Bourget-Gaudreault[1], Jean Lemoyne[3], Emilia Kalinova[4], Alain Steve Comtois[4], Hung Tien Bui[2], Luc Léger[5], Pierre Frémont[6] and Maxime Allisse[7]

[1]Department of Health Sciences, Université du Québec à Chicoutimi, Chicoutimi, QC, Canada, [2]Department of Medicine and Health Sciences, Université de Sherbrooke, Sherbrooke, QC, Canada, [3]Department of Physical Activity Sciences, Université du Québec à Trois-Rivières, Trois-Rivières, QC, Canada, [4]Department of Physical Activity Sciences, Université du Québec à Montréal, Montreal, QC, Canada, [5]School of Kinesiology, Université de Montréal, Montréal, QC, Canada, [6]Department of Kinesiology, Laval University, Quebec, QC, Canada, [7]Department of Kinanthropology, Université de Sherbrooke, Sherbrooke, QC, Canada

Background: In the context of concerns regarding the cardiorespiratory fitness (CRF) of youth populations, the aims of this study were: (1) to update reference values for the VO_2max for school-aged Canadians and (2) to document secular trends in CRF after a 35-year interval.

Methods: Between September 2014 and April 2017, the CRF of 3725 students (53.2% boys; 6.0 to 17.9 yrs) was determined using the 20-m shuttle run test. The sample was collected in 36 different schools from six cities of Québec (Canada).

Results: Median values of VO_2max decreased with age in both sexes ($p \leq 0.05$). By the age of 10, more than 20% of boys showed VO_2max values below the recommended value (42 ml·kg^{-1}·min^{-1}). At the age of 17, that proportion reached 56.8%. A similar proportion of 12 yrs girls (20%) were under the recommended minimal value (37 ml·kg^{-1}·min^{-1}) and that value reached 69.9% at the age of 17. Compared to 1982, the VO_2max at age 17 has declined by 18% for boys and 12% for girls. The situation is worse in terms of functional capacity (number of stages completed) with an overall decrease of more than 30%.

Conclusion: This study demonstrates that, compared to data obtained using the same methodology 35 years ago, the CRF and functional capacity of children and adolescents has declined to levels that should raise concerns from a public health perspective. Thus, the development of strategies to promote a physically active lifestyle in youth is more relevant than ever.

KEYWORDS

normative reference values, VO_2max, functional capacity, secular trends, youth, cardiorespiratory fitness

10.3389/fpubh.2022.1056484

Introduction

According to Health Canada (2016) (1) the prevalence of obesity in youth (5–17 years) has more than tripled over the last 30 years. One of the most common explanations is related to the marked decline in physical activity levels during childhood and adolescence (2, 3). In fact, some recent studies have also shown the huge impact of a physically active lifestyle on the prevention and management of multiple chronic health problems such as cardiometabolic risk factors, several cancers, mental health problems and more (4–6). Data from the Public Health Agency of Canada report (2016) (7) indicate that the vast majority of young Canadians fail to meet recommended levels of physical activity due to increased sedentary behaviors. In fact, nearly 91% of children and youth aged 5–17 do not reach the Canadian Physical Activity Guidelines (8) recommendation of 60 min of moderate to vigorous physical activity daily.

Cardiorespiratory fitness

CRF is such a key determinant of health (4, 9) that it has been proposed as a vital sign that should be monitored in clinical practice (10). In childhood and adolescence specifically, poor CRF is a major precursor to the development of short-term and later-life cardiometabolic risk factors and chronic diseases (10–13). According to the WHO and based on several studies, VO_2max which represents the maximal capacity of the organism to consume oxygen during maximum physical exertion, has long been considered the leading indicator of CRF (14–17). Although some authors have questioned the usefulness and relevance of field tests for the evaluation of the CRF (18, 19) there is a strong consensus in favor of the use of this type of test, particularly for population surveillance (20–22). In fact, over the last 4 decades, the most commonly used test to assess aerobic fitness in school is the 20-m shuttle run test (23). The popularity of this field test relies on the fact that it is easy to manage, requires little equipment and time, is inexpensive and can be administered to several individuals simultaneously. In 2019, Statistics Canada released a set of normative percentile reference values including CRF (24). For practical reasons, the aerobic test chosen was the Modified Canadian Aerobic Fitness Test (mCAFT), a submaximal step test used to estimate an individual's CRF. Due to the very different nature of the procedures, the two tests cannot be interchanged for population surveillance purposes since the estimated VO_2max values will be different.

Thus, the first objective of this study was to provide an update of the reference values for VO_2max for the Canadian youth population (aged 6–17). The second objective was document the suspected secular trends in youth CRF by comparing the data collected in 1982 by Léger et al. (23) with the results of the present study.

Methods

Design

This study is a descriptive comparative research with a cross-sectional design based on a large sample of children and adolescents from Québec (Canada).

Participants

Between September 2014 and April 2017, a total of 3,725 students (boys = 1,983; girls = 1,742) were recruited for this study. The age varied between 6.0 and 17.9 years, which covers elementary and high school education in Canada. The participants were recruited in 36 different schools (elementary school = 24 and high school = 12) from six cities in the province of Québec (Montréal, Québec city, Saguenay, Trois-Rivières, Laval and Sherbrooke). The data was collected in the gymnasium of each school during physical education classes. Parents and students were informed of our presence and could indicate their refusal to participate in the project (a consent form was signed by the school authorities). The Institutional Ethical Committee Board (University of Québec in Chicoutimi) approved the project (no: 602-225-01).

Selection of the school boards, schools and classrooms

A three-stage sampling approach was used for the selection of a representative number of school boards, schools and classrooms. Each school received an invitation letter in order to take part in the project. Following the sending of approximately 1,200 invitations to school principals, over 300 schools expressed their interest to participate in this project. Particular attention was also paid to the equitable representation of the various socioeconomic status in our sample through a socioeconomic school rating from the Québec government (Ministère de l'Éducation et de l'Enseignement Supérieur, 2017).

All schools and classrooms were randomly selected by lot. Apart from very rare exceptions, all students of the same class were assessed, thus eliminating a selection bias. If a chosen school would withdraw, a new draw was then carried out. All participants were free from illnesses, disabilities, or injuries that could have been aggravated by physical activity. The sample size required for conducting this study was determined from a Cohen's d power analysis in order to detect small effects ($d < 0.1$) with a 1-β = 0.95 for $\alpha = 0.05$ using G Power software version 3.1.9.4. Thus, 1,564 youths per sex were required for a total of 3,128 participants.

TABLE 1 Anthropometric and cardiorespiratory profiles of boys and girls aged 6–17 years old.

	Body mass (kg)		Height (cm)		BMI ($kg \cdot m^{-2}$)		VO_2max ($ml \cdot kg^{-1} \cdot min^{-1}$)		Stages (number)	
Age	Mean±SD	CI (95%)	Mean±SD	CI (95%)	Mean±SD	CI (95%)	Mean±SD	CI (95%)	Mean±SD	CI (95%)
Boys										
6.0–6.9 yrs	24.0 ± 5.1	22.7–25.2	121.3 ± 4.9	120.1–122.5	16.1 ± 3.2	15.3–16.8	48.6 ± 2.5	47.7–48.9	2.1 ± 1.0	1.9–2.4
7.0–7.9 yrs	25.2 ± 4.4	24.4–26.0	125.5 ± 5.5	124.5–126.4	15.9 ± 2.2	15.5–16.3	47.9 ± 2.6	47.5–48.4	2.6 ± 1.3	2.4–2.8
8.0–8.9 yrs	28.9 ± 5.6	28.1–29.8	132.1 ± 6.7	131.1–133.1	16.5 ± 2.9	16.1–16.9	47.5 ± 3.9	46.9–48.1	3.2 ± 1.7	3.0–3.5
9.0–9.9 yrs	31.4 ± 5.7	30.6–32.2	136.8 ± 6.9	135.7–137.8	16.8 ± 2.9	16.4–17.3	46.7 ± 4.5	46.0–47.3	3.6 ± 1.9	3.3–3.8
10.0–10.9 yrs	35.3 ± 7.6	34.3–36.4	142.1 ± 6.6	141.2–143.1	17.4 ± 3.2	16.9–17.8	45.9 ± 4.7	45.2–46.6	3.9 ± 2.0	3.6–4.2
11.0–11.9 yrs	40.1 ± 8.0	38.8–41.3	148.1 ± 7.2	146.9–149.2	18.3 ± 3.4	17.7–18.8	43.9 ± 4.5	43.2–44.6	3.8 ± 1.8	3.5–4.1
12.0–12.9 yrs	47.5 ± 12.2	45.8–49.1	153.6 ± 8.5	152.5–154.8	20.0 ± 4.4	19.4–20.6	44.8 ± 5.2	44.1–45.5	5.0 ± 2.0	4.7–5.2
13.0–13.9 yrs	54.4 ± 12.7	52.7–56.0	161.0 ± 8.8	159.9–162.2	20.9 ± 4.1	20.3–21.4	43.8 ± 4.9	43.1–44.4	5.3 ± 1.9	5.0–5.5
14.0–14.9 yrs	57.9 ± 10.4	56.3–59.5	166.4 ± 7.8	165.2–167.6	21.1 ± 4.1	20.5–21.7	44.6 ± 6.7	43.6–45.6	6.1 ± 2.5	5.8–6.5
15.0–15.9 yrs	63.5 ± 12.2	61.9–65.2	170.5 ± 7.0	169.6–171.5	21.9 ± 4.2	21.3–22.5	43.0 ± 6.9	42.1–43.9	6.1 ± 2.5	5.8–6.5
16.0–16.9 yrs	66.6 ± 11.8	64.7–68.4	172.8 ± 7.6	171.6–174.0	22.5 ± 5.0	21.7–23.3	42.8 ± 7.3	41.7–44.0	6.6 ± 2.5	6.2–7.0
17.0–17.9 yrs	71.0 ± 14.9	68.0–74.5	173.5 ±7.9	171.8–175.1	23.6 ± 4.8	22.6–24.6	40.3 ± 7.0	39.4–41.8	6.5 ± 2.4	6.0–7.0
Girls										
6.0–6.9 yrs	22.5 ± 3.7	21.6–23.5	120.1 ± 5.1	118.8–121.4	15.6 ± 1.9	15.1–16.0	47.5 ± 2.0	47.5–48.0	1.7 ± 0.8	1.5–1.9
7.0–7.9 yrs	25.0 ± 4.7	24.1–25.8	125.4 ± 5.5	124.4–126.3	15.8 ± 2.2	15.4–16.2	47.1 ± 2.5	46.6–47.5	2.3 ± 1.0	2.1–2.5
8.0–8.9 yrs	28.9 ± 7.7	27.6–30.2	130.8 ± 6.4	129.7–131.8	16.8 ± 3.8	16.2–17.4	46.3 ± 3.1	45.8–46.8	2.6 ± 1.3	2.6–2.8
9.0–9.9 yrs	31.0 ± 6.1	30.1–31.9	136.2 ± 6.6	135.2–137.1	16.7 ± 2.6	16.3–17.0	44.5 ± 2.6	44.1–44.9	2.6 ± 1.1	2.5–2.8
10.0–10.9 yrs	37.7 ± 8.9	36.3–39.1	144.1 ± 8.3	142.8–145.4	18.1 ± 3.4	17.5–18.6	43.8 ± 3.7	43.3–44.4	3.1 ± 1.5	2.9–3.3
11.0–11.9 yrs	42.3 ± 9.3	40.8–43.9	149.5 ± 7.7	148.3–150.8	18.8 ± 3.6	18.2–19.4	42.5 ± 3.3	42.0–43.1	3.3 ± 1.3	3.1–3.5
12.0–12.9 yrs	49.4 ± 11.8	47.8–50.9	154.7 ± 6.7	153.8–155.5	20.5 ± 4.4	20.0–21.1	41.6 ± 4.4	41.1–42.2	3.7 ± 1.7	3.5–4.0
13.0–13.9 yrs	52.1 ± 11.2	50.6–53.6	157.2 ± 6.9	156.3–158.2	21.1 ± 4.4	20.5–21.7	39.5 ± 4.6	38.9–40.1	3.7 ± 1.8	3.4–3.9
14.0–14.9 yrs	57.6 ± 13.2	55.5–59.8	157.9 ± 6.4	156.9–159.0	23.1 ± 5.1	22.2–23.9	37.3 ± 4.3	36.6–38.0	3.5 ± 1.6	3.2–3.7
15.0–15.9 yrs	57.4 ± 9.2	55.7–59.1	161.4 ± 7.6	160.0–162.8	22.0 ± 3.6	21.3–22.6	38.4 ± 5.6	37.4–39.4	4.6 ± 2.0	4.2–4.9
16.0–16.9 yrs	59.7 ± 10.8	57.9–61.6	162.3 ± 9.0	160.8–163.9	22.7 ± 4.4	22.0–23.5	35.2 ± 5.1	34.3–36.1	4.2 ± 1.9	3.9–4.5
17.0–17.9 yrs	60.9 ± 13.0	57.8–64.0	162.6 ± 8.8	160.4–164.7	22.7 ± 4.2	21.7–23.7	33.9 ± 5.5	32.6–35.2	4.0 ± 1.8	3.6–4.5

SD, Standard deviation; CI, Confidence interval; BMI, Body mass index.

10.3389/fpubh.2022.1056484

Anthropometric measures

Anthropometric variables were collected using procedures proposed by Lohman et al. (25). Body mass (BM) was noted to the nearest 0.1 kg using a Detecto scale (Missouri, USA). Body height (BH) was assessed using a Lafayette stadiometer (Louisiana, USA) at the nearest 0.1 cm. Body mass index (BMI) was also calculated. BMI (typical vs. overweight and obese youths) was classified according to age and sex as suggested by Cole et al. (26).

Cardiorespiratory fitness

CRF was determined in accordance with the 20-m shuttle run test described and validated by Léger et al. (23). Briefly, the test took place in a standard size gymnasium of at least 25 m. The entire classroom (generally around twenty students) took up position on the starting line. Whenever a participant could no longer follow the required running speed, he or she was stopped and the number of the last completed stage was recorded. At the end of the test, the following information was then extracted or estimated for each student: the number of the final stage, the associated running speed ($km{\cdot}h^{-1}$) and the estimated VO_2max value ($ml{\cdot}kg^{-1}{\cdot}min^{-1}$).

Statistical analysis

All descriptive values are reported as mean ± standard deviation (SD). Confidence intervals (CI) were set at the 95% level. Cohen's effect sizes were calculated for various intergroup comparisons. The Shapiro-Wilk test for normality was compiled for each variable. When normality was violated, a Box-Cox transformation (27) was conducted using the following equation:

$$BC = (VAR^{L} - -1){\cdot}L^{-1} when L \neq 0$$
$$BC = Log(VAR) when L = 0$$

Where, BC, Box-Cox transformation; VAR, variable; L, lambda

The Box-Cox power exponential method, which smoothed the curves by cubic splines, has been used to create the curves.

Outliers were identified using the method proposed by Hoaglin et al. (28, 29). The equation reads as follows:

$$[(Q75 - Q25){\cdot}g] - Q25 \textit{ for the lowest value}$$
$$[(Q75 - Q25){\cdot}g] + Q75 \textit{ for the highest value}$$

Where Q75 = 3rd quartile; Q25 = 4th quartile; g = 2.2

Percentiles values were computed using the LMS method, (30) which read as follows:

$$P = M{\cdot}[1 + LSZ]^{1/L}$$

Where, P = percentile; M = median; L = Lambda; S = coefficient of variation; S = Z-score for the desire percentile.

In order to be able to assess changes that have occurred between 1982 and 2017, the data from the present study were compared with the study carried out by Léger et al. (23) using an unpaired *T*-Test. Statistical analysis was produced by the IBM-SPSS software version 24.

Results

Anthropometric (BM, BH and BMI) and cardiorespiratory (number of stages completed and VO_2max) characteristics as a function of age and sex are shown in Table 1. From the age of 10, girls are heavier and taller than boys until about the age of 13 years, which is consistent with puberty in girls. The cardiorespiratory profile presents a different picture where boys already have higher values for all age groups. This difference is particularly marked for the functional component of the test, which is reflected by the number of stages completed in the 20-m shuttle run test.

Percentile curves of VO_2max and functional capacity, for boys and girls aged 6 to 17, are presented in Figures 1A, B. Between age 6 and 17, the median values for VO_2max declines by about 14% for boys and 27% for girls. Also, this trend appears to be strongly affected by the percentile (VO_2max) reached in early childhood. For example, for the 25th percentile value, a decline of 21% for boys and 33% for girls is observed between the age of 6 and 17. In Figures 1C, D, the percentile curves of the number of stages during the 20-m shuttle run test provide useful information regarding the functional aspect of the cardiorespiratory capacity. Thus, individuals in the upper percentiles tend to considerably improve the number of stages completed throughout the physical growth period compared to individuals in the lower percentiles.

Tables 2, 3 provide the standardized values for VO_2max and functional capacity (stages) respectively. All parameters included in the LMS method are reported for each year of chronological age (6–17 years) for both sexes. Additionally, values for the 3rd, 10th, 25th, 50th, 75th, 90th, and 97th percentiles are also shown.

The impact of BMI on VO_2max was also examined (Figures 2A, B). As shown in Table 4, boys in the overweight/obese zone have VO_2max values markedly lower than individuals with typical BMI across all age groups and this difference increases between the age of 14 and 17. In girls, a similar but less important difference is observed between overweight/obese individuals and those with typical BMI follows a slightly shifted curve which increases with age in favor of the former. For the functional aspect of the 20-m shuttle run test, a very large discrepancy is also observed

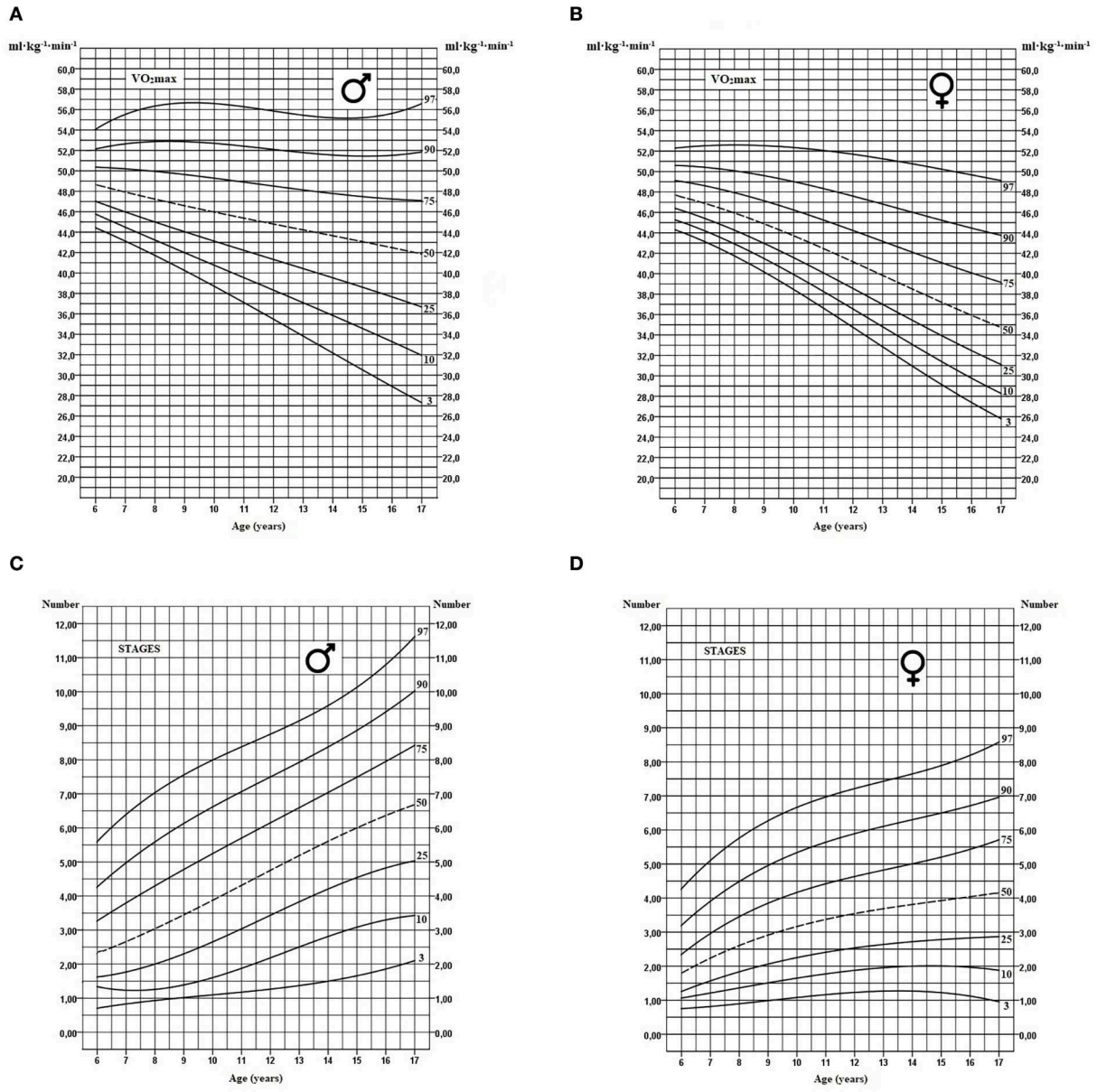


FIGURE 1
Age-specific smoothed percentile curves for VO_2max and the number of stages completed estimated using the 20-m shuttle run test for boys **(A, C)** and girls respectively **(B, D)**.

when comparing individuals from the two BMI categories (Figures 2C, D).

Secular trend for VO_2max (Figures 3A, B) and the number of stages completed in the 20-m shuttle run test (Figures 3C, D) over a 35-year interval are illustrated by comparing data from the present study with data collected in 1982 using the same methodology (23). Over 35 years, median VO_2max decreased by 7.6% for boys and 8.3% for girls at the age of 6 and this difference increases to nearly 18% in boys and 12.2% in girls by the age of 17 (Table 5). Compared to 1982, a significant decrease is also observed for all age groups for the number of stages completed for boys and girls.

Given that the difference in body mass between 1982 and 2017 could influence the VO_2max observed between the two periods, BM normalization was carried out. The discrepancies observed between the 2 periods are not attenuated by BM standardization as shown in Table 6. Similarly, BM normalization did not affect the secular trends observed between 1982 and 2017 regarding the number of stages completed.

TABLE 2 Percentile references values for VO_2max according to age and gender in Québec children and adolescents (N = 3725).

					Percentiles						
	N	L	M	S	3th	10th	25th	50th	75th	90th	97th
Boys											
6.0–6.9 yrs	66	−1.55	48.3	0.052	44.1	45.3	46.7	48.3	50.1	51.8	53.7
7.0–7.9 yrs	123	−0.45	48.0	0.057	43.2	44.7	46.2	48.0	49.9	51.7	53.6
8.0–8.9 yrs	168	−1.70	47.5	0.083	41.4	43.1	45.0	47.5	50.4	53.4	56.9
9.0–9.9 yrs	178	−1.83	47.0	0.097	40.2	42.1	44.3	47.0	50.5	54.3	58.8
10.0–10.9 yrs	192	0.01	46.2	0.104	38.0	40.4	43.1	46.2	49.6	52.8	56.2
11.0–11.9 yrs	158	−0.70	43.9	0.104	36.5	38.6	41.0	43.9	47.2	50.5	54.2
12.0–12.9 yrs	213	0.43	44.6	0.115	35.5	38.3	41.2	44.6	48.1	51.4	54.8
13.0–13.9 yrs	232	1.06	43.8	0.110	34.7	37.6	39.8	43.8	47.0	50.0	52.8
14.0–14.9 yrs	180	0.54	44.8	0.150	32.0	36.6	40.4	44.8	49.4	53.8	58.3
15.0–15.9 yrs	216	1.09	43.1	0.160	30.0	34.2	38.4	43.1	47.7	51.8	55.9
16.0–16.9 yrs	162	0.90	42.8	0.171	29.3	33.5	37.9	42.8	47.8	52.3	56.8
17.0–17.9 yrs	95	0.90	41.6	0.181	27.8	32.1	36.6	41.6	46.7	51.3	55.9
Girls											
6.0–6.9 yrs	62	−1.00	47.5	0.042	44.0	45.1	46.2	47.5	48.9	50.2	51.6
7.0–7.9 yrs	119	−2.00	46.9	0.051	43.0	44.1	45.4	46.9	48.6	50.3	52.2
8.0–8.9 yrs	139	−1.90	46.4	0.067	41.5	42.9	44.4	46.4	48.6	51.0	53.6
9.0–9.9 yrs	180	−2.64	44.5	0.059	40.4	41.5	42.9	44.5	46.4	48.4	50.8
10.0–10.9 yrs	164	−1.05	43.7	0.089	37.7	39.4	41.3	43.7	46.4	49.0	52.0
11.0–11.9 yrs	143	−1.08	42.3	0.084	36.9	38.5	40.2	42.3	44.7	47.0	49.6
12.0–12.9 yrs	240	−0.96	41.9	0.105	35.0	36.9	39.1	41.9	45.1	48.4	52.2
13.0–13.9 yrs	218	−1.60	39.3	0.119	32.5	34.3	36.5	39.3	42.8	46.8	51.8
14.0–14.9 yrs	146	−0.70	37.1	0.115	30.3	32.2	34.4	37.1	40.2	43.4	47.0
15.0–15.9 yrs	123	0.30	37.9	0.145	28.4	31.2	34.3	37.9	41.8	45.5	49.4
16.0–16.9 yrs	135	−0.40	36.6	0.167	27.2	29.8	32.8	36.6	41.1	45.8	51.3
17.0–17.9 yrs	73	−0.70	34.4	0.162	26.1	28.4	31.0	34.4	38.1	43.0	48.4

N, Number of participants; L, lambda; M, median; S, coefficient of variation (SD·mean^{-1}).

10.3389/fpubh.2022.1056484

TABLE 3 Percentile reference values for the number of stages completed during the 20-m shuttle run test according to age and gender in Québec children and adolescents (N = 3725).

					Percentiles						
	N	L	M	S	3th	10th	25th	50th	75th	90th	97th
Boys											
6.0–6.9 yrs	66	0.25	2.22	0.519	0.75	1.00	1.50	2.25	3.00	4.00	5.25
7.0–7.9 yrs	124	0.34	2.71	0.487	1.00	1.25	2.00	2.75	3.75	4.75	6.00
8.0–8.9 yrs	168	0.23	3.35	0.514	1.00	1.50	2.25	3.25	4.75	6.25	8.00
9.0–9.9 yrs	178	0.34	3.85	0.531	1.25	1.75	2.75	3.75	5.50	7.00	9.00
10.0–10.9 yrs	192	0.63	4.19	0.501	1.00	1.75	2.75	4.25	5.75	7.25	8.50
11.0–11.9 yrs	158	0.63	3.67	0.480	1.00	1.75	2.50	3.75	5.00	6.25	7.50
12.0–12.9 yrs	213	0.69	5.13	0.405	1.75	2.75	3.75	5.00	6.50	8.00	9.50
13.0–13.9 yrs	232	1.00	5.50	0.351	1.75	3.00	4.25	5.50	6.75	8.00	9.25
14.0–14.9 yrs	180	0.66	6.18	0.397	2.25	3.25	4.50	6.25	8.00	9.50	11.25
15.0–15.9 yrs	217	1.00	6.00	0.400	1.50	3.00	4.50	6.00	7.50	9.00	10.50
16.0–16.9 yrs	162	0.86	6.57	0.378	2.25	3.50	5.00	6.50	8.25	9.75	11.50
17.0–17.9 yrs	95	0.81	6.59	0.372	2.25	3.50	5.00	6.50	8.25	9.75	11.50
Girls											
6.0–6.9 yrs	62	−0.60	1.73	0.432	0.75	1.00	1.25	1.75	2.50	3.50	5.25
7.0–7.9 yrs	120	0.01	2.25	0.462	1.00	1.25	1.50	2.25	3.00	4.00	5.25
8.0–8.9 yrs	139	0.12	2.84	0.492	1.00	1.50	2.00	2.75	4.00	5.25	6.75
9.0–9.9 yrs	180	0.26	2.67	0.440	1.00	1.50	2.00	2.75	3.50	4.50	5.75
10.0–10.9 yrs	165	0.34	3.20	0.498	1.00	1.50	2.25	3.25	4.50	5.75	7.25
11.0–11.9 yrs	143	0.38	3.16	0.389	1.25	1.75	2.25	3.25	4.00	5.00	6.00
12.0–12.9 yrs	240	0.48	3.74	0.449	1.25	2.00	2.75	3.75	5.00	6.25	7.50
13.0–13.9 yrs	218	0.31	3.81	0.484	1.25	2.00	2.75	3.75	5.25	6.75	8.50
14.0–14.9 yrs	146	0.62	3.15	0.465	1.00	1.50	2.25	3.25	4.25	5.25	6.50
15.0–15.9 yrs	123	0.63	4.16	0.429	1.25	2.00	3.00	4.25	5.50	6.75	8.00
16.0–16.9 yrs	133	0.37	4.30	0.472	1.50	2.25	3.00	4.25	5.75	7.50	9.25
17.0–17.9 yrs	73	0.61	4.18	0.460	1.25	2.00	3.00	4.25	5.50	7.00	8.50

N, Number of participants; L, lambda; M, median; S, coefficient of variation (SD·mean^{-1}); The number of stages has been rounded to the nearest quarter. The speed at the first stage starts at 8.5 km·h^{-1} and than increase by 0.5 km·h^{-1} every minute.

10.3389/fpubh.2022.1056484

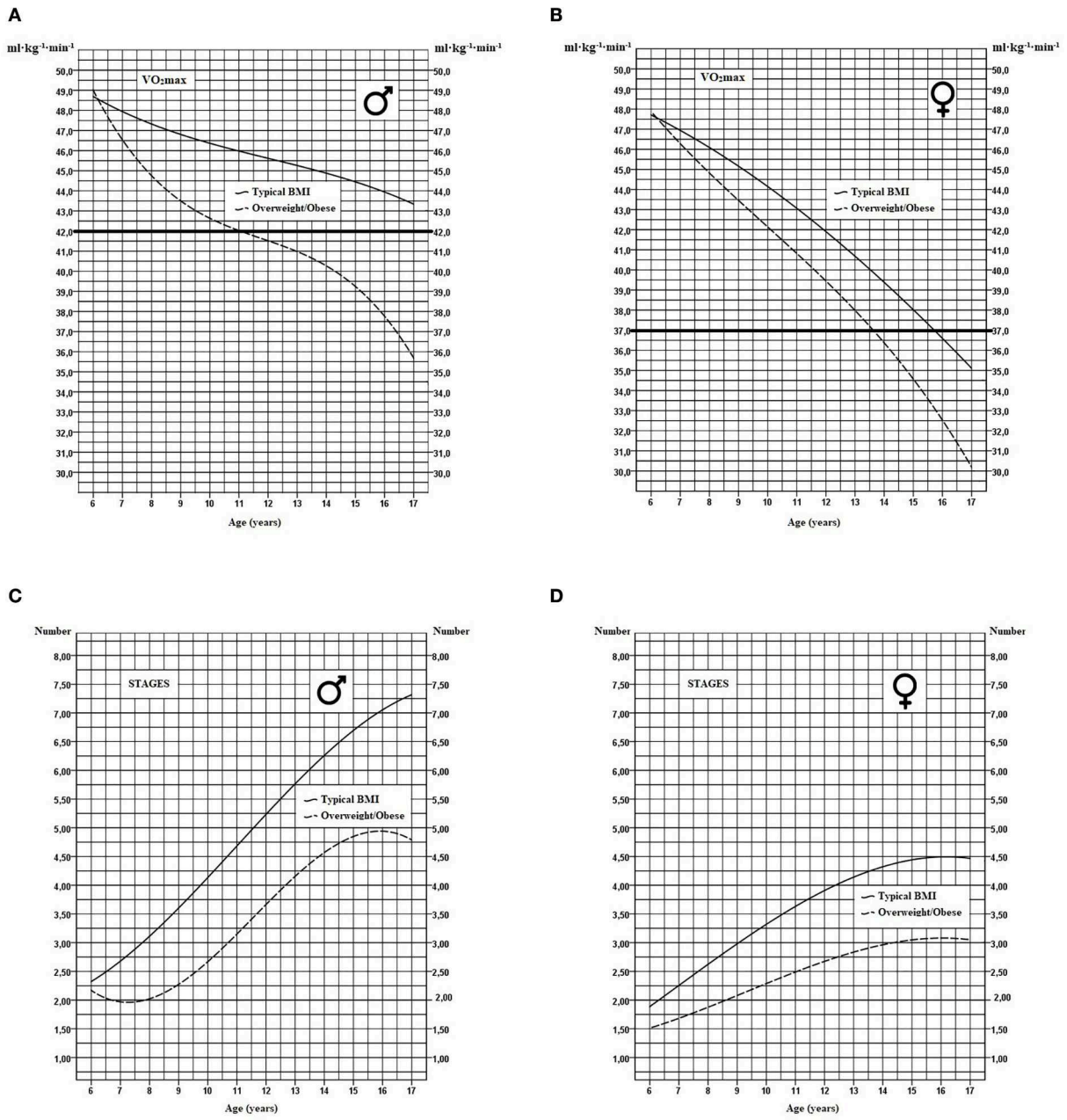


FIGURE 2
Modeling of VO_2max curves and the number of stages completed in youth with typical BMI or with overweight/obese profile in boys **(A, C)** and girls **(B, D)**. The thick horizontal line represents the critical cutoff health zone.

Discussion

This study provides recent reference values for the maximal aerobic 20-m shuttle run test in children and adolescents of the province of Québec (Canada). It also provides unique opportunity to directly compare recent CRF data with reference values initially documented for this test in the same geographic area and age group in 1982 (31).

CRF reference values

According to different studies and regardless of age, it is estimated that a minimum VO_2max value of approximately 42 $ml \cdot kg^{-1} \cdot min^{-1}$ in boys and 37 $ml \cdot kg^{-1} \cdot min^{-1}$ in girls is required to minimize the risk of developing severe health problems (32, 33). Considering these CRF thresholds, the reference values documented in this study raise a powerful red

TABLE 4 Comparison of VO_2max and the number of stages completed in children and adolescents with typical or overweight/obese BMI profile.

	Typical BMI		Overweight/Obese		Δ %		P-values		Cohen's d	
	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls
6.0–6.9 yrs										
VO_2max	48.3 ± 2.6	47.3 ± 1.9	48.5 ± 2.6	48.3 ± 2.4	−0.4	−2.0	0.856	0.193	0.08	0.51
Stages	2.2 ± 1.2	1.7 ± 0.8	2.0 ± 1.0	1.5 ± 0.6	9.1	11.8	0.668	0.542	0.17	0.26
7.0–7.9 yrs										
VO_2max	48.1 ± 2.8	47.3 ± 2.5	47.1 ± 1.9	45.7 ± 1.8	2.1	3.4	0.159	**0.007**	0.37	0.67
Stages	2.7 ± 1.3	2.3 ± 1.1	2.1 ± 1.0	1.6 ± 0.6	22.2	30.4	0.104	**0.000**	0.47	0.68
8.0–8.9 yrs										
VO_2max	47.9 ± 3.9	46.7 ± 3.4	44.9 ± 3.3	44.6 ± 3.1	6.3	4.5	**0.000**	**0.001**	0.78	0.63
Stages	3.4 ± 1.7	2.9 ± 1.4	2.2 ± 1.2	1.8 ± 0.9	24.1	37.9	**0.000**	**0.000**	0.73	**0.84**
9.0–9.9 yrs										
VO_2max	47.1 ± 4.5	44.7 ± 2.6	44.3 ± 4.0	43.4 ± 2.7	2.3	2.9	**0.003**	**0.013**	0.63	0.50
Stages	3.8 ± 1.9	2.7 ± 1.1	2.5 ± 1.6	2.2 ± 1.0	34.2	18.5	**0.001**	**0.014**	0.70	0.46
10.0–10.9 yrs										
VO_2max	46.6 ± 4.6	44.2 ± 3.8	41.9 ± 3.4	42.7 ± 3.3	10.1	3.4	**0.000**	**0.031**	**1.06**	0.41
Stages	4.2 ± 2.0	3.3 ± 1.6	2.4 ± 1.3	2.5 ± 1.3	42.9	24.2	**0.000**	**0.007**	**0.94**	0.52
11.0–11.9 yrs										
VO_2max	44.6 ± 4.5	43.1 ± 3.1	40.8 ± 3.6	40.1 ± 3.2	8.5	7.0	**0.000**	**0.000**	**0.87**	**0.96**
Stages	4.1 ± 1.9	3.5 ± 1.3	2.6 ± 1.3	2.4 ± 1.0	36.6	31.4	**0.000**	**0.000**	**0.83**	**0.88**
12.0–12.9 yrs										
VO_2max	45.8 ± 5.0	41.6 ± 4.1	42.2 ± 4.7	41.8 ± 5.1	7.9	−0.5	**0.000**	0.714	0.73	0.05
Stages	5.3 ± 1.9	4.2 ± 1.7	4.0 ± 1.9	2.8 ± 1.3	24.5	33.3	**0.000**	**0.000**	0.68	**0.88**
13.0–13.9 yrs										
VO_2max	44.7 ± 4.6	40.6 ± 4.5	41.4 ± 4.7	36.6 ± 4.1	8.1	9.9	**0.000**	**0.000**	0.71	**0.91**
Stages	5.6 ± 1.7	4.0 ± 1.8	4.4 ± 1.8	2.7 ± 1.5	21.4	32.5	**0.000**	**0.000**	0.69	0.75
14.0–14.9 yrs										
VO_2max	46.0 ± 6.2	38.5 ± 4.2	39.8 ± 6.6	35.3 ± 3.4	13.5	8.3	**0.000**	**0.000**	**0.99**	**0.81**
Stages	6.7 ± 2.3	3.9 ± 1.6	4.4 ± 2.4	2.7 ± 1.3	34.2	30.8	**0.000**	**0.000**	**0.99**	**0.80**

(Continued)

10.3389/fpubh.2022.1056484

TABLE 4 (Continued)

	Typical BMI		Overweight/Obese		Δ %		P-values		Cohen's d	
	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls
15.0–15.9 yrs										
VO_2max	44.1 ± 6.7	39.6 ± 5.3	39.6 ± 6.8	34.2 ± 4.7	10.2	13.6	**0.000**	**0.000**	0.67	**1.05**
Stages	6.5 ± 2.4	5.0 ± 1.9	4.9 ± 2.4	3.1 ± 1.6	24.6	38.0	**0.000**	**0.000**	0.67	**1.04**
16.0–16.9 yrs										
VO_2max	44.5 ± 6.8	36.4 ± 6.1	38.0 ± 5.9	34.3 ± 5.6	14.6	5.8	**0.000**	0.109	**0.99**	0.35
Stages	7.2 ± 2.4	4.5 ± 2.1	5.0 ± 2.0	3.6 ± 1.7	31.4	20.0	**0.000**	**0.040**	**0.96**	0.45
17.0 yrs +										
VO_2max	42.9 ± 6.3	34.8 ± 4.8	35.4 ± 6.6	30.5 ± 6.3	17.5	12.4	**0.000**	**0.004**	**1.18**	**0.83**
Stages	7.2 ± 2.1	4.3 ± 1.7	4.7 ± 2.1	3.0 ± 2.0	34.7	30.2	**0.000**	**0.010**	**1.19**	0.73

Yrs, years; P-values in bold = significant at ≤0.05; Δ% = percentage of difference; Cohen's d = 0.20 marginal; 0.50 moderate; 0.80 large; Cohen d in bold = large effect (≥0.80).

flag by showing that, by the age of 17 in boys and 15 in girls, the median VO_2max value is below the minimal CRF level associated with favorable health outcomes later in life. These results are consistent with the reference values reported by Tomkinson et al. (6) in a metanalysis of 177 studies, most of which were published between 2000 and 2015.

Functional capacity is also affected, demonstrating that today's youth have a reduced ability to sustain moderate/intense effort. In fact, this decrease begins 1 year earlier than the decline in VO_2max. This finding is certainly as worrying as the decrease in VO_2max.

The results also indicate that the higher the CRF reached at a young age, the greater the chances that it will be maintained during the growth period. Assuming that this tendency persists later in life through adulthood, these results further support the notion that childhood CRF can contribute to prevent the development of cardiometabolic risk factors and diseases later in life (14).

Effect of overweight/obesity on the CRF

Although obesity is recognized as a major cause of morbidity, (1, 32) a recent metanalysis indicated that it is not an independent factor of premature mortality (14). In the present study, data stratification for BMI (typical vs. overweight/obese) shows that, in the later group, a higher proportion evolves toward a VO_2max value below the minimal CRF level associated with favorable health outcomes. In boys with the overweight/obese profile, it is noted that the critical median cutoff value of VO_2max is crossed as soon as the age of 11, which never happens for the typical BMI group.

The number of stages completed as a function of age is also heavily impaired in the overweight/obese BMI group. These results further support the notion that lower CRF and functional capacity are factors that likely contribute to unfavorable cardiometabolic outcomes in youth with BMI that correspond to the definition of overweight and obesity. However, other factors also need to be taken into account since in girls with a normal BMI median VO_2max will eventually fall below the recommended cutoff by the age of 16. Reduced physical activity combined with increased passive activities has been suggested as a likely factor that explains this situation (32, 34, 35).

Secular trends in CRF

The great heterogeneity of CRF assessment procedures makes comparisons between studies complicated. In 1982, Léger and colleagues developed the 20-m shuttle run test and developed reference values for the CRF of youth living in Quebec (23). International reference values for the 20-m shuttle run

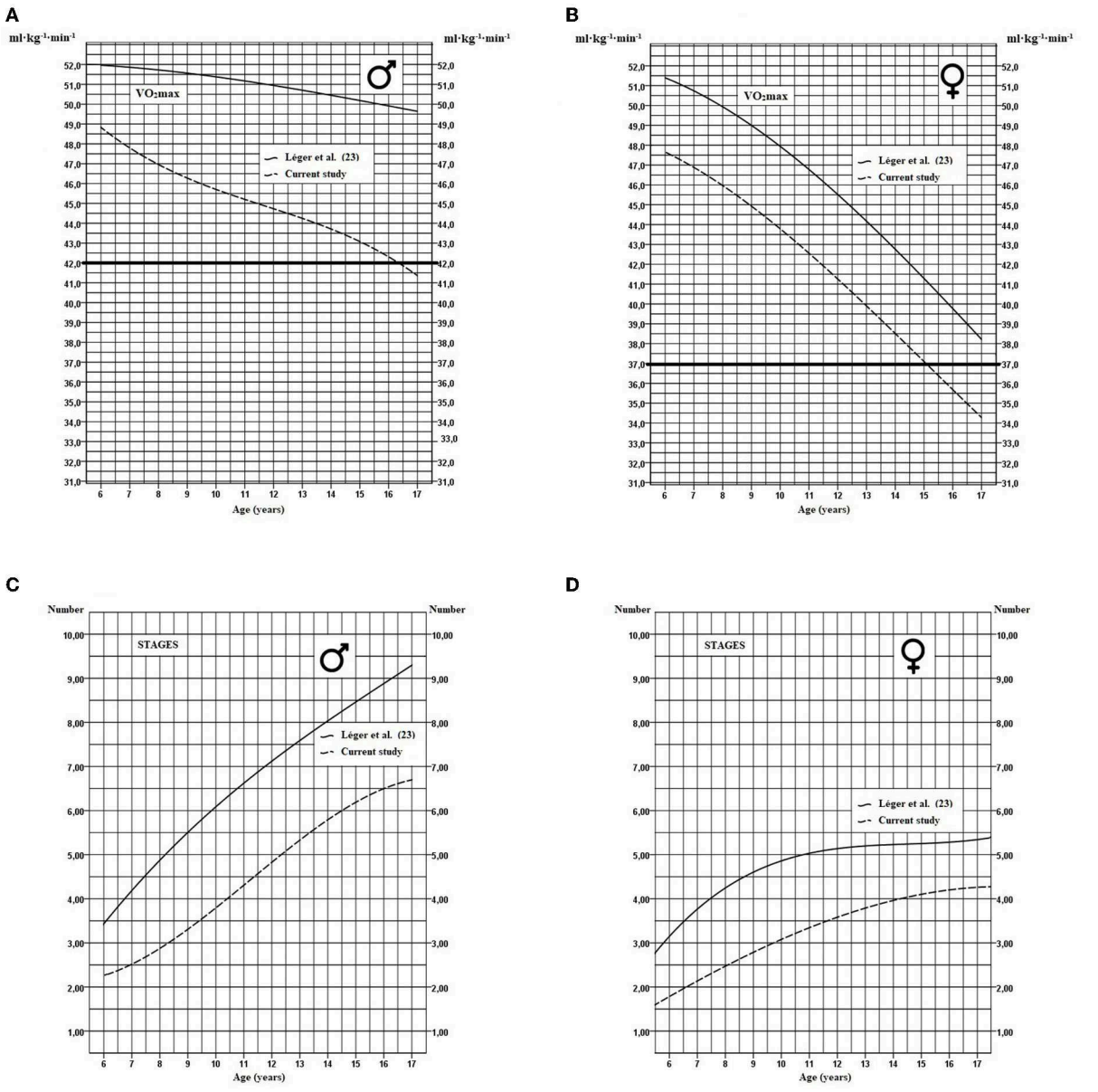


FIGURE 3
Modeling of the secular trend curves for median VO_2max and for the number of stages completed between 1982 and 2017 for 6 to 17 yrs boys **(A, C)** and girls **(B, D)**. The thick horizontal line represents the critical cutoff health zone.

test were recently developed by combining data from studies published up to 2015 (6). However, these more recent reference values do not allow comparison for specific population over time. The present study has the advantage of using the same test, administered under the same conditions, in the same cities and in the same school boards as 35 years earlier by Léger et al. (23).

This methodology resulted in a unique opportunity to objectively appreciate the evolution of CRF in youth between 1982 and 2017. The results confirmed an important decrease of CRF (estimated VO_2max) and functional capacity (number of stages completed) in the study population. This difference tends to accentuate with age, with a VO_2max decrease reaching nearly −18% for males and −12% for females at the age of 17. The functional impact of this situation is even more important in terms of the number of stages completed with an overall decrease of more than −30%. Furthermore, in 1982, all age groups of both sexes displayed VO_2max values above the minimal recommended threshold associated with positive health outcomes. In the present study population, this is no longer the case from the age of 16 for boys and 15 for girls.

TABLE 5 Comparison of VO_2max and the number of stages completed in children and adolescents between 1982 and 2017.

	Léger et al. (23)		Current study		Δ %		P-values		Cohen's d	
	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls
6.0–6.9 yrs										
VO_2max	52.4 ± 2.8	51.8 ± 2.3	48.4 ± 2.5	47.5 ± 2.0	−7.6	−8.3	**0.000**	**0.000**	**1.43**	**1.96**
Stages	3.6 ± 1.4	3.4 ± 1.1	2.1 ± 1.1	1.7 ± 0.7	−41.7	−50.0	**0.000**	**0.000**	**1.15**	**1.74**
7.0–7.9 yrs										
VO_2max	51.2 ± 3.3	50.3 ± 2.6	48.0 ± 2.7	47.0 ± 2.4	−6.3	−6.6	**0.000**	**0.000**	**1.02**	**1.3**
Stages	3.9 ± 1.6	3.5 ± 1.2	2.6 ± 1.3	2.2 ± 1.0	−33.3	−37.1	**0.000**	**0.000**	**0.86**	**1.13**
8.0–8.9 yrs										
VO_2max	51.7 ± 3.9	49.8 ± 3.4	47.5 ± 3.9	46.3 ± 3.1	−8.1	−7.0	**0.000**	**0.000**	**1.11**	**1.06**
Stages	4.9 ± 1.8	4.1 ± 1.5	3.2 ± 1.7	2.7 ± 1.1	−34.7	−36.6	**0.000**	**0.000**	**0.96**	**1.04**
9.0–9.9 yrs										
VO_2max	51.5 ± 4.4	49.2 ± 3.2	46.7 ± 4.5	44.5 ± 2.6	−9.3	−9.6	**0.000**	**0.000**	**1.10**	**1.57**
Stages	5.5 ± 1.9	4.5 ± 1.4	3.6 ± 1.9	2.7 ± 1.1	−41.8	−40.0	**0.000**	**0.000**	**1.26**	**1.38**
10.0–10.9 yrs										
VO_2max	51.6 ± 4.2	46.8 ± 2.8	45.9 ± 4.8	43.8 ± 3.7	−11.2	−6.2	**0.000**	**0.000**	**1.33**	**0.92**
Stages	6.2 ± 1.8	4.9 ± 1.4	3.9 ± 2.0	3.1 ± 1.6	−37.1	−36.7	**0.000**	**0.000**	**1.23**	**1.26**
11.0–11.9 yrs										
VO_2max	51.1 ± 4.5	47.5 ± 4.0	43.9 ± 4.6	42.6 ± 3.3	−14.1	−10.1	**0.000**	**0.000**	**1.60**	**1.24**
Stages	6.7 ± 1.8	5.2 ± 1.6	3.8 ± 1.8	3.3 ± 1.3	−43.3	−36.5	**0.000**	**0.000**	**1.61**	**1.25**
12.0–12.9 yrs										
VO_2max	51.9 ± 5.2	46.7 ± 4.2	44.8 ± 5.2	41.6 ± 4.4	−13.7	−10.9	**0.000**	**0.000**	**1.37**	**1.19**
Stages	7.2 ± 2.0	5.5 ± 1.6	5.0 ± 2.0	3.7 ± 1.7	−30.6	−32.7	**0.000**	**0.000**	**1.10**	**1.09**
13.0–13.9 yrs										
VO_2max	50.1 ± 5.2	44.4 ± 4.8	43.7 ± 4.8	39.5 ± 4.7	−12.6	−11.0	**0.000**	**0.000**	**1.23**	**1.04**
Stages	7.4 ± 2.0	5.3 ± 1.8	5.2 ± 1.8	3.7± 1.8	−29.7	−30.2	**0.000**	**0.000**	**1.15**	**0.89**
14.0–14.9 yrs										
VO_2max	50.1 ± 5.2	41.7 ± 4.7	44.6 ± 6.7	37.3 ± 4.3	−11.0	−10.6	**0.000**	**0.000**	**0.94**	**0.97**
Stages	8.0 ± 1.9	4.8 ± 1.8	6.2 ± 2.5	3.5 ± 1.6	−23.8	−27.1	**0.000**	**0.000**	**0.88**	0.75

(Continued)

10.3389/fpubh.2022.1056484

TABLE 5 (Continued)

	Léger et al. (23)		Current study		Δ %		P-values		Cohen's d	
	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls
15.0–15.9 yrs										
VO_2max	50.2 ± 6.1	41.2 ± 5.1	43.1 ± 6.9	38.4 ± 5.6	−14.3	−6.8	**0.000**	**0.000**	**1.12**	0.55
Stages	8.5 ± 2.2	5.2 ± 1.8	6.1 ± 2.5	4.6 ± 2.0	−28.2	−11.5	**0.000**	**0.000**	**1.03**	0.32
16.0–16.9 yrs										
VO_2max	50.0 ± 5.8	39.5 ± 5.0	42.8 ± 7.3	35.9 ± 6.0	−15.2	−9.1	**0.000**	**0.000**	**1.12**	0.68
Stages	8.9 ± 2.0	5.2 ± 1.7	6.6 ± 2.5	4.3 ± 2.0	−29.2	−17.3	**0.000**	**0.000**	**1.06**	0.67
17.0 yrs +										
VO_2max	49.7 ± 5.9	38.6 ± 5.2	40.9 ± 7.4	33.9 ± 5.5	−17.7	−12.2	**0.000**	**0.000**	**1.38**	**0.89**
Stages	9.3 ± 2.0	5.5 ± 1.8	6.5 ± 2.4	4.1 ± 1.9	−30.1	−25.5	**0.000**	**0.000**	**1.27**	0.76

Yrs, years; P-values in bold = significant at ≤0.05; Δ% = percentage of difference (the negative sign indicates the decrease in percentage since 1982; Cohen's d = 0.20 marginal; 0.50 moderate; 0.80 large; Cohen d in bold = large effect (≥0.80).

While some authors deny the fact that CRF has decreased over the last decades (18, 19) our results clearly show an alarming decline, both in relative ($ml \cdot kg^{-1} \cdot min^{-1}$) and functional values (number of stages). It has been suggested that the decrease in VO_2max when expressed in relative values is predictable given the increase in body mass in youth over the past decades. However, data from the present study indicates that, after normalization for BM, significant differences remain for VO_2max and for the number of stages completed in all age groups for both sexes. It may be noted that even when the body mass of Léger's cohort age groups was heavier, the relative and functional values remain markedly higher in their favor. Under these circumstances, it is reasonable to assume that body mass alone is insufficient to explain these differences.

It is assumed that, in addition to the body mass gain observed in recent decades in children and adolescents, increased time spent on sedentary activities is the factor that probably best explains the decrease in CRF (14, 21). Back in the 1980s when the 20-m shuttle run test was developed, computers and video games were in their infancy. With the development of the Internet and social networks youth became less physical active with an increase of time spent on sedentary activities (36, 37). As of 2016, combined data from 146 countries indicates that over 80% of adolescents do not meet the recommended levels of physical activity (38). Even more recently, the substantial reduction in physical activity due to containment measures related to COVID-19 is expected to further accelerate this decline (39).

Reference values vs. standard values

In this paper, we use two distinct concepts that deserve to be explained. Based on the Centers for Disease Control and Prevention (DCC) in 2002, (40) reference values reflect the current situation without regard to its impact on health (what is). This information should not be interpreted as an objective to be achieved. This seems quite obvious as the VO_2max values as well as the number of stages completed (i.e., functional capacity) have considerably decreased over the last decades. Thus, the role of the reference values is to make possible to measure the actual changes, and perhaps those that may occur in the future. They also allow comparison of current values with those from other studies.

On the other hand, the standard values represent what is minimally desirable in order to protect against certain potential health problems (what should be). In the case of VO_2max, the minimum threshold should be around 42 ml in boys and 37 ml in girls. In order to stay above these thresholds, the reference values indicate that youths should follow at least around the 65th percentile curve throughout the growth period.

TABLE 6 Comparison of VO2max and the number of stages completed between Current study and Léger et al. (23) with adjustment for BM.

	Boys											
	Current study				Léger et al. (23)						Statistics	
Age	N	Body mass	VO_2max	Stages	N	Body mass	P	N	VO_2max	P	Stages	P
6	56	22.0 ± 2.8	48.3 ± 2.6	2.2 ± 1.1	89	23.4 ± 3.0	0.006	121	52.4 ± 2.8	**0**	3.6 ± 1.4	**0**
7	108	24.0 ± 3.2	48.1 ± 2.8	2.7 ± 1.3	221	25.2 ± 4.3	0.011	297	51.2 ± 3.3	**0**	3.9 ± 1.6	**0**
8	144	27.0 ± 3.7	47.9 ± 3.9	3.4 ± 1.6	211	28.0 ± 4.5	0.028	303	51.7 ± 3.9	**0**	4.9 ± 1.8	**0**
9	148	29.6 ± 4.4	47.1 ± 4.5	3.8 ± 1.9	200	31.8 ± 5.7	0	322	51.5 ± 4.4	**0**	5.5 ± 1.9	**0**
10	163	32.8 ± 5.1	46.6 ± 4.6	4.2 ± 1.9	253	34.6 ± 5.9	0.002	404	51.6 ± 4.2	**0**	6.2 ± 1.8	**0**
11	129	36.9 ± 5.5	44.6 ± 4.5	4.1 ± 1.8	247	38.8 ± 7.8	0.014	386	51.1 ± 4.5	**0**	6.7 ± 1.8	**0**
12	153	41.6 ± 7.4	45.8 ± 5.0	5.3 ± 1.9	206	42.7 ± 7.9	0.181	341	51.9 ± 5.2	**0**	7.2 ± 2.0	**0**
13	158	48.0 ± 8.3	44.7 ± 4.5	5.6 ± 1.7	233	47.8 ± 8.6	0.819	325	50.1 ± 5.2	**0**	7.4 ± 2.0	**0**
14	131	53.4 ± 7.0	46.0 ± 6.2	6.7 ± 2.2	237	53.4 ± 9.8	1	289	50.1 ± 5.2	**0**	8.0 ± 1.9	**0**
15	156	58.0 ± 7.7	44.1 ± 6.7	6.5 ± 2.4	254	58.3 ± 9.7	0.743	333	50.2 ± 6.1	**0**	8.5 ± 2.2	**0**
16	117	60.6 ± 8.0	44.5 ± 6.8	7.2 ± 2.3	245	62.6 ± 9.2	0.045	336	50.0 ± 5.8	**0**	8.9 ± 2.0	**0**
17	67	63.5 ± 6.6	42.9 ± 6.3	7.2 ± 2.1	161	64.5 ± 8.9	0.408	212	49.7 ± 5.9	**0**	9.3 ± 2.0	**0**
Girls												
6	51	21.8 ± 2.7	47.3 ± 1.9	1.7 ± 0.8	81	22.8 ± 2.9	0.05	112	51.8 ± 2.3	**0**	3.4 ± 1.1	**0**
7	97	23.3 ± 3.0	47.3 ± 2.5	2.3 ± 1.0	227	24.4 ± 3.6	0.009	299	50.3 ± 2.6	**0**	3.5 ± 1.2	**0**
8	111	26.2 ± 3.6	46.7 ± 3.1	2.9 ± 1.2	231	28.0 ± 5.2	0.001	308	49.8 ± 3.4	**0**	4.1 ± 1.5	**0**
9	152	28.9 ± 3.9	44.7 ± 2.6	2.7 ± 1.1	196	31.4 ± 5.6	0	322	49.2 ± 3.2	**0**	4.5 ± 1.4	**0**
10	128	34.2 ± 6.0	44.2 ± 3.8	3.3 ± 1.5	214	34.6 ± 7.0	0.59	335	46.8 ± 2.8	**0**	4.9 ± 1.5	**0**
11	118	39.5 ± 7.2	43.1 ± 3.1	3.5 ± 1.2	258	39.2 ± 8.5	0.74	382	47.5 ± 4.0	**0**	5.2 ± 1.6	**0**
12	165	43.4 ± 6.3	41.6 ± 4.1	4.2 ± 1.6	204	45.1 ± 9.0	0.041	292	46.7 ± 4.2	**0**	5.5 ± 1.6	**0**
13	161	47.2 ± 7.7	40.6 ± 4.5	4.0 ± 1.7	224	49.2 ± 9.0	0.023	298	44.4 ± 4.8	**0**	5.3 ± 1.8	**0**
14	93	49.7 ± 5.7	38.5 ± 4.2	3.9 ± 1.6	211	50.4 ± 7.3	0.412	260	41.7 ± 4.7	**0**	4.8 ± 1.8	**0**
15	89	53.5 ± 6.8	39.6 ± 5.3	5.0 ± 1.8	189	53.6 ± 7.1	0.912	260	41.2 ± 5.1	**0.012**	5.2 ± 1.8	0.366
16	102	56.0 ± 7.3	36.6 ± 5.9	4.5 ± 2.0	236	54.2 ± 7.8	0.048	332	39.5 ± 5.0	**0**	5.2 ± 1.7	**0.001**
17	54	56.0 ± 8.4	34.8 ± 4.8	4.4 ± 1.6	133	54.4 ± 7.4	0.199	155	38.6 ± 5.2	**0**	5.5 ± 1.8	**0**

N, number of participants; Body mass = kg; VO_2max = ml·kg^{-1}·min^{-1}; Stages = number completed; P-values in bold = significant at ≤ 0.05.

10.3389/fpubh.2022.1056484

Strengths and limitations

The large sample size ($n > 3700$) allows a valid representation of youths living in Québec (Canada). The test used to estimate the VO_2max is internationally accepted as valid and reliable. The procedure used was repeated under the same conditions: same cities, same test and same school boards as the original 1982 study, which allows to assess the secular trends with a reduced number of biases. However, some limitations should also be noted. The cross-sectional nature of the data restricts inferences. VO_2max values were estimated instead of measured directly, which affected the accuracy. Finally, although some towns were in suburban areas, cities in rural zones were not represented.

Conclusion

While providing updated reference values for the 20-m shuttle run test, this study provides direct comparative evidence of an alarming decrease of CRF and functional capacity in a population of children and adolescents since the 1980s. This further highlights the threat of an epidemic of cardiometabolic pathologies in the near future. Thus, development of population surveillance tools and public health strategies to promote a physically active lifestyle is more important than ever.

Data availability statement

The raw data supporting the conclusions of this article will be made available from the corresponding author, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Université du Québec à Chicoutimi (CER). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

ML was involved in the design and concept of the study, data collection, data analysis, drafted the initial, and final version of the manuscript. MA and EK co-ordinated, supervised data collection, involved in the study design, drafted the initial manuscript, reviewed, and revised the manuscript. AC, HB, and JL were involved in the study design, initial analyses, data collection, drafted the initial manuscript, reviewed, and revised the manuscript. LL and PF were involved in the data analysis, reviewed, and drafted the manuscript for important intellectual content. PL co-ordinated, supervised data collection, involved in initial data analysis, drafted the initial manuscript, reviewed, and revised the manuscript. SB-G was involved in the data collection, the initial data analysis, drafted the initial manuscript, reviewed, and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Funding

This study was financially supported by the Center for Interdisciplinary Research on Quality and Healthy Lifestyles – UQAC: Grant no. UBR 324029.

Acknowledgments

The authors wish to acknowledge the principals, physical education teachers, school boards, and students who agreed to participate in this study. Special thanks to the interns who also helped with the data collection.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Health Canada (Government of Canada). *Childhood Obesity*. 2016. Available online at: https://www.canada.ca/en/public-health/services/childhood-obesity/childhoodobesity.html (accessed September 15, 2020).

2. Moraes Ferrari GL, Bracco MM, Matsudo VK, Fisberg M. Cardiorespiratory fitness and nutritional status of school children: 30-year evolution. *J Pediatr*. (2013) 89:366–73. doi: 10.1016/j.jped.2012.12.006

3. Hallal PC, Andersen LB, Bull FC, Guthold R, Haskell W, Ekelund U. Global physical activity levels: surveillance progress, pitfalls, and prospects. *Lancet.* (2012) 380:247–57. doi: 10.1016/S0140-6736(12)60646-1

4. Ozemek C, Laddu DR, Lavie CJ, Claeys H, Kaminski LA, Ross R, et al. An update on the role of cardiorespiratory fitness, Structured Exercise and lifestyle physical activity in preventing cardiovascular disease and health risk. *Prog Cardiovasc Dis.* (2018) 61:484–90. doi: 10.1016/j.pcad.2018.11.005

5. Sun C, Magnussen CG, Ponsonby AL, Schmidt MD, Carlin JB, Huynh Q, et al. The contribution of childhood cardiorespiratory fitness and adiposity to in?ammation in young adults. *Obesity.* (2014) 22:2598–605. doi: 10.1002/oby.20871

6. Tomkinson GR, Lang JJ, Tremblay MS, Dale M, LeBlanc AG, Belanger K, et al. International normative 20 m shuttle run values from 1,142,026 children and youth representing 50 countries. *Br J Sports Med.* (2017) 51:1545–54. doi: 10.1136/bjsports-2016-095987

7. Public Agency of Canada. *How Healthy are Canadians? A Trend Analysis of the Health of Canadians From a Healthy Living and Chronic Disease Perspective*. (2016). Available online at: http://www.publications.gc.ca/site/eng/9.825964/publication.html (accessed September 15, 2020).

8. Canadian Society of Exercise Physiology. *Canadian 24-Hour Movement Guidelines for Children and Youth: An Integration of Physical Activity, Sedentary Behaviour, and Sleep*. (2020). Available online at: https://csepguidelines.ca/wpcontent/themes/csep2017/pdf/Canadian24HourMovementGuidelines2016_2.pdf (accessed September 15, 2020).

9. Sui X, Sarzynski MA, Lee DC, Kokkinos PF. Impact of changes in cardiorespiratory fitness on hypertension, dyslipidemia and survival: an overview of the epidemiological evidence. *Prog Cardiovasc Dis.* (2017) 60:56–66. doi: 10.1016/j.pcad.2017.02.006

10. Högström G, Nordström A, Nordström P. High aerobic fitness in late adolescence is associated with a reduced risk of myocardial infraction later in life: a nationwide cohort study in men. *Eur Heart J.* (2014) 35:3133–40. doi: 10.1093/eurheartj/eht527

11. Lang JJ, Phillips EW, Hoffmann MD, Prince SA. Establishing modified Canadian Aerobic Fitness Test (mCAFT) cut-points to detect clustered cardiometabolic risk among Canadian children and youth aged 9 to 17 years. *Appl Physiol Nutr Metab.* (2020) 45:311–7. doi: 10.1139/apnm-2019-0303

12. Ross R, Blair SN, Arena R, Church TS, Després JP. Franklin Ba, et al. Importance of assessing cardiorespiratory fitness in clinical practice: a case for fitness as a clinical vital sign: a scientific statement from the American heart association. *Circulation.* (2016) 134:e653–99. doi: 10.1161/CIR.0000000000000461

13. García-Hermoso A, Ramírez-Vélez R, García-Alonso Y, Alonso-Martínez AM, Izquierdo M, Ramirez-Vélez R. Association of cardiorespiratory fitness levels during youth with health risk later in life: a systematic review and meta-analysis. *JAMA.* (2020) 174:952–60. doi: 10.1001/jamapediatrics.2020.2400

14. Raghuveer G, Hartz J, Lubans DR, Takken T, Wiltz JL, Mietus-Snyder M, et al. Cardiorespiratory fitness in youth: An important marker of health: a scientific statement from the American heart association. *Circulation.* (2020) 142:e101–18. doi: 10.1161/CIR.0000000000000866

15. Ortega FB, Ruiz JR, Castillo MJ, Sjöström M. Physical fitness in childhood and adolescence: a powerful marker of health. *Int J Obes.* (2008) 32:1–11. doi: 10.1038/sj.ijo.0803774

16. Shephard RJ, Allen C, Benade AJ, Davies CT, Di Prampero PE, Hedman R et al. The maximum oxygen intake. An international reference standard of cardiorespiratory fitness. *Bull World Health Organ.* (1968) 38:757–64.

17. Taylor HL, Buskirk E, Henschel A. Maximal oxygen intake as an objective measure of cardio-respiratory performance. *J Appl Physiol.* (1955) 8:73–80. doi: 10.1152/jappl.1955.8.1.73

18. Armstrong N, Welsman J. Twenty-metre shuttle run: (mis)representation, (mis)interpretation and (mis)use. *Br J Sports Med.* (2019) 53:1199. doi: 10.1136/bjsports-2018-100082

19. Armstrong N, Welsman J. Youth cardiorespiratory fitness: evidence, myths and misconceptions. *Bull World Health Organ.* (2019) 97:777–82. doi: 10.2471/BLT.18.227546

20. Tomkinson GR, Lang JJ, Blanchard J, Léger L, Tremblay MS. The 20-m shuttle run : assessment and interpretation of data in relation to youth aerobic fitness and health. *Pediatr Exerc Sci.* (2019) 31:152–63. doi: 10.1123/pes.2018-0179

21. Tomkinson GR, Lang JJ, Tremblay MS. Temporal trends in the cardiorespiratory fitness of children and adolescents representing 19 high-income and upper middle-income countries between 1981 and 2014. *Br J Sports Med.* (2019) 53:478–86. doi: 10.1136/bjsports-2017-097982

22. Olds T, Tomkinson G, Léger L, Cazorla G. Worldwide variation in the performance of children and adolescents: an analysis of 109 studies of the 20-m shuttle run test in 37 countries. *J Sports Sci.* (2006) 24:1025–38. doi: 10.1080/02640410500432193

23. Léger L, Lambert J, Goulet A. Aerobic capacity of 6 to 17-year-old Quebecois 20-meter shuttle run test with 1 minute stages. *Can J Appl Sport Sci.* (1984) 9:64–9.

24. Hoffmann MD, Colley RC, Doyon CY, Wong SL, Tomkinson GR, Lang JJ. Normative-referenced percentile values for physical fitness among Canadians. *Health Rep.* (2019) 30:14–22. doi: 10.25318/82-003-x201901000002-eng

25. Lohman TG, Roche AF, Martorell R. *Anthropometric Standardization Reference Manual*. Champaign, IL: Human Kinetics Books (1988).

26. Cole TJ, Bellizzi MC, Flegal KM, Dietz WH. Establishing a standard definition for child overweight and obesity worldwide: international survey. *BMJ.* (2000) 320:1240–3. doi: 10.1136/bmj.320.7244.1240

27. Box GEP, Cox DR. An analysis of transformations. *J R Stat Soc Series B Stat Methodol.* (1964) 26:211–52. doi: 10.1111/j.2517-6161.1964.tb00553.x

28. Hoaglin DC, Iglewicz B, Tukey JW. Performance of some resistant rules for outlier labeling. *J Am Stat Assoc.* (1986) 81:991–9. doi: 10.1080/01621459.1986.10478363

29. Hoaglin DC, Iglewicz B. Fine tuning some resistant rules for outlier labeling. *J Am Stat Assoc.* (1987) 82:1147–9. doi: 10.1080/01621459.1987.10478551

30. Cole TJ, Green PJ. Smoothing reference centile curves: the LMS method and penalized likelihood. *Stat Med.* (1992) 11:1305–19. doi: 10.1002/sim.4780111005

31. Tarp J, Fagerland MW, Dalene KE, Johannessen JS, Hansen BH, Jefferis BJ, et al. Device-measured physical activity, adiposity and mortality: a harmonised meta-analysis of eight prospective cohort studies. *Br J Sports Med.* (2021) 56:1–9. doi: 10.1136/bjsports-2021-104827

32. Ruiz JR, Cavero-Redondo I, Ortega FB, Welk GJ, Andersen LB, Martinez-Vizcaino V. Cardiorespiratory fitness cut points to avoid cardiovascular disease risk in children and adolescents; what level of fitness should raise a red flag? A systematic review and meta-analysis. *Br J Sports Med.* (2016) 50:1451–8. doi: 10.1136/bjsports-2015-095903

33. Ruiz JR, Huybrechts I, Cuenca-García M. Cardiorespiratory fitness and ideal cardiovascular health in European adolescents. *Heart.* (2015) 101:766–73. doi: 10.1136/heartjnl-2014-306750

34. Dobbins M, Husson H, DeCorby K, LaRocca RL. School-based physical activity programs for promoting physical activity and fitness in children and adolescents aged 6-18 (Review). *Cochrane Database Syst Rev.* (2013) 4:CD007651. doi: 10.1002/14651858.CD007651.pub2

35. Arango CM, Parra DC, Gómez LF, Lema L, Lobelo F, Ekelund U. Screen time, cardiorespiratory fitness and adiposity among school-age children from Monteria, Colombia. *J Sci Med Sport.* (2014) 17:491–5. doi: 10.1016/j.jsams.2013.09.010

36. Sigmundová D, El Ansari W, Sigmund E, Frömel K. Secular trends: a ten-year comparison of the amount and type of physical activity and inactivity of random samples of adolescents in the Czech Republic. *BMC Public Health.* (2011) 11:731. doi: 10.1186/1471-2458-11-731

37. Ryu S, Kim H, Kang M, Pedisic Z, Loprinzi PD. Secular Trends in Sedentary Behavior Among High School Students in the United States, 2003 to 2015. *Am J Health Promot.* (2019) 33:1174–81. doi: 10.1177/0890117119854043

38. Guthold R, Stevens GA, Riley LM, Bull FC. Global trends in insufficient physical activity among adolescents: a pooled analysis of 298 population-based surveys with 1·6 million participants. *Lancet Child Adolesc Health.* (2020) 4:23–35. doi: 10.1016/S2352-4642(19)30323-2

39. López-Bueno R, Calatayud J, Andersen LL, Casana J, Ezzatvar Y, Casajus JA, et al. Cardiorespiratory fitness in adolescents before and after the COVID-19 confinement: a prospective cohort study. *Eur J Pediatr.* (2021) 180:2287–93. doi: 10.1007/s00431-021-04029-8

40. Kuczmarski RJ. *2000 CDC Growth Charts for the United States: methods and development (No. 246). Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Health Statistics.* (2002). Available online at: https://www.cdc.gov/nchs/data/series/sr_11/sr11_246.pdf (accessed November 9, 2022).

frontiers | Frontiers in Pediatrics

TYPE Original Research
PUBLISHED 06 January 2023
DOI 10.3389/fped.2022.1055526

OPEN ACCESS

EDITED BY
Zhen-Yu Zhang,
KU Leuven, Belgium

REVIEWED BY
Pia Cassanello,
Sant Joan de Déu Hospital, Spain
Joanna E MacLean,
University of Alberta, Canada

*CORRESPONDENCE
Anne Gallagher
anne.gallagher@umontreal.ca

SPECIALTY SECTION
This article was submitted to Pediatric Cardiology, a section of the journal Frontiers in Pediatrics

RECEIVED 27 September 2022
ACCEPTED 25 November 2022
PUBLISHED 06 January 2023

CITATION
Lepage C, Gaudet I, Doussau A, Vinay M-C, Gagner C, von Siebenthal Z, Poirier N, Simard M-N, Paquette N and Gallagher A (2023) The role of parenting stress in anxiety and sleep outcomes in toddlers with congenital heart disease.
Front. Pediatr. 10:1055526.
doi: 10.3389/fped.2022.1055526

The role of parenting stress in anxiety and sleep outcomes in toddlers with congenital heart disease

Charles Lepage[1,2], Isabelle Gaudet[1,2], Amélie Doussau[3], Marie-Claude Vinay[3], Charlotte Gagner[3], Zorina von Siebenthal[3], Nancy Poirier[1,3,4], Marie-Noëlle Simard[1,5], Natacha Paquette[1,2] and Anne Gallagher[1,2]*

[1]Research Center, Sainte-Justine University Hospital Research Center, Montréal, QC, Canada, [2]Department of Psychology, Université de Montréal, Montréal, QC, Canada, [3]Clinique d'investigation neurocardiaque (CINC), Sainte-Justine University Hospital, Montréal, QC, Canada, [4]Department of Surgery, Division of Cardiac Surgery, Faculty of Medicine, Université de Montréal, Montréal, QC, Canada, [5]School of Rehabilitation, Faculty of Medicine, Université de Montréal, Montréal, QC, Canada

Objectives: This retrospective cohort study investigates how parenting stress, measured at 4 months of age by use of a classic three-dimensional parent-reported scale (Parenting Stress Index, 4th Ed. or PSI-4), can predict anxiety symptoms and quality of sleep at 24 months in toddlers with congenital heart disease (CHD).

Study Design: Sixty-six toddlers with CHD followed at our cardiac neurodevelopmental follow-up clinic were included in this study. As part of their systematic developmental assessment program, parents completed questionnaires on their stress level (PSI-4) when their child was 4 months old, and on their child's anxiety symptoms and quality of sleep at 24 months. Eight multiple linear regression models were built on the two measures collected at 24 months using the PSI-4 scores collected at 4 months. For each measure, four models were built from the PSI-4 total score and its three subscales (Parental Distress, Parent-Child Dysfunctional Interaction, Difficult Child), controlling for sex and socioeconomic status.

Results: The PSI-4 Difficult Child subscale, which focuses on parenting anxiety related to the child's behavioral problems and poor psychosocial adjustment, accounted for 17% of the child's anxiety symptoms at 24 months. The two other PSI-4 subscales (Parental Distress and Parent-Child Dysfunctional Interaction) and the PSI-4 total score did not contribute significantly to the models. None of the four regression models on perceived quality of sleep were significant. It is important to note that 33% of parents responded defensively to the PSI-4.

Conclusions: Parenting stress related to the child's behavioral problems and poor psychosocial adjustment, measured when the child is 4 months old, is associated with the child's ulterior anxiety symptoms. As very few standardized tools are available to assess the behavioral and psychoaffective development of infants, this study highlights the importance of early psychosocial screening in parents of infants with CHD. The high rate of significant Defensive Responding Indices reminds us to not take parent reports at face value, as their actual stress levels might be higher.

KEYWORDS

CHD (congenital heart disease), neurodevelopement, quality of sleep, parenting stress, behavior, anxiety, early assessment, psychosocial care

1. Introduction

Children with congenital heart disease (CHD) are at high risk for neurodevelopmental impairments, including behavioral and psychoaffective deficits, which can alter their developmental trajectory and quality of life (1). More specifically, school-age children with CHD seem to display more anxiety and depressive symptoms than their healthy peers (2). Gupta and al (3). found that covert anxiety, fear, depression and behavioral problems were more prevalent in children with CHD who were not exhibiting clinically significant psychosocial impairments, compared to the normative population. They also found that school-age children with cyanotic CHD displayed more physiological signs of anxiety (i.e., shortness of breath, increased heart rate, sweaty hands) than healthy children, which was associated with isolation and lower self-esteem, thus greatly impacting those children's relationships with their family and same-age peers. Even preschool-age children with CHD have 5–7 times higher odds of developing an anxiety disorder (4). This highlights the relevance of examining anxiety outcomes in young children with CHD.

Meanwhile, up to 50% of parents of children with CHD exhibit significant emotional distress (5). During the perinatal period, parents of children with CHD experience considerable stress due to their child's life-threatening medical condition, multiple surgeries, long hospitalizations, and neurodevelopmental and behavioral challenges (6, 7), thus making it harder for them to thrive in their parental role (8, 9). It has also been shown that parents may pass on their anxiety to their child, through overprotective behavior, fears and personal or interpersonal distress (10). Therefore, the more anxious the parent, the more behavioral and psychoaffective problems they tend to identify in their child, and the higher the chances that their child will develop a similar anxious profile (3). Considering the high risk for emotional distress in parents of children with CHD, the relationship between parenting stress and the child's anxiety ought to be further investigated.

Visconti et al. (11) conducted one of the first longitudinal studies on the effects of parenting stress on behavioral and psychoaffective adjustment in children with dextro-transposition of the great arteries (d-TGA) and they found that parents with more stress at 12 months reported more behavioral problems in their children 3 years later. Also using a longitudinal design, Hsiao et al. (12) identified five distinct evolutive patterns of behavioral and psychoaffective difficulties in children with CHD over a two-year period (participants enrolled between the ages of 1,5–10 years old): "persistent normal," "initial problematic," "worsening," "persistent problematic," and "subclinical." Children of all ages whose parents had higher levels of parenting stress were more likely to be categorized into the "initial problematic," "subclinical," and "persistent problematic" patterns, suggesting that behavioral and psychoaffective functioning is influenced by early factors including parenting stress. Altogether, these studies highlight the importance of early detection of parenting stress, in order to promote healthy behavioral and psychoaffective development in children with all types of CHD (13).

High levels of parenting stress have also been associated with more sleep problems in healthy 5-year-olds who exhibit behavioral and psychoaffective problems (14), as well as in ill children (15). It has also been documented that children with CHD are at high-risk of developing sleep pathologies (16) or disrupted sleep patterns, especially when there is increased medical complexity, longer hospitalization stays and lower parental education (17). Sleep plays a fundamental role in the child's development (18, 19), and it has been reported to be among the parent's main concerns (20) due to the adverse effects of sleep deprivation on the child's daily functioning. Since parents of children with CHD experience very high levels of stress (6, 7), it is relevant to examine the relationship between parenting stress and the child's quality of sleep. A better understanding of the potential implications of parenting stress would affirm the need for early preventive screening of distressed families.

Many sociodemographic and clinical factors related to CHD are known to influence neurodevelopmental outcomes (21, 22). Investigating the role of parenting stress on anxiety and sleep outcomes is essential in order to better understand the underlying contributing parental factors (23, 24), which might be modifiable. Therefore, this retrospective study aims to investigate how early parenting stress, measured at 4 months, can explain the child's anxiety symptoms and quality of sleep, measured at 24 months, in a cohort of toddlers with CHD. We expected parenting stress at 4 months to account for a significant part of the variance in anxiety and sleep outcomes at 24 months.

2. Materials and methods

2.1. Procedure and participants

We performed a retrospective examination of all patients aged 24 months and older ($n = 281$) seen at our cardiac neurodevelopmental follow-up clinic and whose parents had consented to their child's medical information being used for research purposes. In order to be included in the study, children had to have an ante- or perinatal diagnosis of CHD, have undergone at least one corrective surgery early in life (palliative or temporary procedures such as the Rashkind procedure or the installation of cardiac stents were not considered) and have in their medical chart all parent-reported questionnaires of interest completed during the systematic follow-up assessments at 4 and 24 months. More specifically, parents filled the Parenting Stress

Index, 4th Edition—Short Form (PSI-4-SF) at 4 months, and the Child Behavior Checklist 1.5–5 years old (CBCL 1.5–5 years old) and the *Échelle de dépistage des troubles de sommeil pédiatriques* (HIBOU; Pediatric Sleep Disorders Screening Scale) at 24 months (see below for detailed descriptions of the parental questionnaires).

2.2. Variables

2.2.1. Parenting stress

Parenting stress levels were measured using the PSI-4-SF (25) when patients with CHD were 4 months old. This questionnaire was completed either by one or both of the patients' parents. If both parents completed the questionnaire, the scores of one of the parents were chosen randomly during data collection (see **Supplementary Table S1**). The PSI-4-SF includes three subscales of 12 items each: Parental Distress (PD; example of item: "I don't enjoy things as I used to."), Parent-Child Dysfunctional Interaction (PCDI; example of item: "My child rarely does things for me that make me feel good.") and Difficult Child (DC; example of item: "My child is very emotional and gets upset easily."). The parent answers using a Likert scale with five anchors ranging from "Strongly Disagree" to "Strongly Agree." The total stress score is calculated by combining the total scores of the three subscales. A raw score of 110 and over (85th percentile) points to a level of parenting stress that is higher than normal. The questionnaire also evaluates the parent's propensity to answer defensively (Defensive Responding Index), whether because the parent who filled out the questionnaire underestimated his or her stress level (deliberately or not) or due to an abnormally low level of parenting stress, possibly related to parental disengagement. Defensive responses are abnormally low scores ("Strongly Disagree") on items to which most parents, not necessarily in clinical contexts, would answer that they somewhat agree. The scores of seven items of the PD subscale are combined (example of an item: "I feel trapped by my responsibilities as a parent.") and the Defensive Responding Index is considered significant if the sum is 10 or less, meaning that the results must be interpreted with caution. The PSI-4-SF has very good psychometric properties [Cronbach's α superior to .80; see reference (26)] and its validity and reliability have been confirmed in various populations (27, 28).

2.2.2. Anxiety

The behavioral, psychosocial and psychoaffective development of the 24-month-old patient was evaluated using the French version of the parent form of the CBCL 1.5–5 years old [*CBCL 1.5–5 ans*; see references (29, 30)]. This questionnaire includes 99 items divided in 15 subscales (i.e., "Attention Problems", "Somatic Complaints", "Internalizing Problems", etc.). The raw score calculated from each subscale's items ("0 = not true; 1 = somewhat or sometimes true; 2 = very true or often true") is converted to a T score and a percentile rank. For each subscale, an above normal or clinical cut-off score is specified. In this study, we considered the "Anxiety Problems" subscale of the questionnaire. This subscale contains 10 items and therefore has a maximum raw score of 20. A raw score of 8 and above indicates clinically significant anxiety symptoms. Validity of the CBCL 1.5–5 years old for assessing the behavioral, psychosocial and psychoaffective development of preschoolers has been corroborated using diverse populations (31, 32). Many authors have confirmed the very good psychometric properties of the questionnaire (Cronbach's α superior to .72 for all subscales)—see among others Ha et al. (33) and Ivanova et al. (34).

2.2.3. Quality of sleep

The patient's quality of sleep at 24 months was assessed using the HIBOU (Pediatric Sleep Disorders Screening Scale). This is a non-standardized parent-reported screening tool translated into French by Godbout and Martello (35) from the original English version (36). This questionnaire has proven to be useful for clinicians, allowing them to easily collect information on the child's sleep habits, thus improving their ability to identify early on potential sleep problems and refer the child to a specialist, if needed (37). The questionnaire includes five subscales: "Irregular schedule and excessive diurnal sleepiness", "Insomnia", "Moves during sleep", "Obstruction" and "Ultra-vigilance". Each subscale refers to 1 or 2 items for which the parent provides a score ranging from 0 to 3. The total raw score ranges from 0 to 27. A total score of 16 and over indicates that the child has significant sleep difficulties and is at high risk of developing a sleep disorder, and a referral to a specialist is recommended. A total score between 10 and 15 indicates sleep difficulties that should be monitored, but that do not yet justify a referral.

2.3. Statistical analyses

Analyses were conducted using the Statistical Package for Social Sciences (SPSS, version 27). First, the data was explored to ensure assumptions of normality were met and Descriptive comparison statistics between participants and non-participants were performed using independent t-tests. Then, to determine the interrelatedness between parenting stress at 4 months (PSI-4 total score and PSI-4 subscale scores PD, Parental Distress; PCDI, Parent-Child Dysfunctional Interaction; and DC, Difficult Child) and our behavioral and psychoaffective measures of interest at 24 months (CBCL Anxiety Problems; HIBOU total score) bivariate Pearson correlations were computed prior to the regression models. The correlation coefficients yielded the maximum degree of linear relationship

that could be obtained between our variables. Finally, multiple linear regression analyses were performed to examine how parenting stress at 4 months could explain ulterior anxiety symptoms and quality of sleep at 24 months.

Four regression models were built on the CBCL Anxiety Problems score at 24 months. The first model included the PSI-4 total stress score at 4 months as a predictor. The three other models each included a PSI-4 subscale score other than the total stress score (PD, PCDI, DC). Since significant differences were found between the PSI-4 scores of parents who responded defensively (see below) to the questionnaire and those who did not, Defensive Responding was included as a dichotomic predictor in all models. Finally, sex (38, 39), socioeconomic status (40, 41) and duration of hospitalization at first surgery (42) were controlled, as all these factors have been shown to have a significant influence on the neurodevelopment of children with CHD.

Four other identical regression models were built on the HIBOU score at 24 months. The exact same variables were controlled. Since the HIBOU questionnaire only generates a raw score, the raw scores of all three questionnaires were used. Moreover, even though the patients were between 2 and 5 years old when the analyses were conducted ($M = 43.16$ months; SD = 7.07; range of 28–58 months), they were all roughly the same age when the questionnaires were completed ($M = 24.24$ months; SD = 0.93; range of 23–29 months; see **Supplementary Table S1**) and were therefore part of the same age-based normative group, meaning that the raw scores represented the same level of challenges encountered. Finally, a Benjamini-Hochberg correction for multiple analyses was applied, because four comparisons were performed on each dependent variable.

3. Results

3.1. Descriptive statistics

Among the 281 patients whose medical charts were reviewed, ten were excluded because they did not require corrective surgery and 205 were excluded because of incomplete questionnaires, interruptions in the follow-up process or late referrals to the clinic (past the 4-month assessment). A total of 66 patients with CHD (42 boys; mean age 43.17 months ±7.07) were ultimately included in this study. See **Supplementary Table S1** for detailed statistics of the patients' characteristics. In order to investigate if our sample was representative of the patients at our cardiac neurodevelopmental follow-up clinic, we compared socio-demographic and clinical variables between the included patients ($n = 66$) and the patients followed at the neurocardiac clinic who were excluded ($n = 205$). These results are presented in **Table 1**.

Results for the PSI-4 revealed that the patients' parents' stress levels were not above the clinical threshold and that 33% of them responded defensively to this questionnaire. Considering the potential influence of the defensive responding bias on parent-reported stress (43), we separated the parents who responded defensively to the PSI-4 from those who did not. As expected, we found a significant difference between total stress ($p < .001$, mean raw score of 48 ± 8 vs. 73 ± 15, respectively), PD ($p < .001$, mean raw score of 16 ± 4 vs. 27 ± 7) and DC ($p < .001$, mean raw score of 18 ± 4 vs. 24 ± 7) scores. However, no difference was found when comparing the PCDI scores ($p = .984$, mean raw score of 20 ± 6–21 for both groups). These results suggest that a variety of patterns could potentially emerge in our analyses, when considering the parents' defensive responding. Thus, Defensive Responding was included as a controlled variable in all regression models. We also compared the PSI-4-SF scores of the patients' parents who completed the questionnaire before their child underwent surgery to that of parents who completed it after the surgical intervention. No difference was found between the two groups in regard to the Total Stress score ($p = .952$, mean raw score of 64 ± 18 vs. 65 ± 18) nor any of the three subscale scores (PD, $p = .474$, mean score of 25 ± 7 vs. 23 ± 8; PCDI, $p = .081$, mean score of 25 ± 24 vs. 19 ± 8; DC, $p = .558$, mean score of 23 ± 7 vs. 22 ± 7). No difference was found when comparing PSI Total Stress scores of parents who received an antenatal diagnosis of CHD to that of parents who received the diagnosis after birth ($p = .969$, mean score of 65 ± 16–18 for both groups).

3.2. Correlations and multiple linear regressions

Bivariate Pearson correlation analyses were performed between the variables of interest (see **Table 2**). When predicting anxiety symptoms at 24 months (CBCL) while controlling for the patient's sex, socioeconomic status and duration of hospitalization at first corrective cardiac surgery, we found that the regression model built with the PSI-4 DC (Difficult Child) score explained 17% ($R^2 = .166$; $p = .048$) of the CBCL Anxiety Problems subscale score. In fact, a closer look at the contribution of each variable included in the model shows that the DC subscale score accounts for 36% ($\beta = .358$; $p = .004$) of the variance in parent-reported anxiety symptoms at 24 months, independently of controlled variables. No significant predictive value of the PSI-4 PD, PCDI and total stress scores on CBCL Anxiety Problems at 24 months was found. No significant predictive value of PSI-4 scores on the HIBOU scores at 24 months was found either with any of the four regression models (PSI-4 total stress, PD, PCDI and DC). See **Table 3** for the detailed results of the linear regression analyses.

TABLE 1 Descriptive statistics of included and excluded patients.

Socio-demographic or medical characteristics	Included patients			Excluded patients		
	M	SD	Range	M	SD	Range
Gestational age (weeks)	38.68	1.22	36.26–41.26	38.58	1.82	32.57–41.57
Age at first corrective surgery (months)	3.87	5.52	0–21.86	114	168.25	0–29.89
Duration of hospitalization at first surgery (days)[a]	19.55	19.19	4–127	31.47	43.09	4–305
	n			*n*		
Sex, males (%)	42 (64)			119		
Born premature (%)	53 (14)			26 (13)		
Cyanotic CHD (%)[a]	9 (80)			139 (68)		

[a]Significant difference found between the groups at $p < .005$. CHD, congenital heart disease.

TABLE 2 Pearson bivariate correlation matrix between PSI scores at 4 months and CBCL anxiety scale and hibou scores at 24 months.

4- and 24-months scores		24-months scores			
		CBCL Anxiety		HIBOU	
PSI-4-SF Total Stress	*r*	0.242	$p = .050$	0.039	$p = .758$
PSI-4-SF PD	*r*	0.160	$p = .199$	0.002	$p = .990$
PSI-4-SF PCDI	*r*	−0.420	$p = .741$	−0.125	$p = .316$
PSI-4-SF DC	*r*	**0.354**	$\mathbf{p = .004}$	0.161	$p = .196$
Def Resp	*r*	0.188	$p = .130$	−0.006	$p = .962$
HIBOU	*r*	**0.274**	$\mathbf{p = .026}$		

HIBOU, *Échelle de dépistage des troubles du sommeil pédiatriques*, Pediatric Sleep Disorders Screening Scale; CBCL, Child Behavior Checklist 1.5-5 years old; PSI-4-SF, Parenting Stress Index, 4th Ed., Short Form; PD, Parental Distress; PCDI, Parent-Child Dysfunctional Interaction; DC, Difficult Child; Def Resp, Defensive Responding.
Bold values represent significant results at $p < .05$.

4. Discussion

This longitudinal retrospective study aimed to investigate the predictive value of parenting stress at 4 months on anxiety outcomes and quality of sleep at 24 months in toddlers with CHD. Our results partly align with the hypothesis that was put forward. First, parenting stress scores at 4 months were significantly associated with the child's anxiety symptoms at 24 months. In fact, parenting stress related to the parent's perception of their child's behavioral problems and poor psychosocial adjustment (DC subscale of the PSI-4) acted as a significant predictor of parent-reported anxiety in their toddler at 24 months. Even when controlling for the child's sex, the family's socioeconomic status, the duration of hospitalization at first corrective cardiac surgery and the Defensive Responding bias, the regression model remained significant. This result suggests that parenting stress is an independent predictor of ulterior anxiety in the child, above and beyond sociodemographic and medical factors known to impact the development of children with CHD (44, 45). Karimzadeh et al. (46) have explained that increased levels of parenting stress could have such an impact through a lack of emotional availability or a tendency to assume that the situation is about to spiral out of control when facing any changes or difficulties with the child, even when minor. The PSI-4 DC subscale notably evaluates the parents' perception of their child's ability to self-regulate and cope with adversity (28). Significant maladaptation and increased levels of anxiety in parents could therefore lead to similar ulterior reactions in children through a number of parental psychosocial factors.

Among the four scores obtained with the PSI-4 (Total stress score, PD, PCDI, and DC subscale scores), only the DC score was significantly correlated with the CBCL Anxiety Problems subscale score at 24 months. Since the total stress score represents the sum of the three dimensions of the PSI-4 scale, it is less specific than the three subscale scores considered individually. Perhaps parents of children with CHD have a generally higher threshold for what they perceive to be stressful, given what they have gone through with their child's medical condition (47), and this could contribute to lowering their self-reports of personal distress (PD subscale). This could alter the predictive value of the total stress score, but not the DC subscale score, which is more oriented towards their worries about the child and proved to significantly predict anxiety at 24 months. To better explain this disparity between the predictive value of the parenting stress subscale scores, we considered the proportion of parents who tended to respond defensively to the questionnaire, which was particularly high in our sample (33%). Social desirability and denial of their child's precarious condition are two of many hypotheses that could explain the parents' defensiveness. Moreover, defensiveness seems to be more frequent in clinical settings, and especially so when the child's situation is particularly difficult and precarious, which is the case for our cardiac neurodevelopmental follow-up clinic's patients (43). Hence, considering the many medical-related factors that could contribute to the parents' anxiety and their impact on the tendency to answer defensively, it is possible that parenting stress levels might have been underestimated in our study. We can also hypothesize that the defensive attitude towards parent-reported questionnaires is more specific to parent-oriented variables, such as the PD and PCDI subscales, which in turn suggests that child-oriented subscales, such as the DC subscale, might be more accurate in describing actual parenting stress levels. This underlines the importance of additional measures to corroborate self-report findings and compensate for defensive responding, since few standardized tools are designed to detect it (48).

TABLE 3 Results of multiple linear regression analyses between 4- and 24-months scores.

Regression models (PSI-4-SF at 4 months)		24-months CBCL Anxiety score	Regression models (PSI-4-SF at 4 months)		24-months HIBOU score
1. Sex	β	−0.050	5. Sex	β	−0.124
Socioeconomic status	β	−0.083	Socioeconomic status	β	−0.025
Duration of hospitalization	β	0.183	Duration of hospitalization	β	0,168
PSI-4-SF Total Stress	β	0.248	PSI-4-SF Total Stress	β	0.038
Defensive Responding	β	0.041	Defensive Responding	β	−0.073
	R^2	0.096		R^2	0.048
2. Sex	β	−0.050	6. Sex	β	−0.124
Socioeconomic status	β	−0.083	Socioeconomic status	β	−0.025
Duration of hospitalization	β	0.183	Duration of hospitalization	β	0,168
PSI-4-SF PD	β	0.155	PSI-4-SF PD	β	−0.027
Defensive Responding	β	0.156	Defensive Responding	β	−0.001
	R^2	0.074		R^2	0.045
3. Sex	β	−0.050	7. Sex	β	−0.124
Socioeconomic status	β	−0.083	Socioeconomic status	β	−0.025
Duration of hospitalization	β	0.183	Duration of hospitalization	β	0,168
PSI-4-SF PCDI	β	−0.034	PSI-4-SF PCDI	β	−0.121
Defensive Responding	β	0.179	Defensive Responding	β	−0.018
	R^2	0.074		R^2	0.059
4. Sex	β	−0.050	8. Sex	β	−0.124
Socioeconomic status	β	−0.083	Socioeconomic status	β	−0.025
Duration of hospitalization	β	0.183	Duration of hospitalization	β	0,168
PSI-4-SF DC	β	**0.358****	PSI-4-SF DC	β	0.165
Defensive Responding	β	0.038	Defensive Responding	β	−0.103
	R^2	**0.166***		R^2	0.079

CBCL, Child Behavior Checklist 1.5-5 years old; HIBOU, *Échelle de dépistage des troubles du sommeil pédiatriques*, Pediatric Sleep Disorders Screening Scale; PSI-4-SF, Parenting Stress Index, 4th Ed., Short Form; PD, Parental Distress; PCDI, Parent-Child Dysfunctional Interaction; DC, Difficult Child.
Bold values represent significant results at two different thresholds (indicated at the bottom of the table).
*$p < 0.05$.
**$p < 0.005$.

Finally, parenting stress scores at 4 months were not associated with the child's perceived quality of sleep at 24 months. This could be due to the broad nature of the HIBOU screening tool, as explained by Martin et al. (49) in their meta-analysis on the interplay between parenting stress and sleep difficulties in children with autism spectrum disorder and attention deficit/hyperactivity disorder. The HIBOU offers a composite score that combines many types of sleep problems which are not individually explored in detail, making it impossible to assess a specific deficit independently, nor its interplay with our other variables of interest. Although objective data obtained through polysomnography is preferable when objectively assessing sleep quality (49), primarily subjective measures such as parent-reported sleep questionnaires act as objective measures in clinical contexts. This is particularly true when the questionnaires have been adapted to clinical populations (50, 51), as for the HIBOU. Nevertheless, we found a significant correlation between the HIBOU score and CBCL Anxiety Problems subscale score at 24 months, demonstrating a relationship between the two variables, possibly through common predicting factors, which is consistent with Chorney et al.'s (52) literature review. Indeed, the authors recommend assessing symptoms of disturbed sleep when measuring anxiety symptoms in children. Though we use the HIBOU to assess sleep at our cardiac neurodevelopmental follow-up clinic, more detailed and specific parent reports, as well as objective sleep data, should be considered.

4.1. Clinical implications

Although the parents do not necessarily report clinically significant parenting stress levels, probably due to the high rate of significant Defensive Responding Indices, our results show that, when administered early, parenting stress scores could have a predictive value of the child's ulterior anxiety during toddlerhood (even when controlling for the tendency to answer defensively). The PSI scores could be used for early identification of parents and children potentially at risk of more important behavioral and psychoaffective challenges, which are difficult to assess with standardized tools at this young age (53). At our cardiac neurodevelopmental follow-up clinic, systematic interdisciplinary follow-up and psychosocial care (including systematic assessments of parenting stress) are offered when children with CHD reach the age of 4 months. Yet, an important proportion of families receive the diagnosis during pregnancy and carry this burden for several weeks before the child is born. Since prenatal stress usually evolves into parenting stress after birth (54), its adverse effects tend to consolidate.

We also found that parenting stress scores at 4 months and the child's perceived quality of sleep at 24 months were both significantly associated with anxiety problems at 24 months. Since sleep difficulties are common in congenital heart disease (55), we must work on informing the parents on the relationship between sleep and anxiety, and promoting healthy sleep habits once the child leaves the hospital. Because stress is known to be significantly high in parents of children

with CHD, and influenced by sleep difficulties in those children (7–15), it must also be considered as one of the important targets of the psychosocial care and interventions offered to families (22).

4.2. Methodological considerations

The current study has limitations that must be considered. First, significant differences were found between participants and non-participants regarding two medically-related variables: a smaller proportion of perinatal diagnosis and a shorter average duration of hospitalization at first corrective cardiac surgery were both found in our sample. Since an antenatal diagnosis is associated with more complex forms of CHD (56), we hypothesize that those parents might be even more diligent in completing questionnaires (especially at 4 months) due to the anxiety caused by the increased risk of post-surgery complications. Parents of children with less severe forms of CHD could therefore have been excluded from the study right from the start, making our results less generalizable to the population (only 30% of the eligible patients' parents had completed all questionnaires). On an exploratory basis, we incorporated the time of diagnosis ante- vs. perinatal) in our linear regression analyses, by replacing the duration of hospitalization at first corrective cardiac surgery (controlled variable for all models). No significant differences were found, meaning that the time of diagnosis does not seem to affect the predictive value of parenting stress on the child's ulterior anxiety. The role of other clinical factors related to CHD is also extremely relevant to investigate and should be considered in further research with an adequate statistical power, allowing to include these variables.

Second, all the questionnaires that we used are standardized except the HIBOU, which provides a measure of the parent's perception of the child's quality of sleep. Nonetheless, it is widely used in both clinical and research contexts throughout the province of Quebec. Its scoring procedure provides a relevant clinical cut-off and allows for early identification of potential sleep disturbances. We put forward the interesting alternative of an at-home sleep monitoring device that would provide objective data on specific parameters of the child's sleep (i.e., oxygen saturation, heart rate, etc.). Using a device that targets cardiorespiratory parameters, Vézina et al. (57) obtained clinically acceptable data in 91% of their 562 healthy 1-year-olds, proving the efficacy of such a device with infants. In a future study, the device could be provided to patients' families at specific times during the systematic follow-up sequence for recordings of one night. Objective and standardized data on the child's sleep could then be compared to the results of parent-reported questionnaires. Monitoring the parents' sleep would also be relevant in further research, given its interplay with the child's quality of sleep and its influence on anxiety symptoms.

5. Conclusions

The present study shows that parenting stress can act as a predictor of anxiety symptoms in toddlers with CHD. Our results revealed that the parents' perception of their child's poor behavioral and psychosocial adjustment at 4 months of age contributed significantly to the prediction of ulterior anxiety at 24 months. Accurate measures of the patients' parents' stress levels could therefore allow for early identification of distressed families. However, the defensive responding bias must be considered, as it might lead to an underestimation of the parenting stress levels during the first months of life. Normal or lower-than-normal stress levels therefore do not necessarily indicate a healthy adaptation to life with the disease, and measures that are more oriented towards the parents' worries about the child, instead of toward themselves, might be more appropriate. The results of this study also bring into consideration the necessity for very early intervention. For families who receive an antenatal diagnosis of CHD, antenatal psychosocial interventions, such as stress management workshops, psychotherapy or psychoeducation follow-up sessions, should be considered in order to optimize developmental outcomes.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

This study involving human participants was reviewed and approved by the Comité d'éthique de la recherche (CER) du CHU Sainte-Justine. Written informed consent to participate in this study was provided by the participants' legal guardian/ next of kin.

Author contributions

CL and IG reviewed the literature, designed the study, performed exploratory and statistical analyses and wrote the manuscript. AD provided significant support in searching through the medical records and database. AD, MCV, CG and ZVS performed the clinical data collection. AG and NP contributed to the design of the study, supervised the research work process by providing precise feedback and suggesting

relevant improvements, and thoroughly revised the manuscript. MNS also supervised the research. NP oversees the research at our cardiac neurodevelopmental follow-up clinic and contributed to patient screening and recruitment, allowing for fruitful scientific and clinical discussions. All authors contributed to the article and approved the submitted version.

Funding

This work was supported by the Canadian Institutes of Health Research (Frederick Banting and Charles Best Canada Graduate Scholarships Master's Award awarded to CL), the Natural Sciences and Engineering Research Council (Undergraduate Student Research Award awarded to CL), the Heart and Stroke Foundation of Canada under grant numbers G-17-0018253 and G-20-0028672, as well as a Canada Research Chair in Child Neuropsychology and Brain Imaging (CRC #950-232661) held by AG. We also recognize the contribution of an excellence prize awarded to CL by the *Association québécoise pour la santé mentale des nourrissons* (AQSMN).

Acknowledgments

We are very grateful to all the families who agreed to the use of their data for research purposes. We also thank our cardiac neurodevelopmental follow-up clinic's interdisciplinary team for its outstanding work with the patients and their families.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2022.1055526/full#supplementary-material.

References

1. Snookes SH, Gunn JK, Eldridge BJ, Donath SM, Hunt RW, Galea MP, et al. A systematic review of motor and cognitive outcomes after early surgery for congenital heart disease. *Pediatrics*. (2010) 125(4):e818–e27. doi: 10.1542/peds.2009-1959

2. Fredriksen PM, Diseth TH, Thaulow E. Children and adolescents with congenital heart disease: assessment of behavioural and emotional problems. *Eur Child Adolesc Psychiatry*. (2009) 18(5):292–300. doi: 10.1007/s00787-008-0730-8

3. Gupta S, Giuffre RM, Crawford S, Waters J. Covert fears, anxiety and depression in congenital heart disease. *Cardiol Young*. (1998) 8(4):491–9. doi: 10.1017/s1047951100007162

4. Gonzalez VJ, Kimbro RT, Cutitta KE, Shabosky JC, Bilal MF, Penny DJ, et al. Mental health disorders in children with congenital heart disease. *Pediatrics*. (2021) 147(2):e20201693 (published online). doi: 10.1542/peds.2020-1693

5. de Man M, Segers EW, Schappin R, van der Leeden K, Wösten-van Asperen RM, Breur H, et al. Parental experiences of their infant's hospital admission undergoing cardiac surgery: a systematic review. *Acta Paediatr*. (2021) 110(6):1730–40. doi: 10.1111/apa.15694

6. Golfenshtein N, Hanlon AL, Deatrick JA, Medoff-Cooper B. Parenting stress in parents of infants with congenital heart disease and parents of healthy infants: the first year of life. *Compr Child Adolesc Nurs*. (2017) 40(4):294–314. doi: 10.1080/24694193.2017.1372532

7. Sood E, Karpyn A, Demianczy AC, Ryan J, Delaplane EA, Neely T, et al. Mothers and fathers experience stress of congenital heart disease differently: recommendations for pediatric critical care. *Pediatr Crit Care Med*. (2018) 19(7):626–34. doi: 10.1097/pcc.0000000000001528

8. Lisanti AJ, Demianczyk AC, Vaughan K, Martino GF, Ohrenschall RS, Quinn R, et al. Parental role alteration strongly influences depressive symptoms in mothers of preoperative infants with congenital heart disease. *Heart Lung*. (2021) 50(2):235–41. doi: 10.1016/j.hrtlng.2020.12.003

9. McMahon E, Chang YS. From surviving to thriving—parental experiences of hospitalised infants with congenital heart disease undergoing cardiac surgery: a qualitative synthesis. *J Pediatr Nurs*. (2020) 51:32–41. doi: 10.1016/j.pedn.2019.12.010

10. Clarke K, Cooper P, Creswell C. The Parental Overprotection Scale: associations with child and parental anxiety. *J Affect Disord*. (2013) 151(2):618–24. doi: 10.1016/j.jad.2013.07.007

11. Visconti KJ, Saudino KJ, Rappaport LA, Newburger JW, Bellinger DC. Influence of parental stress and social support on the behavioral adjustment of children with transposition of the great arteries. *J Dev Behav Pediatr*. (2002) 23(5):314–21. doi: 10.1097/00004703-200210000-00003

12. Hsiao LC, Chiu SN, Chang LY, Wang CC, Weng WC, Chang HY. Patterns and correlates of changes in emotional and behavioral problems among children with congenital heart disease. *J Dev Behav Pediatr*. (2022) 43:399–406. doi: 10.1097/dbp.0000000000001051

13. Cassidy AR, Butler SC, Briend J, Calderon J, Casey F, Crosby LE, et al. Neurodevelopmental and psychosocial interventions for individuals with CHD: a research agenda and recommendations from the Cardiac Neurodevelopmental Outcome Collaborative. *Cardiol Young*. (2021) 1(12):1–12. doi: 10.1017/s1047951121002158

14. Coto J, Garcia A, Hart KC, Graziano PA. Associations between disruptive behavior problems, parenting factors, and sleep problems among young children. *J Dev Behav Pediatr*. (2018) 39(8):610–20. doi: 10.1097/dbp.0000000000000595

15. Bishop MN, Gise JE, Donati MR, Shneider CE, Aylward BS, Cohen LL. Parenting stress, sleep, and psychological adjustment in parents of infants and toddlers with congenital heart disease. *J Pediatr Psychol*. (2019) 44(8):1–11. doi: 10.1093/jpepsy/jsz026

16. Combs D, Edgin JO, Klewer S, Barber BJ, Morgan WJ, Hsu CH, et al. OSA and neurocognitive impairment in children with congenital heart disease. *Chest*. (2020) 158(3):1208–17. doi: 10.1016/j.chest.2020.03.021

17. Sadhwani A, Butler S, Rofeberg V, Espinosa K, Wood L, Cassidy AR, et al. Sleep patterns in young children with congenital heart disease. *J Pediatr*. (2022) 252:S0022-3476(22)00767-3. doi: 10.1016/j.jpeds.2022.08.031

18. Beebe DW. Cognitive, behavioral, and functional consequences of inadequate sleep in children and adolescents. *Pediatr Clin N Am*. (2011) 58 (3):649–65. doi: 10.1016/j.pcl.2011.03.002

19. El-Khatib H, Boulet-Craig A, Gagnon K, Godbout R. Les troubles du sommeil chez l'enfant et l'adolescent atteints de troubles neurodéveloppementaux: une évaluation nécessaire en psychologie. *Clin Appl Neuropsychol*. (2018) 2:34–51. doi: 10.46278/j.ncacn.20180719

20. Quine L. Sleep problems in primary school children: comparison between mainstream and special school children. *Child: Care Health Dev*. (2001) 27 (3):201–21. doi: 10.1046/j.1365-2214.2001.00213.x

21. Wehrle FM, Bartal T, Adams M, Bassler D, Hagmann CF, Kretschmar O, et al. Similarities and differences in the neurodevelopmental outcome of children with congenital heart disease and children born very preterm at school entry. *J Pediatr*. (2022) 250:29–37. doi: 10.1016/j.jpeds.2022.05.047

22. Sanz JH, Anixt J, Bear L, Basken A, Beca J, Marino BS, et al. Characterisation of neurodevelopmental and psychological outcomes in CHD: a research agenda and recommendations from the cardiac neurodevelopmental outcome collaborative. *Cardiol Young*. (2021) 31(6):876–87. doi: 10.1017/s1047951121002146

23. Sood E, Lisanti AJ, Woolf-King SE, Wray J, Kasparian N, Jackson E, et al. Parent mental health and family functioning following diagnosis of CHD: a research agenda and recommendations from the Cardiac Neurodevelopmental Outcome Collaborative. *Cardiol Young*. (2021) 31(6):900–14. doi: 10.1017/s1047951121002134

24. Clancy T, Jordan B, de Weerth C, Muscara F. Early emotional, behavioural and social development of infants and young children with congenital heart disease: a systematic review. *J Clin Psychol Med Settings*. (2020) 27(4):686–703. doi: 10.1007/s10880-019-09651-1

25. Abidin RR. *Parenting stress Index: Professional manual*. 3rd ed. Odessa, FL: Psychological Assessment Resources, Inc. (1995). 124 p.

26. Hasket ME, Ahern LS, Ward CS, Allaire JC. Factor structure and validity of the parenting stress index-short form. *J Clin Child Adolesc Psychol*. (2006) 35 (2):302–12. doi: 10.1207/s15374424jccp3502_14

27. Aracena M, Gómez Muzzio E, Undurraga C, Leiva L, Marinkovic K, Molina Y. Validity and reliability of the Parenting Stress Index Short Form (PSI-SF) applied to a Chilean sample. *J Child Fam Stud*. (2016) 25(12):3554–64. doi: 10.1007/s10826-016-0520-8

28. Lee SJ, Gopalan G, Harrington D. Validation of the parenting stress index-short form with minority caregivers. *Res Soc Work Prac*. (2016) 26(4):429–40. doi: 10.1177/1049731514554854

29. Fombonne E, Chedan F, Carradec AM, Achard S, Navarro N, Reis S. Le Child Behavior Checklist: un instrument pour la recherche en psychiatrie de l'enfant. *Psychiatr Psychobio*. (1988) 3(6):409–18. doi: 10.1017/S0767399X00002297

30. Achenbach TM, Rescorla MA. *Manual for the ASEBA school-age forms et profiles*. Burlington, VT: University of Vermont, Research Center for Children, Youth, et Families (2001). 238.

31. Albores-Gallo L, Hernández-Guzmán L, Hasfura-Buenaga C, Navarro-Luna E. Consistencia interna y validez de criterio de la versión mexicana del Child Behavior Checklist 1.5-5 (CBCL/1.5-5). *Rev Child Pediatr*. (2016) 87(6):455–62. doi: 10.1016/j.rchipe.2016.05.009

32. Kristensen S, Henriksen TB, Bilenberg N. The Child Behavior Checklist for ages 1.5-5 (CBCL/1(1/2)-5): assessment and analysis of parent- and caregiver-reported problems in a population-based sample of Danish preschool children. *Nord J Psychiatry*. (2010) 64(3):203–9. doi: 10.3109/08039480903456595

33. Ha EH, Kim SY, Song DH, Kwak EH, Eom SY. Discriminant validity of the CBCL 1.5-5 in diagnosis of developmental delayed infants. *J Korean Acad Child Adolesc Psychiatry*. (2011) 22(2):120–7. doi: 10.5765/JKACAP.2011.22.2.120

34. Ivanova MY, Achenbach TM, Rescorla LA, Harder VS, Ang RP, Bilenberg N, et al. Preschool psychopathology reported by parents in 23 societies: testing the seven-syndrome model of the child behavior checklist for ages 1.5-5. *J Am Acad Child Adolesc Psychiatry*. (2010) 49(12):1215–24. doi: 10.1016/j.jaac.2010.08.019

35. Godbout R, Martello E. *HIBOU: échelle de dépistage des troubles de sommeil pédiatriques [BEARS sleep screening tool]*. Montréal, QC: CIUSSS du Nord-de-l'Île-de-Montréal (2009). 1 p.

36. Owens JA, Dalzell V. Use of the "BEARS" sleep screening tool in a pediatric residents' continuity clinic: a pilot study. *Sleep Med*. (2005) 6(1):63–9. doi: 10.1016/j.sleep.2004.07.015

37. Shahid A, Wilkinson K, Marcu S, Shapiro CM. BEARS sleep screening tool. In: A Shahid, K Wilkinson, S Marcu, CM Shapiro, editors. *STOP, THAT and one hundred other sleep scales*. New-York, NY: Springer New York (2012). p. 59–61. doi: 10.1007/978-1-4419-9893-4_7

38. Mercuro G, Bassareo PP, Mariucci E, Deidda M, Zedda AM, Bonvicini M. Sex differences in congenital heart defects and genetically induced arrhythmias. *J Cardiovasc Med*. (2014) 15(12):855–63. doi: 10.2459/JCM.0b013e32835ec828

39. Marelli A, Gauvreau K, Landzberg M, Jenkins K. Sex differences in mortality in children undergoing congenital heart disease surgery: a United States population-based study. *Circulation*. (2010) 122(11):234–40. doi: 10.1161/circulationaha.109.928325

40. Backholer K, Peters SAE, Bots SH, Peeters A, Huxley RR, Woodward M. Sex differences in the relationship between socioeconomic status and cardiovascular disease: a systematic review and meta-analysis. *J Epidemiol Community Health*. (2017) 71(6):550–7. doi: 10.1136/jech-2016-207890

41. Boyd M. A socioeconomic scale for Canada: measuring occupational Status from the census. *Can Rev Sociol*. (2008) 45(1):51–91. doi: 10.1111/j.1755-618X.2008.00003.x

42. Mussatto KA, Hoffmann RG, Hoffman GM, Tweddell JS, Bear L, Cao Y, et al. Risk and prevalence of developmental delay in young children with congenital heart disease. *Pediatrics*. (2014) 133(3):570–7. doi: 10.1542/peds.2013-2309

43. LaFiosca T, Loyd BH. Defensiveness and the assessment of parental stress and anxiety. *J Clin Child Psychol*. (1986) 15(3):254–9. doi: 10.1207/s15374424jccp1503_9

44. Llewelyn-Williams JL, Oliver AM, Wright KD, Runalls S, Lahti DS, Bradley TJ, et al. Health anxiety and associated constructs in school-age children and adolescents with congenital heart disease and their parents: a children's healthy-heart activity monitoring program in Saskatchewan cohort study. *J Child Health Care*. (2022) 3:13674935221075896. doi: 10.1177/13674935221075896

45. Best KE, Vieira R, Glinianaia SV, Rankin J. Socio-economic inequalities in mortality in children with congenital heart disease: a systematic review and meta-analysis. *Paediat Perinat Epidemiol*. (2019) 33(4):291–309. doi: 10.1111/ppe.12564

46. Karimzadeh M, Rostami M, Teymouri R, Moazzen Z, Tahmasebi S. The association between parental mental health and behavioral disorders in pre-school children. *Electron Physician*. (2017) 25(9):4497–502. doi: 10.19082/4497

47. Brosig CL, Bear L, Allen S, Simpson P, Zhang L, Frommelt M, et al. Neurodevelopmental outcomes at 2 and 4 years in children with congenital heart disease. *Int J Cardiol*. (2018) 13(5):700–5. doi: 10.1111/chd.12632

48. Menahem S, Halasz G. Parental non-compliance, a paediatric dilemma. A medical and psychodynamic perspective. *Child Care Health Dev*. (2000) 26 (1):61–72. doi: 10.1046/j.1365-2214.2000.00115.x

49. Martin CA, Papadopoulos N, Chellew T, Rinehart NJ, Sciberras E. Associations between parenting stress, parent mental health and child sleep problems for children with ADHD and ASD: systematic review. *Res Dev Disabil*. (2019) 93:103463 (published online). doi: 10.1016/j.ridd.2019.103463

50. Mindell JA, Sadeh A, Kwon R, Goh DY. Cross-cultural differences in the sleep of preschool children. *Sleep Med*. (2013) 14(12):1283–9. doi: 10.1016/j.sleep.2013.09.002

51. Sen T, Spruyt K. Pediatric sleep tools: an updated literature review. *Front Psychiatry*. (2020) 11:317. doi: 10.3389/fpsyt.2020.00317

52. Chorney DB, Detweiler MF, Morris TL, Kuhn BR. The interplay of sleep disturbance, anxiety and depression in children. *J Pediatr Psychol*. (2008) 33 (4):339–48. doi: 10.1093/jpepsy/jsm105

53. Bagner DM, Rodríguez GM, Blake CA, Linares D, Carter AS. Assessment of behavioral and emotional problems in infancy: a systematic review. *Clin Child Fam Psychol Rev*. (2012) 15(2):113–28. doi: 10.1007/s10567-012-0110-2

54. Huizink AC, Menting B, De Moor MHM, Verhage ML, Kunseler FC, Schuengel C, et al. From prenatal anxiety to parenting stress: a longitudinal study. *Arch Womens Ment Health*. (2017) 20(5):663–72. doi: 10.1007/s00737-017-0746-5

55. Hartman DM, Medoff-Cooper B. Transition to home after neonatal surgery for congenital heart disease. *MCN Am J Matern Child Nurs*. (2012) 37(2):95–100. doi: 10.1097/NMC.0b013e318241dac1

56. Wong J, Kohari K, Bahtiyar MO, Copel J. Impact of prenatally diagnosed congenital heart defects on outcomes and management. *J Clin Ultrasound*. (2022) 50(5):646–54. doi: 10.1002/jcu.23219

57. Vézina K, Mariasine J, Young R, Reyna M, Lu Z, Subbarao P, et al. Cardiorespiratory monitoring data during sleep in healthy Canadian infants. *Ann Am Thorac Soc*. (2020) 17(10):1238–46. doi: 10.1513/AnnalsATS.201909-703OC

frontiers | Frontiers in Pediatrics

TYPE Original Research
PUBLISHED 06 January 2023
DOI 10.3389/fped.2022.1052063

OPEN ACCESS

EDITED BY
Shikai Yu,
Tongji University, China

REVIEWED BY
Hongwei Ji,
The Affiliated Hospital of Qingdao University, China
Shanquan Chen,
University of Cambridge, United Kingdom

*CORRESPONDENCE
Yi Xing
✉ cyrss@126.com

SPECIALTY SECTION
This article was submitted to Pediatric Cardiology, a section of the journal Frontiers in Pediatrics

RECEIVED 23 September 2022
ACCEPTED 05 December 2022
PUBLISHED 06 January 2023

CITATION
Ma Q, Liu J, Wu Y, Cui M, Chen M, Ma T, Wang X, Gao D, Li Y, Chen L, Ma Y, Zhang Y, Dong Y, Xing Y and Ma J (2023) Association between parental unhealthy behaviors and offspring's cardiovascular health status: Results from a cross-sectional analysis of parent–offspring pairs in China.
Front. Pediatr. 10:1052063.
doi: 10.3389/fped.2022.1052063

Association between parental unhealthy behaviors and offspring's cardiovascular health status: Results from a cross-sectional analysis of parent–offspring pairs in China

Qi Ma[1], Jieyu Liu[1], Yu Wu[2], Mengjie Cui[1], Manman Chen[1], Tao Ma[1], Xinxin Wang[3], Di Gao[1], Yanhui Li[1], Li Chen[1], Ying Ma[1], Yi Zhang[1], Yanhui Dong[1], Yi Xing[1]* and Jun Ma[1]

[1]Institute of Child and Adolescent Health, School of Public Health, Peking University; National Health Commission Key Laboratory of Reproductive Health, Beijing, China, [2]School of Population Medicine and Public Health, Chinese Academy of Medical Sciences/Peking Union Medical College, Beijing, China, [3]School of Public Health and Management, Ningxia Medical University and Key Laboratory of Environmental Factors and Chronic Disease Control, Yinchuan, China

Background: Cardiovascular health (CVH) in children and adolescents, which might be largely influenced by parental behaviors, may affect the incidence of cardiovascular diseases in adulthood. However, few studies have been conducted to explore the associations between parental behaviors and CVH status of offspring in China.

Methods: Data were obtained from a cross-sectional survey conducted in Chinese children and adolescents aged 7–18 years old, with a total of 10,043 parent–offspring pairs included. Parental behaviors included moderate to vigorous physical activity (MVPA), dietary behaviors, and weight status. The CVH status of offspring was consulted by The American Heart Association, including seven factors. The associations between parental behaviors and CVH status of offspring were evaluated by multilevel logistic regression. Stratified analyses were conducted to explore the potential modifying influence of sociodemographic factors.

Results: Most of the offspring had five ideal CVH factors; only 21.04% had six to seven ideal CVH factors. Parental unhealthy behaviors were associated with high odds of nonideal CVH status of offspring. Parental overweight/obesity, insufficient MVPA, and unhealthy dietary behaviors could increase the odds of owning one to three ideal CVH factors in offspring, with corresponding odds ratios (ORs) (95% confidence interval) of 1.61 (1.32–1.96), 1.31 (1.10–1.56), and 2.05 (1.43–2.94), respectively. There was a dose–response relationship between parental single unhealthy behavior and the odds of nonideal CVH status in offspring (P-trend < 0.001). Offspring with overweight parents had ORs of 1.25 for nonideal CVH status, compared to offspring with normal-weight parents. Among offspring who had the same number of ideal CVH factors, the cumulative association between unhealthy behaviors of parents and offspring's nonideal CVH status increased if parents had more unhealthy behaviors (P-trend < 0.001).

Conclusions: Parental overweight/obesity, insufficient MVPA, and unhealthy dietary behaviors were strongly associated with CVH status in offspring. With a cumulative association, more unhealthy parental behaviors were associated with higher odds of offspring's nonideal CVH status, suggesting that targeting parental behaviors might facilitate attainment of improving CVH status of children and adolescents.

KEYWORDS

lifestyle, cardiovascular health, parents, offspring, cross-sectional study

Introduction

Cardiovascular diseases (CVDs) are the leading cause of death around the world (1). In China, more than two in five deaths were attributed to CVDs, accounting for 45.50% and 43.16% of all deaths in rural and urban areas in 2016, which were higher than the death rate due to cancer or other diseases (2). Making efforts to improve cardiovascular health (CVH), the American Heart Association (AHA) introduced a concept of ideal CVH status, including the simultaneous presence of nonsmoking, as well as the ideal level of body mass index (BMI), physical activity, dietary behaviors, total cholesterol (TC), blood pressure (BP), and fasting plasma glucose (FPG) (3).

The ideal CVH construct appears to be a valid measure for predicting the long-term risk of major adverse cardiovascular events (4, 5). Childhood CVH status was a strong predictor for the incidence of adulthood CVDs (6). A cohort study conducted on young Finns showed that increased ideal CVH factors in children were related to lower risks of hypertension, metabolic syndrome, and carotid artery intima-media thickness (7). In order to achieve primary prevention of adulthood CVDs, substantial work must be done to improve the ideal CVH status in children and adolescents.

However, the prevalence of ideal CVH status in children and adolescents had a similar devastating trend in different countries (8, 9). Although most children and adolescents were born with ideal CVH status, their unhealthy dietary behaviors, physical inactivity, and tobacco smoking they developed gradually would largely influence their CVH status (10). It is well known that parental behaviors are crucial to developing children and adolescents' behaviors. Previous studies had shown that parents' diet quality and energy intake, physical activities, and the duration of screen activities were associated with those behaviors of their offspring (11, 12). In addition, the weight status between two generations was correlated according to gene and environmental factors (13, 14). Parental behaviors, therefore, may be greatly associated with the CVH status in children and adolescents.

In the Framingham Heart Study, parental CVH including BMI and nonsmoking status was positively associated with offspring's CVH status (15). Worse maternal BMI at gestation was significantly associated with worse offspring's CVH status in early adolescence (16). However, since multiple parental factors are reciprocally interacting, few studies explored the associations between the combined behaviors of parents including physical activity, dietary behaviors, and weight status, with the CVH status in Chinese children and adolescents. We hypothesize that parental unhealthy behaviors might increase the likelihoods of offspring's nonideal CVH status, and the odds may continue to increase when parents with more unhealthy behaviors increase. To fill these knowledge gaps and improve the grim situation about CVDs in China, based on large and nationally representative data, we aim to explore the associations between parental behaviors and offspring's CVH status.

Materials and methods

Study design and participants chosen

This is a reanalysis from a previous database, which was collected from a national cross-sectional study from seven Chinese provinces in 2013. More detailed information about this study was presented previously (17). Briefly, we used multistage cluster random sampling to choose participants in seven provinces including Liaoning, Tianjin, Ningxia, Shanghai, Chongqing, Hunan, and Guangdong, which include four differently economic and geographic regions of the mainland of China. A developed and an underdevelopment city were selected in each province at the beginning. Then, 12–16 schools were randomly selected in these cities. Two classes in each grade from each school were randomly chosen subsequently, and their parents were also invited to engage in this survey. A total of 65,347 children and adolescents were included in the study. We selected 15,735 children and adolescents aged 7–18 years old randomly for blood sample examination; those who did not live with their parents or those with missing data on anthropometric measurement, parental questionnaires, and dietary behaviors were excluded. A total of 10,043 parent–offspring pairs were remained in the final analysis (**Figure 1**).

All survey sites used the same protocol during the implementation process, and all processes of randomization were performed by a staff who was not involved in the survey.

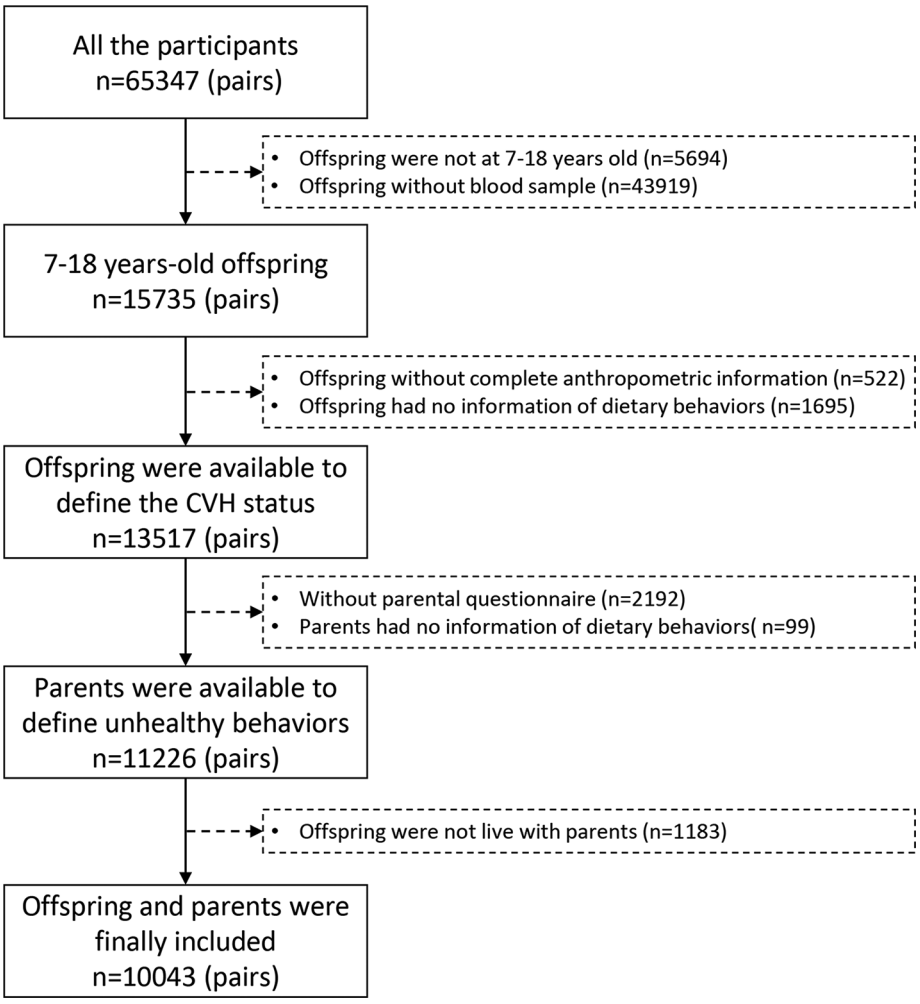


FIGURE 1
Selection process of the participants. CVH, cardiovascular health

This study was approved by the Medical Ethical Committee of Peking University (IRB No. 00001052-12072). All included students and their parents signed the written informed consents.

Data collection in questionnaire

The childhood questionnaire was used to collect information about sex, age, residence area, inhabiting information, smoking, moderate to vigorous physical activity (MVPA), and dietary behaviors. The parental questionnaire was distributed to collect information including the primary respondent of this questionnaire, offspring's birth weight, single-child status, breastfeeding status, parental self-reported height and weight, highest educational attainment, MVPA, dietary behaviors, and family history of chronic diseases. For birth weight classification, low birth weight and high birth weight were defined as weight <2,500 and ≥4,000 g at delivery, respectively (18). All other information collected in the questionnaire is presented in **Supplementary Tables S1, S2**.

The frequency (days) and amount (serving per day) were investigated for dietary behaviors, including the total consumption of vegetables, fruits, sugar-sweetened beverages (SSBs), and meat over the past 7 days. One serving of vegetables/fruits was defined as the size of an ordinary adult's closed fist with roughly 200 g (19); one serving of SSBs was determined as a canned beverage (approximately 250 ml), including orange juice, Nutrition Express, Red Bull, Coca-Cola, and Sprite (20); one portion of meat equaled the size of an adult's palm (approximately 100 g) (21). We calculated the daily dietary intake as (days of consumption × servings in those days)/7. In addition, the frequency (times) over the past 7 days was investigated for fried foods. As set in questionnaires, fried food consumption referred to fried chicken, deep-fried dough sticks, and other common fried foods.

The self-administered child questionnaires were delivered to students (except grades 1–3) in a class meeting by the trained school teacher. Child questionnaires of children grades 1–3 and parental questionnaires were filled by students' fathers or mothers. Trained project members provided appropriate guidance and interpreted all the questions as effectively as possible. Three percent of the questionnaires were rechecked within 1 week for the same participants.

Anthropometric measurements

Anthropometric measurements were conducted to measure the height, weight, and BP of children by trained investigators in schools, according to the principles described in the Chinese Students' Physical Fitness and Health Survey Report 2010 (22). Children were asked to stand straight in light clothing and without shoes. Height was measured using the portable stadiometer with 0.1 cm precision, and weight was measured to the nearest 0.1 kg by a Lever-type might scale. BP was measured in the right arm by a Riva-Rocci sphygmomanometer. Every indicator was measured twice, and the average of the two measurements was used for final analyses. BMI was calculated as the weight (kg) divided by the square of the height (m^2).

Blood sample collection and detection

After overnight fasting for 8–12 h, 5 ml venous blood samples were collected for each child or adolescent into Ethylene Diamine Tetraacetic Acid (EDTA) vacuum tubes. Children were asked to rest for at least 10 min before blood sample collection. Blood specimens were transported in a chilled insulated container immediately, centrifuged at 3,000 rpm for 10 min, and then frozen at −80 °C before transported in dry ice to the laboratory in Beijing, where the samples were stored at −80 °C before laboratory detection. Blood tests were performed by an autoanalyzer (Hitachi 7080, Japan). FPG and TC were tested using the glucose oxidase method, enzymatic method, and clearance method. All biochemical analyses on blood were carried out at a biomedical analyses company, which is accredited by Peking University (17).

Definition of ideal CVH of offspring

CVH status of offspring included smoking status, BMI, MVPA, dietary behaviors, BP, FPG, and TC. According to Chinese standards for overweight/obesity (23) and BP (24), The Chinese Dietary Guideline (2016) (25), and AHA (3), we defined the ideal CVH factors as follows (**Supplementary Table S3**). Children and adolescents meeting 6–7 ideal CVH factors were defined as having ideal CVH status (26), and others were defined as having nonideal CVH status. Participants of nonideal CVH status were divided into three groups according to the numbers of ideal CVH factors they had: 1–3 ideal CVH factors, 4 ideal CVH factors, and 5 ideal CVH factors.

Definition of unhealthy behaviors of parents

Unhealthy behaviors for parents included unhealthy dietary behaviors, insufficient MVPA, and overweight/obesity defined by BMI. All the information about behaviors represented one side of the parents who filled the questionnaire. Parental unhealthy dietary behaviors was determined as <4 healthy dietary factors (the factors was the same to children); insufficient MVPA referred to <150 min/week according to Physical Activity Guidelines for the Chinese Population (2021) (27) and AHA (3); overweight was defined as BMI ≥ 24 and BMI < 28 kg/m^2, and obesity was defined as BMI ≥ 28 kg/m^2 according to the criteria established by the Working Group on Obesity in China (28). The combined unhealthy behaviors of parents were defined by summing the number of single unhealthy behavior.

Statistical analysis

Descriptive analyses were used to present the basic information of the offspring and parents. Differences by sex were examined using Student's t-test for continuous variables and Pearson's χ^2 test for categorical variables.

We used a multilevel logistic regression model to eliminate the effects of province-cluster confounders, with provinces set as a random factor in the model. All the outcomes were treated as disordered, not satisfying the test of parallel lines. To explore the association between different unhealthy behaviors of parents and nonideal CVH status of offspring, parental single behavior was examined as two levels (healthy and unhealthy) and the CVH status of offspring was examined as a multiple-category outcome (had 1–3, 4, 5, and 6–7 ideal CVH factors), using pairwise regression. To assess the dose–response association between single unhealthy behavior of parents and offspring's nonideal CVH status, we examined the single unhealthy behavior of parents as multiple-category outcomes and CVH status of offspring as two variable categories (ideal CVH status and nonideal status, respectively). We also derived a score of parental combined unhealthy behaviors by summing the number of single unhealthy behavior and

evaluated the cumulative association between parental combined unhealthy behaviors and offspring's nonideal CVH status. To assess the influence of sociodemographic factors on the associations between parental unhealthy behaviors and offspring's CVH status, stratified analyses were additionally conducted. *P* for trend values were calculated by including the median of each category of single/combined unhealthy behavior of parents as a continuous variable in the model; the interactions between parental unhealthy behaviors and sociodemographic factors were examined using the likelihood ratio test, with a comparison of the log likelihood of the two models with and without the interaction terms. All the models were adjusted for confounders including provinces, family history of chronic diseases, family monthly income, offspring's age, sex, residence area, birth weight, single-child status, breastfeeding, and parental highest educational attainment. Odds ratio (ORs) and 95% confidence interval (95% CI) were calculated and represented.

The number of each missing variable was approximately 30–884, less than 9% of the total participants (**Supplementary Table S4**). We used linear interpolation and median to refill the missing data of continuous and categorical variables *via* the section of Replace Missing Values in SPSS 25.0. To overcome potential limitations, two separate sensitivity analyses were also conducted: (1) all the incomplete data were excluded to evaluate the bias that the refilling method may have; (2) participants with parental BMI < 18.5 kg/m^2 [which was defined as thinness (28)] was excluded.

All analyses were performed using IBM SPSS Statistics software (version 25.0, SPSS, IBM, Armonk, NY, United States). A two-sided *P*-value <0.05 was considered statistically significant.

Result

Baseline characteristics

Table 1 shows the basic characteristics of 10,043 parent–offspring pairs included in the present study. Offspring were 11.22 years old on average, and 44.69% of them were boys. Most of them had five ideal CVH factors, and only 21.04% had six to seven ideal CVH factors. Among all the CVH factors, healthy dietary behaviors accounted for the lowest proportion (9.06%), while nonsmoking status accounted for the highest proportion (98.91%), which was more evident in girls ($P < 0.001$). Of their parents, more than 50% had the educational attainment of senior high school or above, 47.60% of them had two unhealthy behaviors and only 3.46% had completely combined healthy behaviors.

Epidemiology of single behavior of parents and CVH status of offspring

With the increase of parents' BMI, the decrease of MVPA time, and the number of healthy dietary factors, the percentages of offspring with one to three and four ideal CVH factors increased, and the percentages of six to seven ideal CVH factors decreased (**Figure 2** and **Supplementary Table S5**).

Association between single unhealthy behavior of parents and offspring's nonideal CVH status

Table 2 presents the associations between single unhealthy behavior of parents and offspring's nonideal CVH status. Parental overweight/obesity, insufficient MVPA, and unhealthy dietary behaviors were associated with higher odds of offspring's nonideal CVH status. Parental overweight/obesity, insufficient MVPA, and unhealthy dietary behaviors could increase the odds of owning one to three ideal CVH factors in offspring, with corresponding ORs (95% CI) of 1.61 (1.32–1.96), 1.31 (1.10–1.56), and 2.05 (1.43–2.94).

Figure 3 presents a dose–response relationship between single unhealthy behavior of parents and the odds of nonideal CVH status of offspring (all the *P*-trend < 0.001). Offspring with overweight parents had 25% higher odds (OR = 1.25, 95% CI = 1.10–1.43) for nonideal CVH status compared to offspring whose parents had a normal weight. Parental unhealthy dietary behaviors could increase the odds of offspring's nonideal CVH status by 52% (OR = 1.52, 95%CI = 1.28–1.8) and 65% (OR = 1.65, 95%CI = 1.03–2.65).

Association between combined unhealthy behaviors of parents and offspring's nonideal CVH status

The ORs in different groups of offspring's nonideal CVH status stratified by the number of parental unhealthy behaviors are presented in **Figure 4** and **Supplementary Table S6**. The odds of nonideal CVH status in offspring with parents who had combined unhealthy behaviors were higher than those whose parents had completely healthy behaviors. Among offspring in the same group of nonideal CVH status, the odds of nonideal CVH status in offspring would increase if the number of parental unhealthy behaviors increased (all the *P*-trend < 0.001). For example, compared to offspring with parents who had completely healthy behaviors, offspring with parents who had three, two, and one unhealthy behavior had ORs (95% CI) of 3.13

10.3389/fped.2022.1052063

TABLE 1 Descriptive characteristics of the study population stratified by sex.

Variable	Total	Boys	Girls	*P*-value
Provinces, No. (%)				
Hunan	757 (7.54)	397 (8.04)	360 (7.05)	0.086
Ningxia	827 (8.23)	380 (7.70)	447 (8.76)	
Tianjin	2,050 (20.41)	1,005 (20.35)	1,045 (20.47)	
Chongqing	1,215 (12.10)	592 (11.99)	623 (12.20)	
Liaoning	1,600 (15.93)	777 (15.74)	823 (16.12)	
Shanghai	1,769 (17.61)	908 (18.39)	861 (16.87)	
Guangzhou	1,825 (18.17)	879 (17.80)	946 (18.53)	
Residence area, No. (%)				
Urban	5,564 (55.40)	2,273 (55.14)	2,841 (55.65)	0.609
Rural	4,479 (44.60)	2,215 (44.86)	2,264 (44.35)	
Family history of chronic diseases, No. (%)				
No	3,594 (35.79)	1,828 (37.02)	1,766 (34.59)	0.011
Yes	6,449 (64.21)	3,110 (62.98)	3,339 (65.41)	
Family monthly income (RMB), No. (%)				
<12,000	6,085 (60.59)	2,956 (59.86)	3,129 (61.29)	0.199
≥12,000	900 (8.96)	437 (8.85)	463 (9.07)	
Do not know/missing data	3,058 (30.45)	1,545 (31.29)	1,513 (29.64)	
Offspring characteristics				
Age, mean ± SD	11.22 ± 3.11	11.12 ± 3.08	11.32 ± 3.14	0.002
Breastfeeding, No. (%)				
Yes	8,646 (86.09)	4,229 (85.64)	4,417 (86.52)	0.202
No	1,397 (13.91)	709 (14.36)	688 (13.48)	
Birth weight (g), No. (%)				
<2,500	169 (1.68)	78 (1.58)	91 (1.78)	<0.001
2,500–4,000	8,083 (80.48)	3,851 (77.99)	4,232 (82.90)	
≥4,000	1,791 (17.83)	1,009 (20.43)	782 (15.32)	
Single children, No. (%)				
Yes	6,851 (68.22)	3,553 (71.95)	3,298 (64.60)	<0.001
No	3,192 (31.78)	1,385 (28.05)	1,807 (35.40)	
BMI, mean ± SD	18.84 ± 3.93	19.16 ± 4.15	18.54 ± 3.68	<0.001
Number of healthy dietary factors, No. (%)				
0–3	9,133 (90.94)	4,510 (91.33)	4,623 (90.56)	0.177
4–5	910 (9.06)	428 (8.67)	482 (9.44)	
Smoking status, No. (%)				
Smoking in past 30 days	109 (1.09)	73 (1.48)	36 (0.71)	<0.001

(*continued*)

TABLE 1 Continued

Variable	Total	Boys	Girls	*P*-value
Nonsmoking in past 30 days	9,934 (98.91)	4,865 (98.52)	5,069 (99.29)	
MVPA (min/day), No. (%)				
<60	6,880 (68.51)	3,141 (63.61)	3,739 (73.24)	<0.001
≥60	3,163 (31.49)	1,797 (36.39)	1,366 (26.76)	
TC (mmol/L), No. (%)				
≥5.17	557 (5.55)	249 (5.04)	308 (6.03)	0.030
<5.17	9,486 (94.45)	4,689 (94.96)	4,797 (93.97)	
FPG (mmol/L), No. (%)				
≥5.60	213 (2.12)	152 (3.08)	61 (1.19)	<0.001
<5.60	9,830 (97.88)	4,786 (96.92)	5,044 (98.81)	
BP, No. (%)				
High	2,466 (24.55)	1,378 (27.91)	1,088 (21.31)	<0.001
Normal	7,577 (75.45)	3,560 (72.09)	4,017 (78.69)	
Weight status, No. (%)				
Overweight/obesity	2,555 (25.44)	1,537 (31.13)	1,018 (19.94)	<0.001
Normal	7,488 (74.56)	3,401 (68.87)	4,087 (80.06)	
Number of ideal CVH factors, No. (%)				
1–3	775 (7.72)	471 (9.54)	304 (5.95)	<0.001
4	2,525 (25.14)	1,321 (26.75)	1,204 (23.58)	
5	4,630 (46.10)	2,102 (42.57)	2,528 (49.52)	
6–7	2,113 (21.04)	1,044 (21.14)	1,069 (20.94)	
Parental characteristics				
Parental highest educational attainment, No. (%)				
Junior high school or below	4,666 (46.46)	2,311 (46.80)	2,355 (46.13)	0.502
Senior high school or above	5,377 (53.54)	2,627 (53.20)	2,750 (53.87)	
Unhealthy behaviors, No. (%)				
0	347 (3.46)	167 (3.38)	180 (3.53)	0.466
1	3,881 (38.64)	1,947 (39.43)	1,934 (37.88)	
2	4,780 (47.60)	2,321 (47.00)	2,321 (47.00)	
3	1,035 (10.31)	503 (10.19)	503 (10.19)	

SD, standard deviation; BMI, body mass index; MVPA, moderate to vigorous physical activity; TC, total cholesterol; FPG, fasting plasma glucose; BP, blood pressure; CVH, cardiovascular health.
P-value was calculated by T-test for continuous variables and by Pearson's chi-squared test for categorical variables.

(2.16–4.53), 2.20 (1.59–3.05), and 1.65 (1.19–2.29), respectively, for owning four ideal CVH factors.

Notably, the associations between parental combined unhealthy behaviors and offspring's nonideal CVH status did not change stratified by sociodemographic factors (**Supplementary Table S7**).

Sensitivity analysis

Associations between parental unhealthy behaviors and offspring's nonideal CVH status were robust in all sensitivity analyses, including the following: (1) all the incomplete data were excluded (**Supplementary Tables S8–S10**); (2)

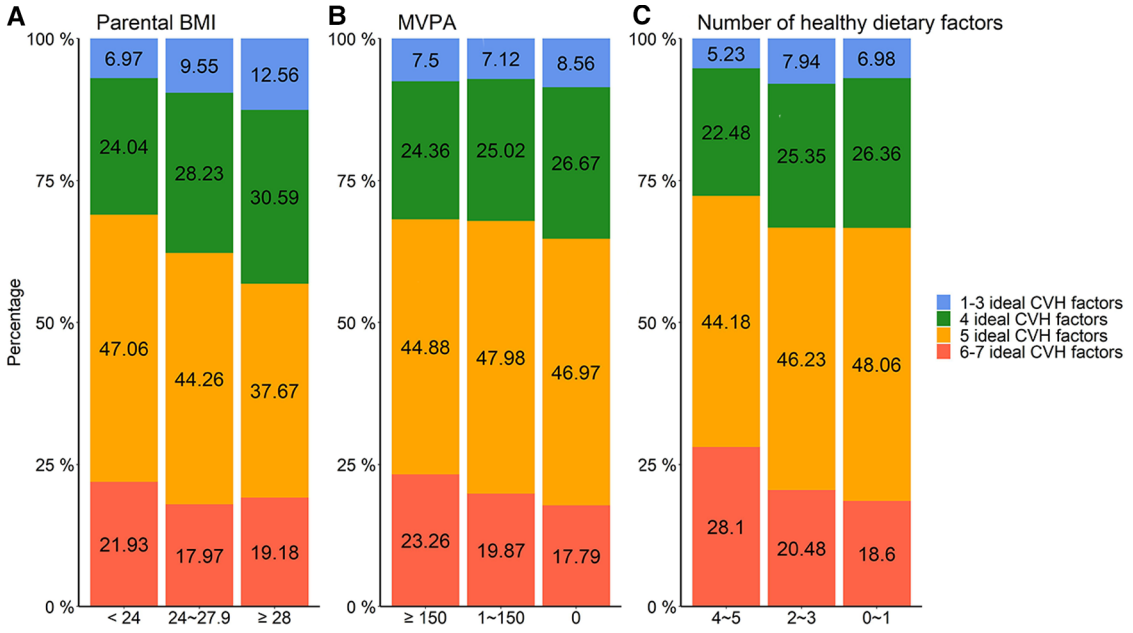


FIGURE 2
Distribution of participants in different CVH status according to parental behaviors: (A) parental BMI, (B) MVPA, and (C) number of healthy dietary factors. CVH, cardiovascular health; BMI, body mass index; MVPA, moderate to vigorous physical activity.

TABLE 2 Association between single unhealthy behavior of parents and offspring's different groups of nonideal CVH status.

Parental unhealthy behaviors	1–3 ideal CVH factors, OR (95% CI)	4 ideal CVH factors, OR (95% CI)	5 ideal CVH factors, OR (95% CI)	6–7 ideal CVH factors, OR (95% CI)
Parental overweight/obesity (vs. normal weight)	**1.61(1.32–1.96)**	**1.41 (1.22–1.62)**	1.11 (0.97–1.26)	1 (Reference)
Insufficient MVPA (vs. sufficient)	**1.31 (1.10–1.56)**	**1.33 (1.18–1.50)**	**1.29 (1.16–1.44)**	1 (Reference)
Unhealthy dietary behaviors (vs. healthy)	**2.05 (1.43–2.94)**	**1.57 (1.27–1.95)**	**1.42 (1.18–1.70)**	1 (Reference)

A multilevel logistic regression model was used, with pairwise regression, respectively. Data adjusted for provinces, family history of chronic diseases, family monthly income, offspring's sex, age, resident area, birth weight, single-child status, breast feeding status, and parental highest education attainment.
CVH, cardiovascular health; MVPA, moderate to vigorous physical activity; OR, odds ratio; CI, confidence interval.
The bold values indicated the ORs were statistically significant.

participants with parental BMI < 18.5 kg/m^2 were excluded (**Supplementary Tables S11–S13**).

Discussion

To our knowledge, parental unhealthy behaviors play a crucial role in the offspring's CVH status in China. Parental overweight/obesity, insufficient MVPA, and unhealthy dietary behaviors were independently strongly associated with nonideal CVH status of offspring, with dose–response associations presented in all behaviors. We also found that the odds of nonideal CVH status of offspring continued to increase as the number of parental unhealthy behaviors increased. Our study emphasized the importance of family-focused community-based prevention programs, proposing that parental behaviors should receive more attention in childhood obesity prevention policies.

In the present study, considering parental behaviors as part of factors of CVH, both single and combined unhealthy behaviors of parents were associated with nonideal CVH status in offspring. One previous study indicated that worse maternal CVH status (included five factors excepted dietary behaviors and MVPA) at gestation was significantly associated with offspring's worse CVH status in early adolescence (16), and a strong correlation between CVH factors of parents and their offspring was also found when they were at similar ages (15). In the present study, we extended the contents of

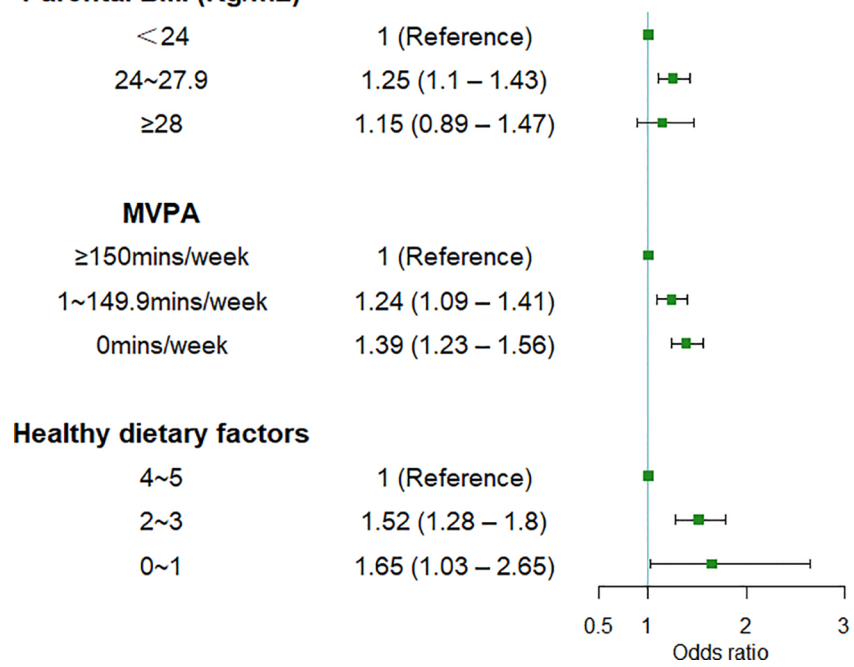


FIGURE 3
Association between different levels of single behavior of parents and offspring's nonideal CVH status. Error bar was 95% CI. Multilevel logistic regression was used, and CVH status was defined as nonideal status or ideal CVH status. Data adjusted for provinces, resident area, family history of chronic diseases, family monthly income, offspring's sex, age, birth weight, single-child status, breast feeding status, and parental highest education attainment. CVH, cardiovascular health; BMI, body mass index; MVPA, moderate to vigorous physical activity; OR, odds ratio; CI, confidence interval.

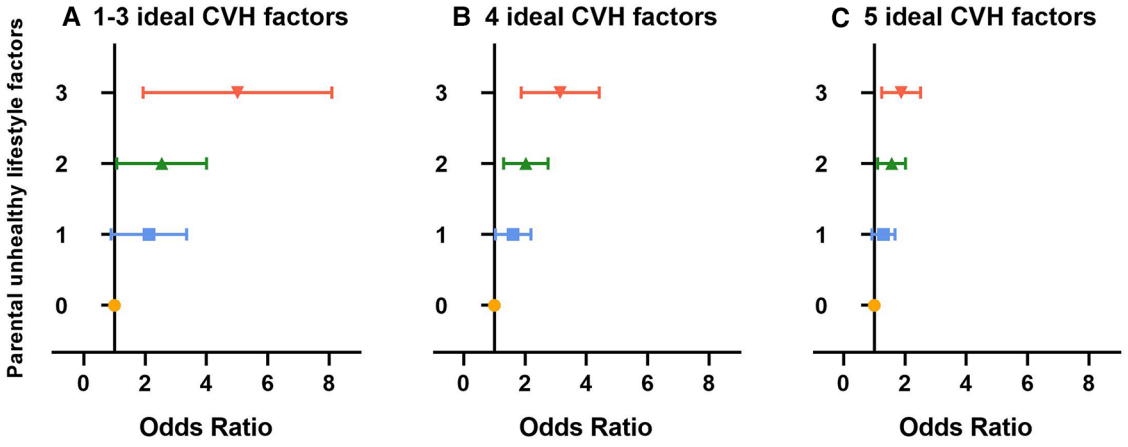


FIGURE 4
Association between combined unhealthy behaviors of parents and offspring's different groups of nonideal CVH status: (A) 1-3 ideal CVH factors, (B) 4 ideal CVH factors, (C) 5 ideal CVH factors. Error bar was 95% CI. The combined behaviors of parents were examined as riable (vs. ideal CVH status). Data adjusted for provinces, resident area, family history of chronic diseases, family monthly incng's sex, age, birth weight, single-child status, breast feeding status, and parental highest education attainment. CVH, cardiovascular health.

offspring's CVH status, and only three kinds of behaviors (overweight/obesity, MVPA, and dietary behaviors) for parental CVH status were selected. Thus, the present study paid more attention on the associations between modifiable behaviors of parents and offspring's CVH status. Muchira et al. analyzed the association between parental CVH factors and time to onset of CVDs in the offspring and found that offspring would have a longer CVD-free survival if their parents had ideal CVH status (26). Considering one's ideal CVH status could predict his risk of major CVDs in the future and affect the CVH status of his offspring (4, 5), our study may provide new evidence from parental CVH status to offspring's future CVDs. However, we did not detect significant differences in associations between parental combined unhealthy behaviors and offspring's CVH status when stratified by sociodemographic characteristics, and more research studies are urgently needed to verify our conclusions.

The close relationships of multiple lifestyle behaviors between two generations are the potential explanation of the findings. It was well acknowledged that the diet quality and energy intake of parents and their offspring were closely associated in the family (11), same as the pattern of physical activities (12). In addition, parental BMI was a predictor for offspring BMI, exactly as the genetic and environmental factors explicated (13, 29, 30). Family habits contribute the most in modeling children's lifestyle behaviors as they represent an important moment of parent–child interaction (31), which could also explain the dose–response/cumulative association between single/combined unhealthy behaviors of parents and nonideal CVH status of offspring. In detail, mothers, who were preoccupied with their own weight and eating habit, reported higher levels of encouraging their daughters to lose weight thus leading to daughters' restrained eating habits (32). Parental behaviors may have a broad and long-term influence on offspring's CVH status (33); the underlying potential mechanism might be attributed to the following reasons. Offspring loaded heavily on fried foods, SSBs, and refined grain had increased risks of impaired glucose tolerance, dyslipidemia, and hypertension (34, 35); the total blood volume increases with increasing BMI through central (renin-angiotensin and sympathetic systems) and peripheral (e.g., baroreceptors and autonomic dysregulation) mechanisms (36); and insufficient MVPA might disrupt the lipid metabolism through inactivating the lipoprotein lipase and preventing C-reactive protein reduction (37). Thus, although dietary behaviors, MVPA, and weight status of offspring could be influenced by parental behaviors directly, changes in these behaviors with the passage of time could disturb the body homeostasis and result in abnormal BP, TC, and FPG (38–40). In addition, overweight and obesity have long been recognized as key indicators for cardiovascular diseases (41). The potential abnormal metabolic and cardiovascular indicators could pass down to offspring through epigenetic pathways if parents have been at overweight/obesity status for a long period (42, 43). Although phenotype was based on the heritability, there are differences between family-cluster phenotype and heritability owing to the interaction of gene and environment (44). For instance, frequent physical activity could mitigate the impact of genetic factors on the development of high BMI and waist circumference (45); and the specific contents of CVH status between two generations were different owing to the environment (15). Family-targeted improvement strategies should, therefore, be included to promote their offspring's CVH status, and comprehensive interventions should be considered and encouraged at family's dimensions.

Our study has practical values for public health. Since parental behaviors are modifiable and they are major contributors to ideal CVH status, only 15% of ideal CVH status is heritable (15). Parental healthy behaviors play a prominent part in the improving the CVH status of offspring under the context of Chinese culture of valuing family connections and supervision. We emphasize that even mild improvements of parental behaviors will benefit their offspring's CVH status in the context of the dose–response relationship. In addition, as previously described (16), both single and combined unhealthy behaviors of parents would influence offspring's nonideal CVH status, public service should encourage all parents to improve their healthy behaviors rather than only focus on those parents whose offspring had worse CVH status, and the whole family should be encouraged to be involved in the educational interventions to prevent unhealthy behaviors in children and adolescents.

The strength of the present study was the large sample size collected from seven Chinese provinces including all the economic and geographic regions, which made our findings be generalized to all Chinese school-age population. In addition, we used high-quality CVH factor measurements for offspring, including standardized protocols and repeated operations for anthropometric and BP measurements, as well as professional blood sample detection. In addition, we conducted multiple analyses for both parental unhealthy behaviors and offspring's CVH status, making the results become more reliable. However, several limitations should be mentioned. First, information during pregnancy was absent, including maternal disease and prenatal care, which limited us to make further inferences. Second, the self-reported physical activity, parental height, and weight might not be as accurate as measured directly. However, self-reported physical activity has been proved to be useful in large epidemiological studies (46), and self-reported height and weight in adults were demonstrated to be highly reliable (47, 48). Third, potential selection bias might influence the results, but we adjusted for socioeconomic and sociodemographic variables in order to avoid the possible deviations to a large extent. In addition, we collected only one side of the parents' behaviors, and thus

whether maternal or paternal behaviors were more important on offspring CVH status could not be speculated. Finally, we only examined the associations between some of the parental behaviors (overweight/obesity, MVPA, and dietary behaviors) and offspring's CVH status but did not include parental smoking status due to the limited information of the database. Prospective research studies examining more comprehensive behaviors' regulations on such parent–offspring associations are still needed.

Conclusion

Parental overweight/obesity, insufficient MVPA, and unhealthy dietary behaviors were strongly associated with offspring's nonideal CVH status, with dose–response associations. In addition, more unhealthy parental behaviors are associated with higher risks of childhood nonideal CVH status. Targets to improve parental lifestyle behaviors might facilitate the attainment of improving CVH status of offspring, and the whole family should be encouraged to be involved in the educational interventions to benefit to their offspring's lifelong cardiovascular health.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Medical Ethical Committee of Peking University (IRB No. 00001052-12072). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

All authors contributed to conceiving and designing this study. QM and JL performed the data analysis. QM, MCu, MCh, TM, XW, DG, and YL interpreted, wrote, and finalized the manuscript. YW revised the manuscript. LC, YM, YZ, YD, YX, and JM participated in reviewing the manuscript. All authors contributed to the article and approved the submitted version.

Funding

This study was funded by the National Natural Science Foundation of China (grant 91846302) awarded to YX, the Research Special Fund for Public Welfare Industry of Health (201202010) awarded to JM, and the National Key R&D Program of China (2016YFA0501604) awarded to YX.

Acknowledgments

The authors are grateful to all children and their parents who participated in the study and all the staff involved in the study for data collection and measurements.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2022.1052063/full#supplementary-material.

References

1. WHO. Cardiovascular diseases (CVDs), 11 June 2021. Available from: https://www.who.int/zh/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds) (accessed January 3, 2022)

2. Ma LY, Chen WW, Gao RL, Liu LS, Zhu ML, Wang YJ, et al. China cardiovascular diseases report 2018: an updated summary. *J Geriatr Cardiol.* (2020) 17(1):1–8. doi: 10.11909/j.issn.1671-5411.2020.01.001

3. Lloyd-Jones DM, Hong Y, Labarthe D, Mozaffarian D, Appel LJ, Van Horn L, et al. Defining and setting national goals for cardiovascular health promotion and disease reduction: the American Heart Association's Strategic Impact Goal through 2020 and beyond. *Circulation*. (2010) 121(4):586–613. doi: 10.1161/CIRCULATIONAHA.109.192703

4. Nguyen ATH, Saeed A, Bambs CE, Swanson J, Emechebe N, Mansuri F, et al. Usefulness of the American Heart Association's ideal cardiovascular health measure to predict long-term major adverse cardiovascular events (from the heart SCORE study). *Am J Cardiol*. (2021) 138:20–5. doi: 10.1016/j.amjcard.2020.10.019

5. Berenson GS, Srinivasan SR, Bao W, Newman WP, Tracy RE, Wattigney WA. Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults. *N Engl J Med*. (1998) 338(23):1650–6. doi: 10.1056/NEJM199806043382302

6. Li S, Chen W, Srinivasan SR, Bond MG, Tang R, Urbina EM, et al. Childhood cardiovascular risk factors and carotid vascular changes in adulthood: the Bogalusa Heart Study. *JAMA*. (2003) 290(17):2271–6. doi: 10.1001/jama.290.17.2271

7. Raitakari OT, Juonala M, Kähönen M, Taittonen L, Laitinen T, Mäki-Torkko N, et al. Cardiovascular risk factors in childhood and carotid artery intima-media thickness in adulthood: the Cardiovascular Risk in Young Finns Study. *JAMA*. (2003) 290(17):2277–83. doi: 10.1001/jama.290.17.2277

8. Dong H, Yan Y, Liu J, Zhao X, Cheng H, Hou D, et al. Alarming trends in ideal cardiovascular health among children and adolescents in Beijing, China, 2004 to 2014. *Int J Cardiol*. (2017) 231:264–70. doi: 10.1016/j.ijcard.2016.12.027

9. Shay CM, Ning H, Daniels SR, Rooks CR, Gidding SS, Lloyd-Jones DM. Status of cardiovascular health in US adolescents: prevalence estimates from the National Health and Nutrition Examination Surveys (NHANES) 2005–2010. *Circulation*. (2013) 127(13):1369–76. doi: 10.1161/CIRCULATIONAHA.113.001559

10. Abrignani MG, Lucà F, Favilli S, Benvenuto M, Rao CM, Di Fusco SA, et al. Lifestyles and cardiovascular prevention in childhood and adolescence. *Pediatr Cardiol*. (2019) 40(6):1113–25. doi: 10.1007/s00246-019-02152-w

11. Robson SM, Couch SC, Peugh JL, Glanz K, Zhou C, Sallis JF, et al. Parent diet quality and energy intake are related to child diet quality and energy intake. *J Acad Nutr Diet*. (2016) 116(6):984–90. doi: 10.1016/j.jand.2016.02.011

12. Xu H, Wen LM, Rissel C. Associations of parental influences with physical activity and screen time among young children: a systematic review. *J Obes*. (2015) 2015:546925. doi: 10.1155/2015/546925

13. Næss M, Holmen TL, Langaas M, Bjørngaard JH, Kvaløy K. Intergenerational transmission of overweight and obesity from parents to their adolescent offspring—the HUNT study. *PLoS One*. (2016) 11(11):e0166585. doi: 10.1371/journal.pone.0166585

14. Bahreynian M, Qorbani M, Khaniabadi BM, Motlagh ME, Safari O, Asayesh H, et al. Association between obesity and parental weight status in children and adolescents. *J Clin Res Pediatr Endocrinol*. (2017) 9(2):111–7. doi: 10.4274/jcrpe.3790

15. Muchira JM, Gona PN, Mogos MF, Stuart-Shor E, Leveille SG, Piano MR, et al. Temporal trends and familial clustering of ideal cardiovascular health in parents and offspring over the life course: an investigation using the Framingham Heart Study. *J Am Heart Assoc*. (2020) 9(12):e016292-e. doi: 10.1161/JAHA.120.016292

16. Perak AM, Lancki N, Kuang A, Labarthe DR, Allen NB, Shah SH, et al. Associations of maternal cardiovascular health in pregnancy with offspring cardiovascular health in early adolescence. *JAMA*. (2021) 325(7):658–68. doi: 10.1001/jama.2021.0247

17. Chen Y, Ma L, Ma Y, Wang H, Luo J, Zhang X, et al. A national school-based health lifestyles interventions among Chinese children and adolescents against obesity: rationale, design and methodology of a randomized controlled trial in China. *BMC Public Health*. (2015) 15:210. doi: 10.1186/s12889-015-1516-9

18. Yuan ZP, Yang M, Liang L, Fu JF, Xiong F, Liu GL, et al. Possible role of birth weight on general and central obesity in Chinese children and adolescents: a cross-sectional study. *Ann Epidemiol*. (2015) 25(10):748–52. doi: 10.1016/j.annepidem.2015.05.011

19. Liu J, Li Y, Wang X, Gao D, Chen L, Chen M, et al. Association between fruit consumption and lipid profile among children and adolescents: a national cross-sectional study in China. *Nutrients*. (2021) 14(1):63. doi: 10.3390/nu14010063

20. Gui ZH, Zhu YN, Cai L, Sun FH, Ma YH, Jing J, et al. Sugar-sweetened beverage consumption and risks of obesity and hypertension in Chinese children and adolescents: a national cross-sectional analysis. *Nutrients*. (2017) 9(12):1302. doi: 10.3390/nu9121302

21. Hicks TM, Knowles SO, Farouk MM. Global provisioning of red meat for flexitarian diets. *Front Nutr*. (2018) 5:50. doi: 10.3389/fnut.2018.00050

22. Group CSPaHR. *Chinese students' physical fitness and health research report 2010*. Beijing: High Education Publication (2015).

23. China NHCotPsRo. *Screening for overweight and obesity among school-age children and adolescents*. Beijing (2018).

24. Commission CNH. *Reference of screening for elevated blood pressure among children and adolescents aged 7–18 years*. Report no. WS/T610-2018. Beijing: National Health Commission of the People's Republic of China (2018). p. 4–6 http://www.nhc.gov.cn/wjw/pqt/201807/6cee88c1d050493ab50a411a2978f901.shtml (accessed January 10, 2022)

25. The Chinese Dietary Guidelines (2016). Available from: http://dg.cnsoc.org/article/2016b.html (accessed January 3, 2022)

26. Muchira JM, Gona PN, Mogos MF, Stuart-Shor E, Leveille SG, Piano MR, et al. Parental cardiovascular health predicts time to onset of cardiovascular disease in offspring. *Eur J Prev Cardiol*. (2022) 29(6):883–91. doi: 10.1093/eurjpc/zwaa072

27. Physical activity guidelines for Chinese population (2021). Chinese CDC (2022). Available from: https://www.chinanutri.cn/yyjkzxpt/yyjkkpzx/hdjl/202201/t20220104_255480.html (accessed January 5, 2022)

28. Zhou BF. Effect of body mass index on all-cause mortality and incidence of cardiovascular diseases—report for meta-analysis of prospective studies open optimal cut-off points of body mass index in Chinese adults. *Biomed Environ Sci*. (2002) 15(3):245–52. PMID: 12500665

29. Jääskeläinen A, Pussinen J, Nuutinen O, Schwab U, Pirkola J, Kolehmainen M, et al. Intergenerational transmission of overweight among Finnish adolescents and their parents: a 16-year follow-up study. *Int J Obes (Lond)*. (2011) 35(10):1289–94. doi: 10.1038/ijo.2011.150

30. Ma L, Ding Y, Wen X, Gao L, Zhao L, Xue B, et al. Parent-child resemblance in BMI and obesity status and its correlates in China. *Public Health Nutr*. (2021) 24(16):5400–13. doi: 10.1017/S1368980020005108

31. Mahmood L, Flores-Barrantes P, Moreno LA, Manios Y, Gonzalez-Gil EM. The influence of parental dietary behaviors and practices on children's eating habits. *Nutrients*. (2021) 13(4):1138. doi: 10.3390/nu13041138

32. Francis LA, Birch LL. Maternal influences on daughters' restrained eating behavior. *Health Psychol*. (2005) 24(6):548–54. doi: 10.1037/0278-6133.24.6.548

33. Brotons C. Healthy habits and risk factors of parents can have long-term clinical consequences in their offspring. *Eur J Prev Cardiol*. (2022) 29(6):880–2. doi: 10.1093/eurjpc/zwaa111

34. Doostvandi T, Bahadoran Z, Mozaffari-Khosravi H, Mirmiran P, Azizi F. Food intake patterns are associated with the risk of impaired glucose and insulin homeostasis: a prospective approach in the Tehran Lipid and Glucose Study. *Public Health Nutr*. (2016) 19(13):2467–74. doi: 10.1017/S1368980016000616

35. Hosseini-Esfahani F, Hosseinpour-Niazi S, Asghari G, Bahadoran Z, Moslehi N, Golzarand M, et al. Nutrition and cardio-metabolic risk factors: findings from 20 years of the Tehran Lipid and Glucose Study. *Int J Endocrinol Metab*. (2018) 16(4 Suppl):e84772. doi: 10.5812/ijem.84772

36. Pausova Z. From big fat cells to high blood pressure: a pathway to obesity-associated hypertension. *Curr Opin Nephrol Hypertens*. (2006) 15(2):173–8. doi: 10.1097/01.mnh.0000214775.42103.a5

37. Sulague RM, Suan NNM, Mendoza MF, Lavie CJ. The associations between exercise and lipid biomarkers. *Prog Cardiovasc Dis*. (2022) 75:59–68. doi: 10.1016/j.pcad.2022.11.004

38. Gao J, Sun H, Liang X, Gao M, Zhao H, Qi Y, et al. Ideal cardiovascular health behaviors and factors prevent the development of hypertension in prehypertensive subjects. *Clin Exp Hypertens*. (2015) 37(8):650–5. doi: 10.3109/10641963.2015.1047938

39. Wang X, Dong B, Huang S, Ma Y, Zou Z, Ma J, et al. Body mass index trajectory and incident hypertension: results from a longitudinal cohort of Chinese children and adolescents, 2006–2016. *Am J Public Health*. (2020) 110(11):1689–95. doi: 10.2105/AJPH.2020.305873

40. Pacor JM, Younus A, Malik R, Osondu CU, Aziz M, Ogunmoroti O, et al. Prevalence of ideal cardiovascular health metrics in children & adolescents: a systematic review. *Prog Pediatr Cardiol*. (2016) 43:141–6. doi: 10.1016/j.ppedcard.2016.09.002

41. WHO. Obesity and overweight. Geneva: WHO (2021). Available from: https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight (accessed January 7, 2022)

42. Jimenez-Chillaron JC, Isganaitis E, Charalambous M, Gesta S, Pentinat-Pelegrin T, Faucette RR, et al. Intergenerational transmission of glucose

intolerance and obesity by in utero undernutrition in mice. *Diabetes*. (2009) 58 (2):460–8. doi: 10.2337/db08-0490

43. Carpenter BL, Zhou W, Madaj Z, DeWitt AK, Ross JP, Grønbæk K, et al. Mother-child transmission of epigenetic information by tunable polymorphic imprinting. *Proc Natl Acad Sci U S A*. (2018) 115(51):E11970–7. doi: 10.1073/pnas.1815005115

44. Silventoinen K, Rokholm B, Kaprio J, Sørensen TI. The genetic and environmental influences on childhood obesity: a systematic review of twin and adoption studies. *Int J Obes (Lond)*. (2010) 34(1):29–40. doi: 10.1038/ijo.2009.177

45. Mustelin L, Silventoinen K, Pietiläinen K, Rissanen A, Kaprio J. Physical activity reduces the influence of genetic effects on BMI and waist circumference: a study in young adult twins. *Int J Obes (Lond)*. (2009) 33 (1):29–36. doi: 10.1038/ijo.2008.258

46. Welk GJ, Corbin CB, Dale D. Measurement issues in the assessment of physical activity in children. *Res Q Exerc Sport*. (2000) 71(2 Suppl):S59–73. doi: 10.1080/02701367.2000.11082788

47. Peixoto Mdo R, Benício MH, Jardim PC. Validity of self-reported weight and height: the Goiânia study, Brazil. *Rev Saude Publica*. (2006) 40(6):1065–72. doi: 10.1590/S0034-89102006000700015

48. Xie YJ, Ho SC, Liu ZM, Hui SS. Comparisons of measured and self-reported anthropometric variables and blood pressure in a sample of Hong Kong female nurses. *PLoS One*. (2014) 9(9):e107233. doi: 10.1371/journal.pone.0107233

frontiers | Frontiers in Pediatrics

TYPE Original Research
PUBLISHED 13 January 2023
DOI 10.3389/fped.2022.1090928

OPEN ACCESS

EDITED BY
Zhen-Yu Zhang,
KU Leuven, Belgium

REVIEWED BY
Tanıl Kendirli,
Ankara University, Turkey
Hiromichi Hamada,
Chiba University, Japan

*CORRESPONDENCE
Adli Ali
✉ adli.ali@ppukm.ukm.edu.my

SPECIALTY SECTION
This article was submitted to Pediatric Cardiology, a section of the journal Frontiers in Pediatrics

RECEIVED 06 November 2022
ACCEPTED 20 December 2022
PUBLISHED 13 January 2023

CITATION
Cheah CS, Lee WWL, Suhaini SA, Azidin AH, Khoo MS, Ismail NAS and Ali A (2023) Kawasaki disease in Malaysia: Biochemical profile, characterization, diagnosis and treatment. Front. Pediatr. 10:1090928. doi: 10.3389/fped.2022.1090928

Kawasaki disease in Malaysia: Biochemical profile, characterization, diagnosis and treatment

Chooi San Cheah[1], Wendy Wei Li Lee[1], Siti Aisyah Suhaini[1], Abdullah Harith Azidin[1], Mohammad Shukri Khoo[2], Noor Akmal Shareela Ismail[3] and Adli Ali[1,2]*

[1]Department of Pediatric, Faculty of Medicine, Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia, [2]Department of Pediatric, Universiti Kebangsaan Malaysia Specialist Children's Hospital (HPKK), Kuala Lumpur, Malaysia, [3]Department of Biochemistry, Faculty of Medicine, Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia

Introduction: Kawasaki disease (KD) is an acute idiopathic systemic vasculitis with a self- limiting course that predominantly affects children under 5 years old, particularly in the East Asian countries. Nevertheless, to date, the data on KD in Malaysia are limited. This study aimed to evaluate the epidemiology, clinical features, treatment, and outcomes of KD among the pediatric patients admitted to Hospital Canselor Tunku Muhriz (HCTM), Kuala Lumpur, Malaysia.
Method: A retrospective cohort study of 66,500 pediatric patients presented at HCTM from the year 2004 to 2021 was conducted.
Results: 62 KD cases out of 66,500 pediatric admissions were reported, with a male-to-female ratio of 1.58 to 1. Majority of KD patients (95.0%) were younger than 5 years old. Prior infection was reported in 5 KD patients (8.1%). Apart from the classical features, manifestations of various organ systems including cardiovascular (16.1%), gastrointestinal (43.5%), neurological (1.61%), musculoskeletal (1.61%), and genitourinary (17.7%) systems were observed. There was a significant association between sterile pyuria and coronary artery aneurysm (CAA) ($p < 0.05$). Interestingly, abnormal liver parameters ($p < 0.05$) and incomplete KD ($p < 0.05$) were significantly related to IVIG resistance.
Discussion: The presence of family history, immunological disorder, and previous infection in our KD patients suggested that there is a possibility of genetic, immunological, and infectious roles in the pathophysiology of KD. IVIG resistance is more likely to occur in KD patients with hepatic dysfunction or incomplete KD presentation. These findings highlighted the significant contribution of laboratory parameters to the prognosis of KD, prompting more in-depth research on the KD scoring systems and their relevance in this country.

KEYWORDS

systemic vasculitis, incomplete kawasaki disease, sterile pyuria, coronary artery aneurysm, intravenous immunoglobulin, resistance

Introduction

Kawasaki Disease (KD) is an acute systemic febrile vasculitis of unknown etiology mainly affecting children younger than 5 years old (1). KD was first reported in Japan in 1961 with a total of 50 patients being profiled and eventually published by Dr Tomisaku Kawasaki in 1967 (2). Since then, KD is recognized as the commonest cause of acquired heart disease among children in developed countries, with the occurrence of coronary artery aneurysm (CAA) in a quarter of the untreated children. Other possible non-coronary cardiovascular sequelae include myocardial dysfunction, valvular abnormalities, and KD shock syndrome (1, 3, 4). To date, the etiology of KD remains unclear. Various studies proposed that viral or bacterial pathogens (5–7), environmental toxins (8, 9), seasonality (10–12), or genetic background (13, 14) of the patients play vital roles in the pathophysiology of KD. In addition, Noval Rivas & Arditi found that dysregulated and exacerbated genetically-controlled immune response to common stimulus occurred in KD patients, contradictory to the previous perception of normal immunity of KD patient when exposed to pathological agent (15). According to the American Heart Association (AHA), KD is diagnosed with a constellation of clinical criteria, classifying KD into complete and incomplete types. Laboratory parameters and echocardiographic evaluation only serve as supportive tools in assisting the diagnosis of KD (1). The annual incidence rate of KD worldwide showed a rising trend throughout the years, particularly in the northeastern Asian countries (16–18). In Malaysia, KD was first described as 'Kawasaki Syndrome' with 19 cases being reported in 1985 by Asma Omar (19). Subsequently, several studies highlighted the increasing incidence rate of KD over the past 3 decades (20–22). Latest study by Mat Bah et al. found that male, late diagnosis, and intravenous immunoglobulin (IVIG) resistance were significantly related to CAA (22). However, the publication by Mat Bah et al. was limited to only one of the states in Malaysia, which is Johor and a detailed relationship between the clinical features and disease outcome remain unknown among the Malaysian pediatric population. Referring to the scarcity of in-depth data regarding KD in this country, this study will provide a more comprehensive insight on the epidemiology of KD in Malaysia.

Material and methods

Study location and period

This study was carried out at Hospital Canselor Tuanku Muhriz (HCTM). HCTM is a tertiary medical center and is one of the university hospitals in Malaysia. It is located in Bandar Tun Razak, Kuala Lumpur and is administered by Universiti Kebangsaan Malaysia. The study was conducted from October 2021 until October 2022.

Study design and participants

In this retrospective study, patients' data were retrieved from the HCTM Case Mix system using the International Classification of Diseases (ICD) code, ICD-10 (M30.3) Mucocutaneous lymph node syndrome [Kawasaki]. A total of 103 patients who attended HCTM with the diagnosis of KD from 2004 until 2021 were included. 41 patients were excluded due to misdiagnosis [24], missing records [10], and duplicated medical records [7]. The remaining 62 patients were enrolled in the study and classified into 2 groups: complete KD and incomplete KD. The medical records of the patients were reviewed and analyzed. This includes demographic data, clinical features, laboratory results at the time of diagnosis, echocardiographic findings, treatment, and clinical outcomes. These data were collected from December 2021 until May 2022.

Inclusion and exclusion criteria

All registered data of patients who were admitted to HCTM between 2004 and 2021 with the diagnosis of KD based on the health information system were included in this study. With this approach, there were two methodological limitations. The first limitation was type I error, which happened when non-KD patients were coded as KD in the system. These patients did not meet the criteria to be diagnosed as complete or incomplete KD and were excluded from this study. The second limitation was type II error, which happened when KD patients were not coded as KD in the system. These patients' data could not be traced and subsequently not included in this study.

Meanwhile, the exclusion criteria of this study are (i) patients' data with repeated names and reference numbers, (ii) patients' data that could not be accessed at all due to loss of information or patient's file. Repetitions of data were considered as a single entry. However, any incomplete dataset was accepted and reported as it is.

Research instrument

A data collection form was formed through extensive literature review and focused group discussion with the pediatric specialists. The form was constructed using Google Form to ease the data collection process of KD patients. Patients' information that was extracted were (i) demographic data; (ii) predisposing factors; (iii) clinical features; (iv) laboratory results; (v) echocardiographic

findings; (vi) IVIG treatment; (vii) secondary treatment, and (viii) clinical outcome.

Complete and incomplete KD were diagnosed according to the AHA guideline. In this guideline, complete KD is diagnosed based on the definition of fever occurrence of ≥5 days and the presence of ≥4 out of 5 principal clinical criteria. These clinical criteria consisted of [i] oral mucosal changes such as strawberry tongue; [ii] bilateral non-exudative conjunctival injection; [iii] polymorphous rash; [iv] changes of extremities such as erythema, oedema, or desquamation; [v] cervical lymphadenopathy. Incomplete KD is diagnosed when the patient only fulfills less than 4 of the principal clinical criteria or if there is any supportive laboratory or echocardiographic findings (1). Laboratory parameters upon admission were recorded and analyzed. Echocardiographic studies were performed among our KD patients within 2 weeks of diagnosis, or 5 to 12 weeks after the initial diagnosis. The extent of coronary artery size dilation was assessed using a guideline by the Japanese Circulation Society (JCS) (23). Small aneurysm was defined as dilation of ≤ 4 mm or < 1.5 times of adjacent segments, whereas medium aneurysm as ≤ 8 mm or 1.5 to 4 times of adjacent segments. Dilation of > 8 mm or >4 times of adjacent segment was considered as giant aneurysm. 98% of our KD patients who were diagnosed within 10 days of symptoms onset received a single course of 2 g/kg IVIG. IVIG resistance is defined as the persistence of fever beyond 36 h after completing IVIG treatment (24). Cardiac presentations developed during acute illness and in subsequent follow-up were considered as cardiac complications. Data from the Google Form were transferred to the Statistical Package for Social Science (SPSS) version 28 for analysis.

Statistical analysis

SPSS version 28 was used to analyze the data. Frequencies and percentages were used to describe the categorical variables while continuous data were presented as median (interquartile range; IQR). Descriptive statistics were used to describe the demographic backgrounds of our KD patients. Meanwhile, parametric tests such as student T-test for normally distributed continuous data, Mann Whitney U test for continuous data that were not normally distributed and non-parametric tests such as the X^2 test for categorical data were used to identify any significant differences between the compared variables. The level of statistical significance was set at $p < 0.05$.

Results

Epidemiology of kawasaki disease

In our study, there were 62 patients with KD, with a male-to-female ratio of 1.5 to 1 with 20 patients (32.0%) diagnosed with incomplete KD and 42 patients (68.0%) diagnosed with complete KD. There are 59 patients (95.0%) who were less than 5 years old, and within this age cohort there were 42 patients (71.0%) who were less than 2 years old. Among all the races, Malay (68.0%, $n = 42$) had the highest occurrence rate compared to Chinese (27.4%, $n = 17$) while other races including Burmese, mixed Chinese Japanese, and Indian were less than 5%.

Incidence of kawasaki disease

The incidence of KD by year generally increased for the past 17 years (**Figure 2A**), and the monthly KD occurrences from 2004 to 2021 are shown in **Figure 2B**. In our study, KD seemed to peak in January (14.5%), April (12.9%) and August (12.9%). The lowest incidence of KD was noted in May (4.8%), November (4.8%), and December (4.8%). The incidence rates of KD by age groups are presented in **Figure 2C**. The median age at diagnosis was 12.0 months (interquartile range = 6.50 to 28.50 months) while the peak age was 6 months.

Risk factors of kawasaki disease

Out of 62 patients, 1 patient (1.6%) had a positive family history of KD. Another patient (1.6%) had a positive family history of immune thrombocytopenic purpura (ITP). In terms of infection, there were 5 patients who presented with history of infections within 4 weeks before the diagnosis of KD including rotavirus (1.6%, $n = 1$), upper respiratory tract infection virus (3.2%, $n = 2$), varicella zoster virus (1.6%, $n = 1$) and, Group A streptococcus (1.6%, $n = 1$). In regard to breastfeeding being suggested as a protective factor from KD (25), 35 patients diagnosed with KD were breastfed with 20 (57%) of them diagnosed with complete KD and another 15 (43%) with incomplete KD.

Clinical features of kawasaki disease

All 62 patients had fever upon admission. (**Table 1**) The average temperature was 38.6 °C, with the highest temperature of 40°C. The average days of fever among the patientswas 6.5 days with the longest duration of 10 days and the shortest duration of 2 days. The median days between the symptoms' onset and the day of diagnosis was 6 days, and the interquartile range was 4 to 8 days. 51.6% of the patients ($n = 32$) had different initial diagnoses before they were diagnosed with KD. Out of the 5 classical criteria for KD apart from fever, the most common feature was polymorphous rash which was presented in 91.9% ($n = 57$) of the patients. This

was followed by cervical lymphadenopathy (87.1%, $n = 54$), conjunctival injection (83.9%, $n = 52$), erythematous oral cavity (71.0%, $n = 44$), and palmar erythema (45.2%, $n = 28$).

Apart from the classical features, other systemic involvements were also considered. The most commonly involved was the gastrointestinal system, with vomiting and diarrhea as the most common symptoms (43.5%, $n = 27$). Cardiovascular manifestation only presented in 16.1% ($n = 10$) of KD patients during presentation with 6 of them having CAA upon admission. Joint manifestation and aseptic meningitis were only present in 1 patient each respectively in this study. Other common feature was flaring of the Bacillus Calmette-Guerin (BCG) scar which was observed in 38.7% of the patients ($n = 24$). The details on the frequency of each clinical feature are documented in **Table 1**.

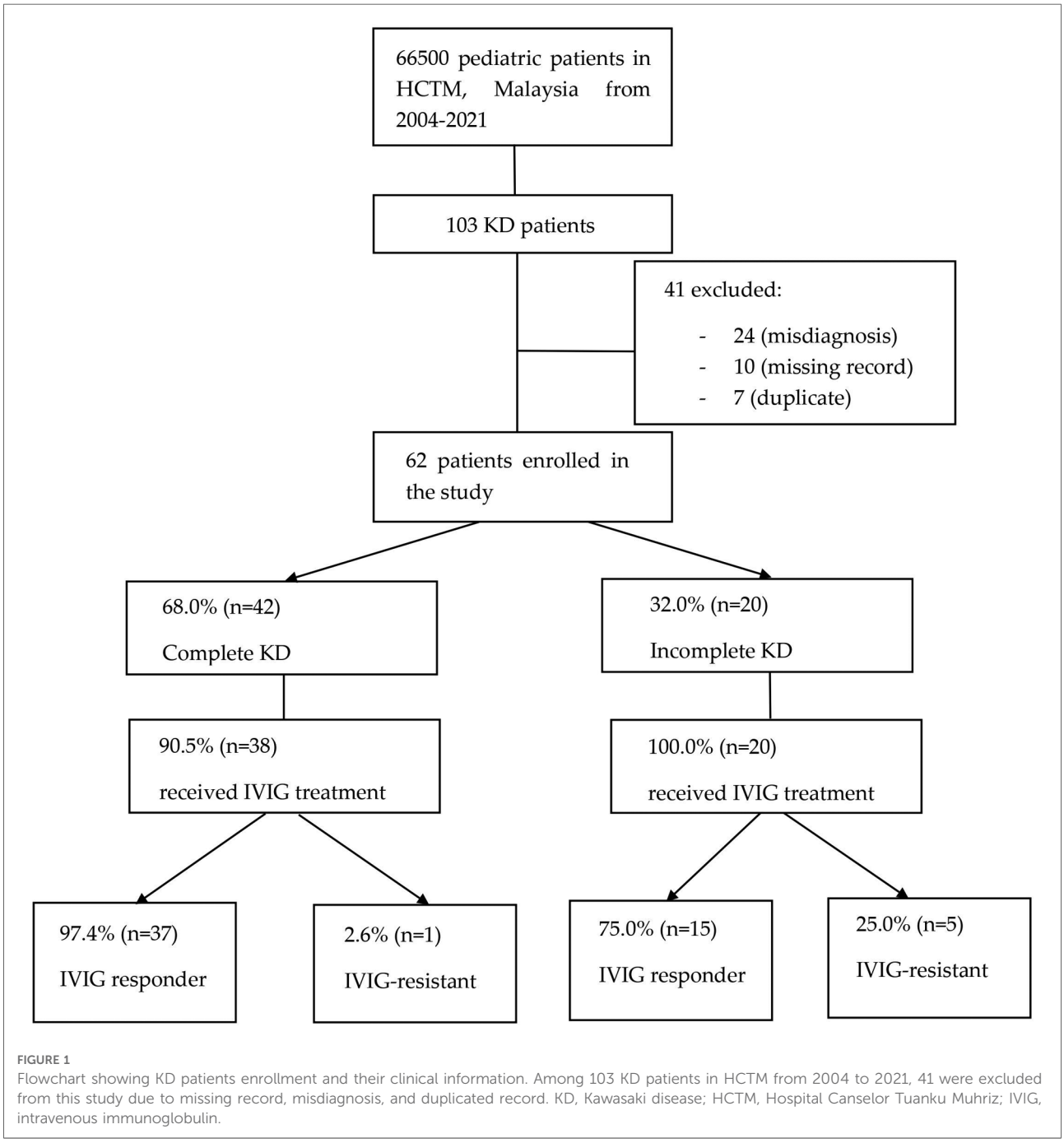


FIGURE 1
Flowchart showing KD patients enrollment and their clinical information. Among 103 KD patients in HCTM from 2004 to 2021, 41 were excluded from this study due to missing record, misdiagnosis, and duplicated record. KD, Kawasaki disease; HCTM, Hospital Canselor Tuanku Muhriz; IVIG, intravenous immunoglobulin.

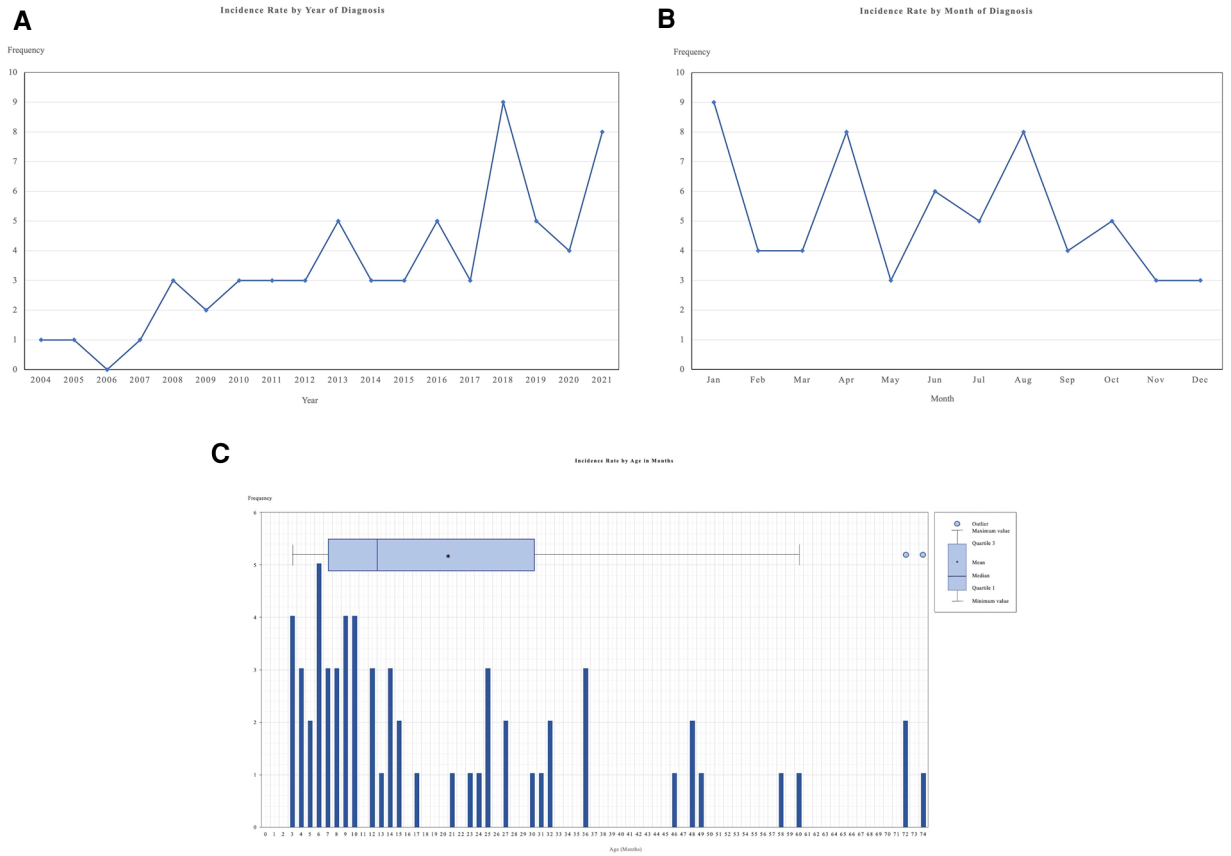


FIGURE 2
This figure shows the incidence of KD in HCTM, Malaysia. (**A**) Incidence rate of KD patients by year of diagnosis; (**B**) Incidence rate of KD patient by months of diagnosis; (**C**) Incidence rate of KD patients by age in months during diagnosis. HCTM, Hospital Canselor Tuanku Muhriz.

Laboratory investigations

Evaluation of the hematological parameters showed elevated white cell count in 48.4% ($n = 25$), with neutrophilia in 66.1% ($n = 41$) of the patients. Anemia was reported in 40.3% ($n = 25$) of the patients with a median hemoglobin level of 10.8 g/dl. As for the platelet count, 38.7% ($n = 24$) of children with KD had thrombocytosis. Interestingly, patients with complete KD had a significantly higher platelet count than those with incomplete KD ($p = 0.03$) (**Table 2**). A significant proportion of patients had raised C-reactive protein (CRP) (93.55%, $n = 58$) and erythrocyte sedimentation rate (ESR) (64.52%, $n = 40$) due to the inflammatory nature of KD. Nevertheless, there were no significant difference of hemoglobin level ($p = 0.38$), CRP level ($p = 0.54$), and sodium level ($p = 0.22$) between complete KD and incomplete KD patients.

Liver abnormalities were also documented in our patients. Out of 56 KD patients who underwent liver profile investigations, 51.8% ($n = 29$) of the patients had increased alanine aminotransferase (ALT) level ranging from 23 to 1435 U/l while hypoalbuminemia was observed in 90.9% ($n = 50$) of the KD patients. Only 18.2% ($n = 10$) of the KD patients had raised bilirubin. None of the patients had elevated gamma-glutamyl transferase (GGT). Among 42 children who developed hyponatremia, those younger than 2 years old were predominantly affected (69%, $n = 29$). Hypokalemia was only found in 9.7% ($n = 6$) of the KD patients.

Treatment

A total of 91.9% ($n = 57$) of KD patients received IVIG and aspirin as the first line of treatment. 4.8% ($n = 3$) of KD patients were treated with aspirin alone due to late presentation while one patient was given IVIG only. 10.3% ($n = 6$) of KD patients who were given IVIG treatment were IVIG resistant and required a second dose of IVIG. None of the patients received third dose of IVIG, steroids or any other immunosuppressive therapy. Of note, deranged hepatic parameters such as raised

TABLE 1 Frequency of clinical manifestations in KD patients.

Clinical Manifestation	Frequency *n* (%)
Fever	62 (100)
Conjunctival Injection	52 (83.9)
Bilateral non-purulent	47 (75.8)
Bilateral purulent	5 (8.0)
Palmar Erythema	28 (45.2)
Oral changes	44 (71.0)
Polymorphous rash	57 (91.9)
Cervical lymphadenopathy	54 (87.1)
Total GI involvement	27 (43.5)
Vomiting	14 (22.6)
Diarrhea	13 (20.1)
Jaundice	2 (3.2)
Gall bladder hydrops	2 (3.2)
Hepatitis/Hepatomegaly	5 (8.1)
Joint involvement	1 (1.6)
Aseptic meningitis	1 (1.6)
BCG scar flaring	24 (38.7)
Cardiovascular involvement	10 (16.1)
Pericardial effusion	3 (4.8)
Valvular regurgitation (tricuspid, mitral, pulmonary and aortic)	2 (3.2)
Coronary artery aneurysm	6 (9.7)

TABLE 2 Laboratory parameters in complete KD and incomplete KD patients.

Variable[a]	Complete KD	Incomplete KD	*P*
Age in months (median ± IQR)	12.00 ± 24	15.50 ± 23	0.488
GIT involvement*, *N* (%)	20 (47.6)	7 (35.0)	0.349
BCGitis, *N* (%)	17 (41.5)	7 (35.0)	0.628
Sterile pyuria, *N* (%)	5 (13.9)	4 (30.8)	0.220
Hb level (median ± IQR)	10.75 ± 1	10.80 ± 1.9	0.377
Platelet count (median ± IQR)	386.50 ± 179	329.00 ± 83	**0.031**
CRP (median ± IQR)	10.31 ± 8.18	11.51 ± 12.40	0.542
Sodium level (median ± IQR)	133.50 ± 6	135.00 ± 3	0.224
IVIG resistance, *N* (%)	1 (2.4)	5 (25.0)	**0.011**
CAA, N (%)	3 (9.4)	3 (16.7)	1.000

[a]GIT, gastrointestinal tract; BCG, Bacillus Calmette-Guerin; Hb, hemoglobin; CRP, C-reactive protein; IVIG, intravenous immunoglobulin; CAA, coronary artery aneurysm.
*includes vomiting, diarrhoea, jaundice, gall bladder hydrops, hepatomegaly and hepatitis % is calculated based on the respective KD presentation group.

ALT level and hypoalbuminemia were documented in all IVIG-resistant patients ($p = 0.03$). Meanwhile, there was a significant association between incomplete KD and IVIG resistance in which 83.3% ($n = 5$) of the IVIG-resistant patients had incomplete KD ($p < 0.05$). Side effects of IVIG were observed in 2 (3.5%) of the KD patients on IVIG treatment, with one suspected to have autoimmune hemolytic anemia (AIHA) while another patient developed anaphylactic reactions.

Complications and outcome

Cardiovascular complications were detected in 16.1% ($n = 10$) of the KD patients, mainly presented with CAA (60%, $n = 6$), of which 4 (66.7%) of them presented with small aneurysm and 2 (33.3%) with medium aneurysm. Younger children were identified to be complicated with CAA with a median age of 12.50 ± 7.89 months compared to older children (21.52 ± 20.22 months) (**Table 3**). We also found that KD patients presented with sterile pyuria were more likely to develop CAA ($p = 0.03$). However, there were no significant correlation between: IVIG-resistance ($p = 1.00$); gender ($p = 1.00$); timing of diagnosis ($p = 0.07$); with CAA in this cohort. Echocardiographic follow-up after at least one month showed CAA regression in 3 (75%) of the KD patients, with one (25%) had persistent aneurysm, while the other two defaulted the follow up. On the other hand, valvular insufficiency (mitral and tricuspid regurgitation, ventricular septal defect) was noted in 2 (3.2%) and pericardial effusion in 3 (4.8%) KD patients, respectively. The duration of follow-up for our KD patients ranged from 2 months to 10 years (median: 2 months), with longer duration particularly noted in those with cardiovascular sequelae. No death cases were reported.

Discussion

KD incidence was on a rising trend in HCTM, Malaysia for the past 17 years, which was consistent with other Asian countries including Japan, China, South Korea, India, Iran and Australia. (18, 24, 26–28). The postulated hypothesis of this growing incidence in our centre was the improved awareness of KD among the health care providers and the increased accessibility to public healthcare facilities. However, KD incidence in Europe and North America remained stable

TABLE 3 Univariate analysis of risk factors for coronary artery aneurysm.

Variable[a]	Coronary artery aneurysm* ($n = 6$) (%)	Normal coronary artery ($n = 56$) (%)	*P*
Gender			1.000
Male	3 (10.7)	25 (89.3)	
Female	3 (13.6)	19 (86.4)	
Age in months (median ± IQR)	12.50 ± 7.89	21.52 ± 20.22	0.054
Timing of diagnosis			0.066
Early diagnosis (≤10 days)	4 (8.7)	42 (91.3)	
Late diagnosis (>10 days)	2 (50.0)	2 (50.0)	
Sterile pyuria	6 (66.7)	3 (33.3)	**0.030**
IVIG resistance	0 (0.0)	6 (100.0)	1.000

[a]IVIG, Intravenous immunoglobulin.
*KD patients with unknown echocardiography results were excluded.

over time, suggesting possible genetic predisposition in Asian children (29, 30). In this study, the incidence of KD was statistically significant among the Malay ethnicity compared to other ethnicities, which contrasts with the finding reported by another study in Malaysia (22). Interestingly, in other countries like the United States, there was also a clear variation of KD incidence by race and ethnicity with Asian having the highest incidence compared to the blacks, whites, and Americans Indians, similar to the UK and Ireland (31, 32). In terms of gender, a male predominance was detected in the study with the ratio of 1.5 to 1. This finding is in parallel to other studies in Iran and southern Malaysia where the male was more prone to KD with a male-to-female ratio of 1.8 to 1 and 2 to 1 respectively (22, 28). This was further supported by the evidence that male was more predominantly affected by KD due to the presence of susceptible male-specific FCGR2A His167Arg genetic polymorphism (33).

Out of 62 KD patients, 95% of them who were less than 5 years old upon the diagnosis of KD. This was similarly reported in Japan in which children less than 5 years old had the highest incidence of KD with 1 in 65 patients developed KD followed by Korea and Taiwan (34, 35). In addition, the latest study in Japan noted that 100% of children diagnosed with KD were less than 5 years old ((36). The peak age of our KD patients was 6 months which was also similar to another study (37) which showed that the peak onset of KD was between 6 and 24 months of age. It is important to highlight that there was a low incidence of KD among patients less than 3 months of age (38–40) which was similar to our study in which only 4 patients diagnosed with KD at the age of less than 3 months of age. This phenomenon can be explained by the presence of protective effect of passive immunity from the mother and the lower possibility of the children to be in contact with unknown pathogen due to lesser outdoor activity. It could also be due to no accurate marker for KD, thus late diagnosis is made based on the combination of the clinical features. Multiple studies also showed a high incidence of incomplete KD was diagnosed among young children which led to delayed diagnosis of KD and treatment (41, 42). Among all the patients diagnosed with KD in HCTM, 32% ($n = 20$) were diagnosed with incomplete KD with 19 of them are less than 5 years old. Similarly, a study in Switzerland reported 29% of incomplete KD cases, indicating increasing challenges to diagnose KD (43) There is no clear evidence that incomplete KD cases are actual KD, as it could mimic other diseases such as rubella, rabies, and streptococcal infection (44). This further complicates the clinical decision to diagnose KD. Nonetheless, due to the more severe potential complications of KD, all patients with suspected incomplete KD should be treated as per KD cases, with IVIG and aspirin therapy.

The etiological basis of KD is still unknown, but there are some proposed predisposing factors of KD. One of the predisposing factors of KD is family history and, in our study, there was one patient with positive family history of KD. A genetic basis of susceptibility to KD was also observed in other studies while several studies had shown increased incidence of KD among siblings and parents (35, 44–46). Other than that, one patient in our study has a sibling who had ITP. There were several cases reporting the association of KD with ITP (47–49), although the main mechanism of ITP causing KD is still unknown. Although thrombocytosis is a more common associated finding in KD, thrombocytopenia should always be considered as one of the expected findings in KD patients (47–49). KD is also suggested to be associated with infection and our cohort revealed 5 patients presented with infection prior to the diagnosis of KD (46, 50).

Fever onset of at least 5 days is a compulsory feature and was seen in some patients in our cohort and multiple other studies (28, 51–53). However, KD can be diagnosed if fever occurred for 4 days with at least 4 out of 5 of the classical features were present (1). Apart from fever, polymorphous rash was noted to be the most common classic feature (91.9%), suggesting the potential difficulty in diagnosing KD as similar rash may appear in various common childhood diseases. Cervical lymphadenopathy was also more frequently reported in our KD patients (87.1%). The reason of this high percentage was still unclear as majority of other studies found cervical lymphadenopathy to be the least common classical feature in KD (1, 54, 55).

In our study, 43.5% of the patients had gastrointestinal symptoms, namely vomiting and diarrhea This was higher

compared to a study in Iran (38.4%) and was significantly higher than a previous study in southern Malaysia (6%) (22, 28). The most common gastrointestinal symptom in our study is vomiting (22.6%) similar to the finding by Nasri etal. where vomiting was also represented as the most common gastrointestinal manifestation (28.9%) in comparison to diarrhea (16.9%) (56). The gastrointestinal manifestations are observed to be commonly reported in several studies on KD thus, should be considered as part of KD clinical constellation (1, 57–59). The manifestation of gastrointestinal symptoms in multisystem inflammatory syndrome in children (MIS-C) and KD has been attracting attention among researchers. Both KD and MIS-C share similar initial symptoms which include vomiting, diarrhea and abdominal pain (58). However, gastrointestinal symptoms were more commonly observed in MIS-C with fewer classical KD symptoms which can help differentiate MIS-C from KD (60) In addition, neurological symptoms and hypotension were more frequently reported in MIS-C (20%) compared to KD. Similarly, our study reported fewer KD patients with neurological manifestation (1.6%).

In this study, our KD patients had leukocytosis (48.4%), anemia (40.3%) and thrombocytosis (38.7%) which were in line with most reported literature (61, 62). We also found that there was a significant difference of platelet count between complete KD and incomplete KD patients. On contrary, in another study, complete KD and incomplete KD were just two sides of the same coin with similar laboratory findings including platelet count and CRP level between the two groups (63). No significant difference of blood cell counts in patients with different KD presentation were noted (64). Our study reported a higher percentage of KD patients with raised ALT (50%) and hypoalbuminemia (81%) compared to a previous report (65) suggesting possible increasing incidence of hepatic dysfunction among KD patients in Malaysia or higher detection rate due to more assessment of the liver function in our cohort of patients. Several studies showed that KD patients with abnormal liver function test (LFT) is significantly associated with IVIG resistance (66, 67). Similarly, we reported a significant association between deranged LFT and IVIG resistance in our patients. This could be explained by the hypothesis of more severe ongoing inflammation in KD patients with abnormal liver function, thus the efficacy of IVIG treatment was reduced (68, 69).

Most of our KD patients (91.9%, $n = 57$) received IVIG as the first line of treatment, which aimed to halt immunological responses to reduce cardiac sequelae in KD patients (22, 28, 70). 10.3% of our IVIG-treated patients were found to be IVIG-resistant which was lower compared to other reported studies (11.8–19.7%) (16, 28, 71, 72). This could be explained by the low-level awareness of disease entity. In addition, we realized that incomplete KD may appear as a risk factor for developing IVIG resistance which was also reported in another study (73). Therefore, the addition of this criteria into the pre-existing risk scoring systems should be considered and we urge further studies on evaluating the compatibility of the KD risk scoring systems in our country to be conducted. A case of hemolytic anemia as a complication of IVIG therapy was observed in our study, thus close monitoring is necessary throughout the IVIG treatment (74, 75).

KD predominantly affected the coronary arteries as the major sequelae in KD patients (1). In our population, 16.1% ($n = 10$) of them presented with cardiac complication, mainly presenting with CAA ($n = 6$). This finding was higher than that of a wide-scale study done in Japan (9%) and another study in Canada (2.4%), which probably attributed to delayed diagnosis and initiation of treatment in our population (16, 22, 76). Various studies reported that CAA more frequently affected KD patients of younger age (28, 78, 78). Our results concurred with the findings with a lower median age (12.50 ± 7.89 months) found in KD patients with CAA, suggesting age as a possible indicator predicting the development of CAA. Interestingly, sterile pyuria was statistically related to CAA in our population, which resonated with the previous observations (66, 79), probably due to the underlying extended vasculitis involving the renal vessel vasculitis. Thus, we recommend further laboratory tests such as urinalysis and routine echocardiography to be carried out in KD patients particularly the younger age group for earlier detection of CAA. Nonetheless, IVIG resistance was found to be not significantly associated with subsequent CAA development in our KD patients ($p > 0.05$) which was contradictory to other studies (22, 80). This could be explained by the small population of KD patients in our study. A notable evidence of higher regression rate was identified in KD patients with small CAA compared to medium aneurysm (81). On a similar note, subsequent echocardiography outcome in our study demonstrated regression in 75% of KD patients with CAA, all of which had small aneurysm. Another KD patient with medium aneurysm developed persistent CAA. Thus, a longer duration of echocardiographic surveillance for those KD patients with medium or giant CAA is nearly always indicated. Other non-coronary cardiac manifestations including pericardial effusion and valvular regurgitation were only detected in 3.2% and 4.8% of our KD patients, which was lower than the incidence (9.2%, 14.7%) reported by a study in China (18).

Several limitations of this study include a small sample size and incomplete data due to the retrospective approach of the study. Thus, a large-scale nationwide prospective surveillance study is recommended to provide a more comprehensive view of current KD epidemiologic features in this country. Furthermore, Z-score, a more accurate tool to evaluate CAA as recommended by the American Heart Association (AHA) guidelines was not used in this study due to lacking data on height and weight in some of our KD patients (1).

Conclusion

KD incidence in our center showed an increasing trend which was similarly observed in other studies. Nevertheless, it is still lower compared to other East Asian countries particularly Japan and Korea. Children younger than 5 years old and males were predominantly affected by KD. Our study further revealed the presence of sterile pyuria to be associated with CAA, and IVIG resistance in KD is likely among those with hepatic dysfunction or incomplete KD diagnosis. These findings highlighted the significant contribution of laboratory parameters to the prognosis of KD, prompting more in-depth research on the KD scoring systems and the relevance in this country.

Data availability statement

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

Ethics statement

This study was approved by the institutional review board of the Universiti Kebangsaan Malaysia (JEP 2021-868). All the requirements for informed consent were waived for this retrospective study.

Author contributions

All authors (CSC, WWLL, SAS, AHA, MSK, NASI, AA) are equally responsible for the initial conceptualization. CSC, WWLL, SAS and AHA collected data and wrote the paper. CSC performed statistical analysis and grammatical check. WWLL, SAS and AHA designed the study and provided resources. MSK, NASI and AA supervised the study and reviewed the paper. All authors contributed to the article and approved the submitted version.

Acknowledgments

We would like to express our gratitude towards the Faculty of Medicine, Universiti Kebangsaan Malaysia for supporting our publication.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2022.1090928/full#supplementary-material.

References

1. McCrindle BW, Rowley AH, Newburger JW, Burns JC, Bolger AF, Gewitz M, et al. Diagnosis, treatment, and long-term management of kawasaki disease: a scientific statement for health professionals from the American heart association. *Circ.* (2017) 135(17):e927–99. doi: 10.1161/CIR.0000000000000484

2. Kawasaki T. [Acute febrile mucocutaneous syndrome with lymphoid involvement with specific desquamation of the fingers and toes in children]. *Arerugi.* (1967) 16:178–222. PMID: 6062087.

3. Duarte R, Cisneros S, Fernandez G, Castellon D, Cattani C, A Melo C, et al. Kawasaki disease: a review with emphasis on cardiovascular complications. *Insights Imaging.* (2010) 1:223–31. doi: 10.1007/s13244-010-0035-6

4. Newburger JW, Takahashi M, Burns JC. Kawasaki disease. *J Am Coll Cardiol.* (2016) 67:1738–49. doi: 10.1016/j.jacc.2015.12.073

5. Kang J-M, Jung J, Kim Y-E, Huh K, Hong J, Kim DW, et al. Temporal correlation between kawasaki disease and infectious diseases in South Korea. *JAMA Netw Open.* (2022) 5:e2147363. doi: 10.1001/jamanetworkopen.2021.47363

6. Rowley AH, Shulman ST. The epidemiology and pathogenesis of kawasaki disease. *Front Pediatr.* (2018) 6:374. doi: 10.3389/fped.2018.00374

7. Nakamura A, Ikeda K, Hamaoka K. Aetiological significance of infectious stimuli in kawasaki disease. *Front Pediatr.* (2019) 7:244. doi: 10.3389/fped.2019.00244

8. Manlhiot C, Mueller B, O'Shea S, Majeed H, Bernknopf B, Labelle M, et al. Environmental epidemiology of kawasaki disease: linking disease etiology, pathogenesis and global distribution. *PLoS ONE.* (2018) 13:e0191087. doi: 10.1371/journal.pone.0191087

9. Rodó X, Ballester J, Curcoll R, Boyard-Micheau J, Borràs S, Morguí J-A. Revisiting the role of environmental and climate factors on the epidemiology of kawasaki disease. *Ann N Y Acad Sci.* (2016) 1382:84–98. doi: 10.1111/nyas.13201

10. Ozeki Y, Yamada F, Saito A, Kishimoto T, Yashiro M, Makino N, et al. Epidemiologic features of kawasaki disease distinguished by seasonal variation: an age-specific analysis. *Ann Epidemiol.* (2018) 28:796–800. doi: 10.1016/j.annepidem.2018.08.004

11. Huang Y-H, Lin K-M, Ho S-C, Yan J-H, Lo M-H, Kuo H-C. Increased incidence of kawasaki disease in Taiwan in recent years: a 15 years nationwide population-based cohort study. *Front Pediatr*. (2019) 7:121. doi: 10.3389/fped.2019.00121

12. Burns JC, Herzog L, Fabri O, Tremoulet AH, Rodó X, Uehara R, et al. Seasonality of kawasaki disease: a global perspective. *PLoS One*. (2013) 8: e74529. doi: 10.1371/journal.pone.0074529

13. Onouchi Y. Genetics of kawasaki disease. *Circ J*. (2012) 76:1581–6. doi: 10.1253/circj.CJ-12-0568

14. Elakabawi K, Lin J, Jiao F, Guo N, Yuan Z. Kawasaki disease: global burden and genetic background. *Cardiol Res*. (2020) 11:9–14. doi: 10.14740/cr993

15. Noval Rivas M, Arditi M. Kawasaki disease: pathophysiology and insights from mouse models. *Nat Rev Rheumatol*. (2020) 16:391–405. doi: 10.1038/s41584-020-0426-0

16. Ae R, Makino N, Kosami K, Kuwabara M, Matsubara Y, Nakamura Y. Epidemiology, treatments, and cardiac complications in patients with kawasaki disease: the nationwide survey in Japan, 2017-2018. *J Pediatr*. (2020) 225:23–29.e2. doi: 10.1016/j.jpeds.2020.05.034

17. Kim GB, Eun LY, Han JW, Kim SH, Yoon KL, Han MY, et al. Epidemiology of kawasaki disease in South Korea: a nationwide survey 2015–2017. *Pediatr Infect Dis J*. (2020) 39:1012–6. doi: 10.1097/INF.0000000000002793

18. Xie L, Yan W, Huang M, Huang M, Chen S, Huang G, et al. Epidemiologic features of kawasaki disease in Shanghai from 2013 through 2017. *J Epidemiol*. (2020) 30:429–35. doi: 10.2188/jea.JE20190065

19. Omar A. Kawasaki syndrome in Malaysia. *Med J Malaysia*. (1985) 40:20–3. PMID: 3831728.

20. Liang Choo H. Epidemiology and short-term outcome of kawasaki disease in Malaysian children. *Malaysia J Paediatr and Child Health*. (2007) 15:1.

21. Malik AS. Kawasaki disease in Malaysia. *Ann Trop Paediatr*. (1996) 16:213–20. doi: 10.1080/02724936.1996.11747829

22. Mat Bah MN, Alias EY, Razak H, Sapian MH, Foo FH, Abdullah N. Epidemiology, clinical characteristics, and immediate outcome of kawasaki disease: a population-based study from a tropical country. *Eur J Pediatr*. (2021) 180:2599–606. doi: 10.1007/s00431-021-04135-7

23. Guidelines for diagnosis and management of cardiovascular sequelae in kawasaki disease (JCS 2013). *Circ J*. (2014) 78:2521–62. doi: 10.1253/circj.CJ-66-0096

24. Lin M-T, Wu M-H. The global epidemiology of kawasaki disease: review and future perspectives. *Glob Cardiol Sci Pract*. (2018) 2017(3):e201720. doi: 10.21542/gcsp.2017.20

25. Wang S, Xiang D, Fang C, Yao B. Association between breastfeeding and kawasaki disease: a case–control study. *Eur J Pediatr*. (2020) 179:447–53. doi: 10.1007/s00431-019-03529-y

26. Saundankar J, Yim D, Itotoh B, Payne R, Maslin K, Jape G, et al. The epidemiology and clinical features of kawasaki disease in Australia. *Pediatr*. (2014) 133:e1009–14. doi: 10.1542/peds.2013-2936

27. Singh S, Kawasaki T. Kawasaki disease in India–lessons learnt over the last 20 years. *Indian Pediatr*. (2016) 53:119–24. doi: 10.1007/s13312-016-0804-5

28. Sadeghi P, Izadi A, Mojtahedi SY, Khedmat L, Jafari M, Afshin A, et al. A 10-year cross-sectional retrospective study on kawasaki disease in Iranian children: incidence, clinical manifestations, complications, and treatment patterns. *BMC Infect Dis*. (2021) 21:368. doi: 10.1186/s12879-021-06046-2

29. Piram M. Epidemiology of kawasaki disease in Europe. *Front Pediatr*. (2021) 9:469. doi: 10.3389/fped.2021.673554

30. Kim GB. Reality of kawasaki disease epidemiology. *Korean J Pediatr*. (2019) 62:292–6. doi: 10.3345/kjp.2019.00157

31. Uehara R, Yashiro M, Nakamura Y, Yanagawa H. Kawasaki disease in parents and children. *Acta Paediatr*. (2007) 92:694–7. doi: 10.1111/j.1651-2227.2003.tb00602.x

32. Tulloh RMR, Mayon-White R, Harnden A, Ramanan AV, Tizard EJ, Shingadia D, et al. Kawasaki disease: a prospective population survey in the UK and Ireland from 2013 to 2015. *Arch Dis Child*. (2019) 104:640–6. doi: 10.1136/archdischild-2018-315087

33. Kwon Y-C, Kim J-J, Yun SW, Yu JJ, Yoon KL, Lee K-Y, et al. Male-specific association of the FCGR2A His167Arg polymorphism with kawasaki disease. *PLoS ONE*. (2017) 12:e0184248. doi: 10.1371/journal.pone.0184248

34. Lin M-C, Lai M-S, Jan S-L, Fu Y-C. Epidemiologic features of kawasaki disease in acute stages in Taiwan, 1997–2010: effect of different case definitions in claims data analysis. *J Chin Med Assoc*. (2015) 78:121–6. doi: 10.1016/j.jcma.2014.03.009

35. Kim GB, Han JW, Park YW, Song MS, Hong YM, Cha SH, et al. Epidemiologic features of kawasaki disease in South Korea. *Pediatr Infect Dis J*. (2014) 33:24–7. doi: 10.1097/INF.0000000000000010

36. Makino N, Nakamura Y, Yashiro M, Sano T, Ae R, Kosami K, et al. Epidemiological observations of kawasaki disease in Japan, 2013-2014. *Pediatr Int*. (2018) 60:581–7. doi: 10.1111/ped.13544

37. Yeom JS, Woo HO, Park JS, Park ES, Seo J-H, Youn H-S. Kawasaki disease in infants. *Korean J Pediatr*. (2013) 56:377–82. doi: 10.3345/kjp.2013.56.9.377

38. Iino M, Igarashi H, Samada K, Shiraishi H, Momoi MY. A case of kawasaki disease in NICU. *Pediatr Res*. (2003) 53:181–181. doi: 10.1203/00006450-200301000-00167

39. Tsuchida S, Yamanaka T, Tsuchida R, Nakamura Y, Yashiro M, Yanagawa H. Epidemiology of infant kawasaki disease with a report of the youngest neonatal case ever reported in Japan. *Acta Paediatr*. (1996) 85:995–7. doi: 10.1111/j.1651-2227.1996.tb14201.x

40. Lee EJ, Park YW, Hong YM, Lee JS, Han JW. Epidemiology of kawasaki disease in infants 3 months of age and younger. *Korean J Pediatr*. (2012) 55:202–5. doi: 10.3345/kjp.2012.55.6.202

41. Garrido-García LM, Gutiérrez-Alanis JH, Ramírez-Perea AI, Tremoulet A, Yamazaki-Nakashimada MA. Kawasaki disease in infants in the first 3 months of age in a Mexican population: a cautionary tale. *Front Pediatr*. (2020) 8:397. doi: 10.3389/fped.2020.00397

42. Salgado AP, Ashouri N, Berry EK, Sun X, Jain S, Burns JC, et al. High risk of coronary artery aneurysms in infants younger than 6 months of age with kawasaki disease. *J Pediatr*. (2017) 185:112–116.e1. doi: 10.1016/j.jpeds.2017.03.025

43. de La Harpe M, di Bernardo S, Hofer M, Sekarski N. Thirty years of kawasaki disease: a single-center study at the university hospital of lausanne. *Front Pediatr*. (2019) 7:11. doi: 10.3389/fped.2019.00011

44. Huang W-C, Huang L-M, Chang I-S, Chang L-Y, Chiang B-L, Chen P-J, et al. Epidemiologic features of kawasaki disease in Taiwan, 2003–2006. *Pediatrics*. (2009) 123:e401–5. doi: 10.1542/peds.2008-2187

45. Dergun M, Kao A, Hauger SB, Newburger JW, Burns JC. Familial occurrence of kawasaki syndrome in North America. *Arch Pediatr Adolesc Med*. (2005) 159:876–81. doi: 10.1001/archpedi.159.9.876

46. Galeotti C, Kaveri SV, Cimaz R, Koné-Paut I, Bayry J. Predisposing factors, pathogenesis and therapeutic intervention of kawasaki disease. *Drug Discov Today*. (2016) 21:1850–7. doi: 10.1016/j.drudis.2016.08.004

47. Kupelian C, Sathi B, Singh D. Autoimmune hemolytic Anemia and immune thrombocytopenia: a unique presentation of kawasaki disease. *Case Rep Rheumatol*. (2021) 2021:1–5. doi: 10.1155/2021/6640006

48. Ishiguro N, Takahashi Y. Kawasaki disease associated with idiopathic thrombocytopenic purpura. *Eur J Pediatr*. (1989) 148:379–379. doi: 10.1007/BF00444140

49. Lipnick RN. Kawasaki disease with thrombocytosis followed by thrombocytopenia Purpura in the same patient. *Arch Pediatr Adolesc Med*. (1989) 143:139. doi: 10.1001/archpedi.1989.02150140021008

50. Yıldırım DG, Demirdağ TB, Tokgöz ST, Tapısız A, Bakkaloğlu SA, Buyan N. Viral infections associated with kawasaki disease. *Turk Arch of Pediatr*. (2021) 56:272–4. doi: 10.5152/TurkArchPediatr.2021.20250

51. Özdemir H, Çiftçi E, Tapisiz A, Ince E, Tutar E, Atalay S, et al. Clinical and epidemiological characteristics of children with kawasaki disease in Turkey. *J Trop Pediatr*. (2010) 56:260–2. doi: 10.1093/tropej/fmp110

52. Jindal AK, Pilania RK, Guleria S, Vignesh P, Suri D, Gupta A, et al. Kawasaki disease in children older than 10 years: a clinical experience from northwest India. *Front Pediatr*. (2020) 8:24. doi: 10.3389/fped.2020.00024

53. Shamsizadeh A, Kajbaf TZ, Razavi M, Cheraghian B. Clinical and epidemiological characteristics of kawasaki disease. *Jundishapur J Microbiol*. (2014) 7:11014. doi: 10.5812/JJM.11014

54. Kanegaye JT, van Cott E, Tremoulet AH, Salgado A, Shimizu C, Kruk P, et al. Lymph-Node-First presentation of kawasaki disease compared with bacterial cervical adenitis and typical kawasaki disease. *J Pediatr*. (2013) 162:1259–1263.e2. doi: 10.1016/j.jpeds.2012.11.064

55. Jun WY, Ann YK, Kim JY, Son JS, Kim S-J, Yang HS, et al. Kawasaki disease with fever and cervical lymphadenopathy as the sole initial presentation. *Korean Circ J*. (2017) 47:107. doi: 10.4070/kcj.2016.0160

56. Nasri P, Adibmajlesi Z, Rahimi H, Saneian H, Famouri F, Khademian M, et al. Gastrointestinal manifestations in children with kawasaki disease in isfahan, Iran. *Arch Pediatr Infect Dis*. (2020) 8(20):e103072. doi: 10.5812/pedinfect.103072

57. Fabi M, Corinaldesi E, Pierantoni L, Mazzoni E, Landini C, Bigucci B, et al. Gastrointestinal presentation of kawasaki disease: a red flag for severe disease? *PLoS ONE*. (2018) 13(9):e0202658. doi: 10.1371/JOURNAL.PONE.0202658

58. Singh R, Ward C, Walton M, Persad R. Atypical kawasaki disease and gastrointestinal manifestations. *Paediatr Child Health*. (2007) 12:235. doi: 10.1093/PCH/12.3.235

59. Suhaini SA, Azidin AH, Cheah CS, Lee Wei Li WLW, Khoo MS, Ismail NAS, et al. Kawasaki disease with hepatobiliary manifestations. *Med (B Aires)*. (2022) 58:1833. doi: 10.3390/medicina58121833

60. Lee M-S, Liu Y-C, Tsai C-C, Hsu J-H, Wu J-R. Similarities and differences between COVID-19-related multisystem inflammatory syndrome in children and kawasaki disease. *Front Pediatr*. (2021) 9:640118. doi: 10.3389/fped.2021.640118

61. Huu Son N, Kiem Hao T, Hoang Anh NT. A retrospective cohort study of kawasaki disease in hue central hospital for 10 years (2010–2019). *Open Access Maced J Med Sci*. (2020) 8:99–103. doi: 10.3889/oamjms.2020.3858

62. Lee W, Cheah CS, Suhaini SA, Azidin AH, Khoo MS, Ismail NAS, et al. Clinical manifestations and laboratory findings of kawasaki disease: beyond the classic diagnostic features. *Medicina (B Aires)*. (2022) 58:734. doi: 10.3390/medicina58060734

63. Manlhiot C, Christie E, McCrindle BW, Rosenberg H, Chahal N, Yeung RSM. Complete and incomplete kawasaki disease: two sides of the same coin. *Eur J Pediatr*. (2012) 171:657–62. doi: 10.1007/s00431-011-1631-2

64. Perrin L, Letierce A, Guitton C, Tran T-A, Lambert V, Koné-Paut I. Comparative study of complete versus incomplete kawasaki disease in 59 pediatric patients. *Joint Bone Spine*. (2009) 76:481–5. doi: 10.1016/j.jbspin.2008.11.015

65. Sanchez-Manubens J, Anton J, Prada F, Bou R, Iglesias E, Calzada-Hernandez J, et al. Incidence and clinical features of kawasaki disease in catalonia (Spain). *Pediatric Rheumatol*. (2014) 12:123. doi: 10.1186/1546-0096-12-S1-P123

66. ElAdawy M, Dominguez SR, Anderson MS, Glodé MP. Abnormal liver panel in acute kawasaki disease. *Pediatr Infect Dis J*. (2011) 30:141–4. doi: 10.1097/INF.0b013e3181f6fe2a

67. Xie T, Wang Y, Fu S, Wang W, Xie C, Zhang Y, et al. Predictors for intravenous immunoglobulin resistance and coronary artery lesions in kawasaki disease. *Pediatric Rheumatol*. (2017) 15:17. doi: 10.1186/s12969-017-0149-1

68. Tomita Y, Fukaya T, Yamaura Y, Tsujiguchi R, Muratani H, Shimaya M. Implications of hepatic dysfunction in kawasaki disease: time-related changes in aspartate aminotransferase, alanine aminotransferase, total bilirubin, and C-reactive protein levels. *Pediatr Investig*. (2019) 3:19–26. doi: 10.1002/ped4.12112

69. Liu L, Yin W, Wang R, Sun D, He X, Ding Y. The prognostic role of abnormal liver function in IVIG unresponsiveness in kawasaki disease: a meta-analysis. *Inflammation Res*. (2016) 65:161–8. doi: 10.1007/s00011-015-0900-3

70. Maggio MC, Corsello G, Prinzi E, Cimaz R. Kawasaki disease in sicily: clinical description and markers of disease severity. *Ital J Pediatr*. (2016) 42:92. doi: 10.1186/s13052-016-0306-z

71. Kim GB, Park S, Eun LY, Han JW, Lee SY, Yoon KL, et al. Epidemiology and clinical features of kawasaki disease in South Korea, 2012–2014. *Pediatr Infect Dis J*. (2017) 36:482–5. doi: 10.1097/INF.0000000000001474

72. Durongpisitkul K, Sangtawesin C, Khongphatthanayopthin A, Panamonta M, Sopontammarak S, Sittiwangkul R, et al. Epidemiologic study of kawasaki disease and cases resistant to IVIG therapy in Thailand. *Asian Pac J Allergy Immunol*. (2006) 24:27–32. PMID: 16913186.

73. Shenoy B, Arun BC. Retrospective cohort study of clinical profile and IVIg resistance in children with incomplete kawasaki disease in a tertiary care center. *Pediatr Infect Dis*. (2022) 4:83–5. doi: 10.5005/jp-journals-10081-1281

74. Berard R, Whittemore B, Scuccimarri R. Hemolytic anemia following intravenous immunoglobulin therapy in patients treated for kawasaki disease: a report of 4 cases. *Pediatric Rheumatol*. (2012) 10:10. doi: 10.1186/1546-0096-10-10

75. Desborough MJ, Miller J, Thorpe SJ, Murphy MF, Misbah SA. Intravenous immunoglobulin-induced haemolysis: a case report and review of the literature. *Transfusion Med*. (2014) 24:219–26. doi: 10.1111/tme.12083

76. Robinson C, Chanchlani R, Gayowsky A, Brar S, Darling E, Demers C, et al. Incidence and short-term outcomes of kawasaki disease. *Pediatr Res*. (2021) 90:670–7. doi: 10.1038/s41390-021-01496-5

77. Cimaz R, Fanti E, Mauro A, Voller F, Rusconi F. Epidemiology of kawasaki disease in Italy: surveillance from national hospitalization records. *Eur J Pediatr*. (2017) 176:1061–5. doi: 10.1007/s00431-017-2947-3

78. Smorczewska-Kiljan A, Marszał M, Friedman-Gruszczyńska J, Wieteska-Klimczak A, Książyk J, Jaworski M, et al. Clinical characteristics of kawasaki disease in Polish children: a retrospective study. *Kardiol Pol*. (2022) 80:657–63. doi: 10.33963/KP.a2022.0090

79. Ram Krishna M, Sundaram B, Dhanalakshmi K. Predictors of coronary artery aneurysms in kawasaki disease. *Clin Pediatr (Phila)*. (2014) 53:561–5. doi: 10.1177/0009922814530802

80. Yan F, Pan B, Sun H, Tian J, Li M. Risk factors of coronary artery abnormality in children with kawasaki disease: a systematic review and meta-analysis. *Front Pediatr*. (2019) 7:374. doi: 10.3389/fped.2019.00374

81. Santimahakullert K, Vijarnsorn C, Wongswadiwat Y, Chanthong P, Khrongsrattha S, Panamonta M, et al., A retrospective cohort study of major adverse cardiac events in children affected by kawasaki disease with coronary artery aneurysms in Thailand. *PLoS One*. (2022) 17:e0263060. doi: 10.1371/journal.pone.0263060

frontiers | Frontiers in Cardiovascular Medicine

TYPE Original Research
PUBLISHED 15 February 2023
DOI 10.3389/fcvm.2023.1067072

OPEN ACCESS

EDITED BY
Zhen-Yu Zhang,
KU Leuven,
Belgium

REVIEWED BY
Shohreh Naderimagham,
Tehran University of Medical Sciences,
Iran
Andrea Gomes Bernardes,
State University of Londrina, Brazil

*CORRESPONDENCE
Yue Zhang
✉ yuezhang@sxmu.edu.cn
Xiaopan Li
✉ xiaopanli0224@126.com
Zheng Luo
✉ zhengluo86@foxmail.com

†These authors have contributed equally to this work

SPECIALTY SECTION
This article was submitted to Pediatric Cardiology, a section of the journal Frontiers in Cardiovascular Medicine

RECEIVED 11 October 2022
ACCEPTED 20 January 2023
PUBLISHED 15 February 2023

CITATION
Zhang Y, Lin C, Liu M, Zhang W, Xun X, Wu J, Li X and Luo Z (2023) Burden and trend of cardiovascular diseases among people under 20years in China, Western Pacific region, and the world: An analysis of the global burden of disease study in 2019.
Front. Cardiovasc. Med. 10:1067072.
doi: 10.3389/fcvm.2023.1067072

Burden and trend of cardiovascular diseases among people under 20years in China, Western Pacific region, and the world: An analysis of the global burden of disease study in 2019

Yue Zhang[1*†], Changjian Lin[2†], Ming Liu[3,4†], Wei Zhang[5], Xiaoyun Xun[5], Jinyi Wu[6], Xiaopan Li[3*] and Zheng Luo[5*]

[1]School of Public Health, Department of Epidemiology, Shanxi Medical University, Taiyuan, China, [2]Department of Cardiovascular Medicine, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China, [3]Department of Health Management Center, Zhongshan Hospital, Shanghai Medical College of Fudan University, Shanghai, China, [4]Shanghai Engineering Research Center of AI Technology for Cardiopulmonary Diseases, Zhongshan Hospital, Fudan University, Shanghai, China, [5]Shanghai University of Medicine and Health Sciences Affiliated Zhoupu Hospital, Shanghai, China, [6]Department of Public Health, Wuhan Fourth Hospital, Wuhan, China

Objectives: Cardiovascular disease (CVD) is a global public health concern, but its disease burden and trend have been poorly studied in people younger than 20years. This study aimed to fill this gap by evaluating the CVD burden and trend in China, Western Pacific Region, and the world from 1990 to 2019.

Methods: We applied the 2019 Global Burden of Diseases (GBD) analytical tools to compare the incidence, mortality, and prevalence of CVD, years lived with disability (YLDs), years of life lost (YLLs), and disability-adjusted life years (DALYs) among people younger than 20years from 1990 to 2019 in China, the Western Pacific Region, and the world. The trends of disease burden between 1990 and 2019 evaluated using the average annual percent change (AAPC) and the 95% uncertainty interval (UI) were reported.

Results: Globally, in 2019, there were 2.37 (95% UI: 1.82 to 3.05) million incidence of CVD, 16.85 (95% UI: 12.56 to 22.03) million prevalence of CVD, and 74386.73 (95% UI: 64543.82 to 86310.24) deaths due to CVD among people under 20years of age. The trends for DALYs decreased among children and adolescents in China, Western Pacific Region, and the world (AAPC=−4.29, 95% CI: −4.38% to −4.20%; AAPC=−3.37, 95% CI: −3.48% to −3.26%; AAPC=−2.17, 95% CI: −2.24% to −2.09%; $p<0.001$, respectively) between 1990 and 2019. With the increase in age, the AAPC values of mortality, YLLs, and DALYs showed a notable downward trend. The AAPC values of mortality, YLLs, and DALYs in female patients were significantly greater than those in male patients. For all subtypes of CVD, the AAPC values showed a downward trend, with the largest reduction observed for stroke. From 1990 to 2019, a decline in the DALY rate for all CVD risk factors was observed, with a significant decrease in environmental/occupational risk factors.

Conclusion: Our study shows a decline in the burden and trend of CVD among people younger than 20years, which reflects the success in reducing disability, premature death, and the early incidence of CVD. More effective and targeted preventive policies and interventions aimed at mitigating preventable CVD burden and addressing risk factors from childhood are urgently needed.

KEYWORDS

cardiovascular diseases, burden of disease, disability-adjusted life years, trend analysis, average annual percent change

Introduction

Cardiovascular diseases (CVDs) are chronic non-communicable diseases (NCDs) that seriously threaten human health. The global burden of disease (GBD) in 2019 shows that CVD is responsible for 18.5 million deaths worldwide, accounting for approximately 31% of total deaths (1). According to the statistics of China Cardiovascular Health and Disease Report 2020 (2), the number of patients with CVD in China is up to 330 million, and the number of deaths is 4.58 million, which accounts for more than 40%, ranking the first in the total cause of death, and two out of every five deaths are caused by CVD. The Sustainable Development Goals (SDGs) released the target of a reduction in premature mortality owing to NCDs by one-third by 2030, and the State Council of China subsequently endorsed an important document aimed at reducing the age-standardized mortality rate of CVD in 2015 by 15% by 2025 (3). Thus, a consistent, comparable, and comprehensive analysis of the long-term trend at the global, regional, and national levels is essential to guide public policy and provide resource allocation for decision-makers.

Childhood and adolescence are vulnerable periods and a key window for adult health. However, a large number of studies have found that the incidence of CVD is scarce over this period (4). The majority of CVDs manifest in the middle age and beyond, and it is now clear that their origin may be during childhood and adolescence. Many traditional risk factors for CVD, such as hypertension, dyslipidemia, obesity, unhealthy diet, and smoking, begin during childhood and then tend to accumulate and increase with age. Social risk factors, such as low socioeconomic status and poor education, also increase the risk of developing CVD at a very young age. Research suggests very few adolescents, including children, have an ideal CVD health profile (5). Therefore, it is of great public health importance to focus on the burden and trend of CVD during this period. In addition, children and adolescents with an underlying heart disease, either congenital or acquired, deserve special consideration with regard to future CVDs. A report showed that congenital heart disease accounts for nearly one-third of all congenital birth defects, and a focus on congenital heart disease is indispensable to eliminating preventable child deaths and additional injury to the coronary arteries in the era of the SDGs (6). Given the enormous disease burden and health resource constraints, to stem the tide of CVD requires a life course approach with a preventive strategy starting from early childhood and adolescence.

The Global Burden of Diseases, Injuries, and Risk Factors Study 2019 (GBD 2019) framework, with a broad collection of data sources and statistical modeling approaches, enables the comparable assessment of CVD burden in terms of incidence, mortality, years of life lost (YLLs), years lived with disability (YLDs), and disability-adjusted life years (DALYs). GBD also provides information to understand both the trends in risk exposure and the trends in burden attributable to risks. Currently, the burden of CVD is studied predominantly in adults, with few studies in children and adolescents, and even fewer studies on the attributable disease burden. In this study, we aimed to estimate the burden of CVD and its trend among people under the age of 20 years, stratified by gender and subtypes, as well as CVD-related DALYs associated with potentially modifiable behavioral, environmental, and metabolic risk factors from 1990 to 2019 in the world, the Western Pacific Region, and China by using the data from the GBD 2019 study.

Methods

Data sources and definitions

Data for this study were obtained from the GBD 2019 study. The GBD 2019 generates estimates due to 369 diseases and injuries, 87 risk factors, and a combination of risk factors in 204 countries and territories. The details of the GBD 2019 eligibility criteria, the literature search strategy, and data extraction have been published elsewhere (7–9). We produced standard epidemiological measures such as incidence, prevalence, and mortality, as well as summary measures of health (YLLs, YLDs, and DALYs) among people younger than 20 years due to CVD. YLL is a measure of premature death within a group of people. YLD measures the amount of time people lose due to diseases and injuries that reduce their health but do not cause death. DALY is a comprehensive indicator to assess the disease burden of disability and premature death, which is obtained by adding YLLs and YLDs. In our analyses, CVD subtypes included hypertensive heart disease, ischemic heart disease, non-rheumatic valvular heart disease, rheumatic heart disease, stroke, aortic aneurysm, cardiomyopathy and myocarditis, endocarditis, and other cardiovascular and circulatory diseases. Three major risk factors, such as behavioral, environmental/occupational, and metabolic risk factors, were considered to be associated with CVD in GBD 2019. We covered four age groups: less than 5 years, 5–9 years, 10–14 years, and 15–19 years. To ensure transparency and replicability, our study follows the Guidelines for Accurate and Transparent Health Estimates Reporting (GATHER) (10). All data used in this study were obtained from the Institute for Health Metrics and Evaluation (IHME) website.

Statistical analyses

We computed counts, rates (per 100,000), and DALYs to quantify the burden of CVD stratified by sex, age, and subtypes of people under 20 years. The trends of disease burden between 1990 and 2019 were evaluated using average annual percent change (AAPC), which was calculated by the Joinpoint Regression Program (Version 4.9.0.0. March 2021) (11). For each estimated metric, the 95% uncertainty interval (UI) was reported. 95% UI was calculated by taking 1,000 draws from the posterior distribution of each quantity, using the 2.5th and 97.5th ordered draw of the uncertainty distribution (12). We considered a p-value of <0.05 to be significant.

Results

The absolute number and rate of incidence, prevalence, deaths, YLLs, YLDs, DALYs, and AAPC from 1990 to 2019 caused by CVD in people younger than 20 years in China, the Western Pacific Region, and the world are shown in Table 1. From 1990 to 2019, the absolute number,

TABLE 1 Absolute number and rate of incidence, prevalence, deaths, YLLs, YLDs, and DALYs due to CVD among people younger than 20years and APCC for 1990–2019 in China, the Western Pacific Region, and the world.

Metrics		China		Western Pacific Region		Global	
		1990	2019	1990	2019	1990	2019
Incidence (95%UI)	Absolute number	409300.76	203195.69	475659.93	281124.2	1827746.25	2373195.97
		(327352.27,504066.70)	(160256.44,255326.61)	(381650.78,581603.92)	(223730.33,350821.12)	(1450692.42,2294789.46)	(1829940.75,3051990.37)
	Rate, per 100,000 people	91	67.75	79.52	63.36	80.39	92.01
		(72.78,112.07)	(53.43,85.13)	(63.80,97.23)	(50.42,79.07)	(63.81,100.93)	(70.95,118.33)
	% (AAPC, 95%CI)	−0.87(−1.03, −0.71)*		−0.65(−0.80, −0.51)*		0.63 (0.55, 0.71)*	
Prevalence (95%UI)	Absolute number	2178911.814	1263148.913	2551936.98	1740261.8	11727242.46	16858400.17
		(1617433.26,2905474.49)	(932371.44,1675385.97)	(1906707.59,3355515.46)	(1304688.62,2272508.71)	(8854546.46,15263375.59)	(12565499.27,22032406.43)
	Rate, per 100,000 people	484.43	421.17	426.63	392.21	515.81	653.61
		(359.60,645.96)	(310.88,558.62)	(318.76,560.98)	(294.05,512.17)	(389.46,671.34)	(487.17,854.21)
	%, (AAPC, 95%CI)	0.21(−0.10,0.53)		0.30 (0.03,0.57)		1.07 (0.99,1.16)*	
Deaths (95%UI)	Absolute number	30135.18	4835.28	34787.46	8,250	139668.54	74386.73
		(26396.41,33960.60)	(4210.49,5513.12)	(30822.47,38943.28)	(7409.09,9156.37)	(121153.25,155316.95)	(64543.82,86310.24)
	Rate, per 100,000 people	6.7	1.61	5.82	1.86	6.14	2.88
		(5.87,7.55)	(1.40,1.84)	(5.15,6.51)	(1.67,2.06)	(5.33,6.83)	(2.50,3.35)
	%, (AAPC, 95%CI)	−4.79(−4.89, −4.69)*		−3.73(−3.83, −3.62)*		−2.46 (−2.53, −2.38)*	
YLLs (95%UI)	Absolute number	2472750.926	379256.3768	2847258.14	647555.03	11423222.51	5889324.54
		(2158901.23,2797897.97)	(330625.85,433093.92)	(2516179.36,3198558.80)	(581496.01,718859.32)	(9817748.43,12759023.73)	(5082198.99,6853521.31)
	Rate, per 100,000 people	549.75	126.45	476.01	145.94	502.44	228.33
		(479.98,622.04)	(110.24,144.41)	(420.66,534.74)	(131.06,162.01)	(431.82,561.19)	(197.04,265.72)
	% (AAPC, 95%CI)	−4.95(−5.06, −4.85)*		−3.89(−4.00, −3.78)*		−2.55(−2.63, −2.47)	
YLDs (95%UI)	Absolute number	204348.9393	123301.8668	251189.77	176682.5	968145.51	1287283.25
		(139843.14,287175.38)	(84632.77,173058.83)	(173158.12,349811.63)	(121704.92,244895.39)	(655710.36,1348218.25)	(856137.21,1805917.41)
	Rate, per 100,000 people	45.43	41.11	41.99	39.82	42.58	49.91
		(31.09,63.85)	(28.22,57.70)	(28.95,58.48)	(27.43,55.19)	(28.84,59.30)	(33.19,70.02)
	% (AAPC, 95%CI)	0.06(−0.13,0.25)		0.15(−0.01,0.31)		0.72 (0.66,0.78)	

(Continued)

10.3389/fcvm.2023.1067072

10.3389/fcvm.2023.1067072

TABLE 1 (Continued)

Metrics		China		Western Pacific Region		Global	
		1990	2019	1990	2019	1990	2019
DALYs (95%UI)	Absolute number	2677099.87 (2360248.96,3024204.21)	502558.24 (439544.21,574888.74)	3098447.91 (2745675.08,3461643.39)	824237.53 (733779.14,920751.44)	12391368.02 (10781927.39,13776519.04)	7176607.79 (6263462.47,8259236.44)
	Rate, per 100,000 people	595.19 (524.74,672.36)	167.57 (146.56,191.68)	518 (459.02,578.72)	185.76 (165.38,207.52)	545.02 (474.23,605.94)	278.24 (242.84,320.22)
	% (AAPC, 95%CI)	−4.29(−4.38, −4.20)*		−3.37(−3.48, −3.26)*		−2.17(−2.24, −2.09)*	

*$p < 0.001$, DALYs, disability-adjusted life years; YLDs, years lived with disability; YLLs, years of life lost; UI, uncertainty interval; CI, confidence interval.

rate of incidence, and prevalence of CVD and also deaths due to CVD among people under 20 years of age in China, the Western Pacific Region, and the world showed a continuous declining trend. Globally in 2019, there were 2.37 million (95% UI 1.82 to 3.05) incidence of CVD, 16.85 million (95% UI 12.56 to 22.03) prevalence of CVD, and 74386.73 (95% UI 64543.82 to 86310.24) deaths due to CVD among people under 20 years of age. The incidence of cases of CVD has almost become half from 409300.76 (95% UI 327352.27 to 504066.70) in 1990 to 203195.69 (95% UI 160256.44 to 255326.61) in 2019 in China. In 2019, rates on YLLs, YLDs, and DALYs for CVD were 228.33/100,000, 49.91/100,000, and 278.24/100,000, respectively, globally. The trends of DALYs and YLLs also decreased in children and adolescents in China, Western Pacific Region, and the world. At the global level, the absolute number of DALYs due to CVD in 1990 (12.39 million [95% UI 10.78–13.77]) significantly exceeded that in 2019 (7.17 million [6.26–8.25]). The disease burden of CVD among people under 20 years of age in China is lower than that in the global and Western Pacific Regions. From 1990 to 2019, the AAPC of mortality due to CVD among people younger than 20 years in China, the Western Pacific Region, and the world decreased by 4.79% (95% CI: −4.89% to −4.69%, $p < 0.001$), 3.73% (95%CI: −3.83% to −3.62%, $p < 0.001$), and 2.46% (95% CI: −2.53% to −2.38%, $p < 0.001$), respectively. The YLLs all showed a downward trend ($p < 0.001$), while DALYs due to CVD decreased in China, the Western Pacific Region, and the world (AAPC = −4.29, 95% CI: −4.38% to −4.20%; AAPC = −3.37, 95% CI: −3.48% to −3.26%; AAPC = −2.17, 95% CI: −2.24% to −2.09%; $p < 0.001$, respectively) between 1990 and 2019. Figure 1 intuitively shows the DALY values of CVD among people under the age of 20 years in different WHO regions. It was found that the AAPC values of CVD in the Western Pacific Region, the Eastern Mediterranean Region, and China have decreased by more than 2.5%.

Table 2 shows the AAPC of incidence, prevalence, deaths, YLLs, YLDs, and DALYs due to CVD among people younger than 20 years during 1990–2019 in China, the Western Pacific Region, and the world. With the increase in age, the values of AAPC of mortality, YLLs, and DALYs showed a notable downward trend. From 1990 to 2019, global DALYs from CVD decreased by 3.33%, 1.87%, 0.90%, and 1.09% annually among people under 5 years, 5–9 years, 10–14 years, and 15–19 years, respectively, but at the global level, the AAPC of the incidence and prevalence of CVD was observed to increase from 1990 to 2019. Compared with the global and Western Pacific Regions, the AAPC of DALYs in children under 20 years of age in China decreased the fastest ($p < 0.001$).

The AAPC of incidence, prevalence, deaths, YLLs, YLDs, and DALYs due to CVD among people under 20 years of age, stratified by gender from 1990 to 2019 in China, Western Pacific Region, and the world is shown in Figure 2. We found that a reduction in the AAPC of mortality, YLLs, and DALYs for both sexes combined was observed, with a greater reduction among female patients than male patients significantly (all $p < 0.001$). However, at the global level, there was a slower increase in the AAPC of incidence (male patients: AAPC = 0.58%; female patients: AAPC = 0.69%).

Figure 3 displays the long-term trend of DALYs among people under 20 years for all subtypes of CVD from 1990 to 2019. For all subtypes of CVD, the AAPC values showed a downward trend, regardless of the world, the Western Pacific Region, and China. The largest reduction was observed for stroke, such as DALYs in China, which went from 286.89/100,000 in 1990 to 62.51/100,000 in 2019, whereas other subtypes of CVD showed only a slight decrease. The AAPC of DALYs for all subtypes of CVD was significantly decreasing

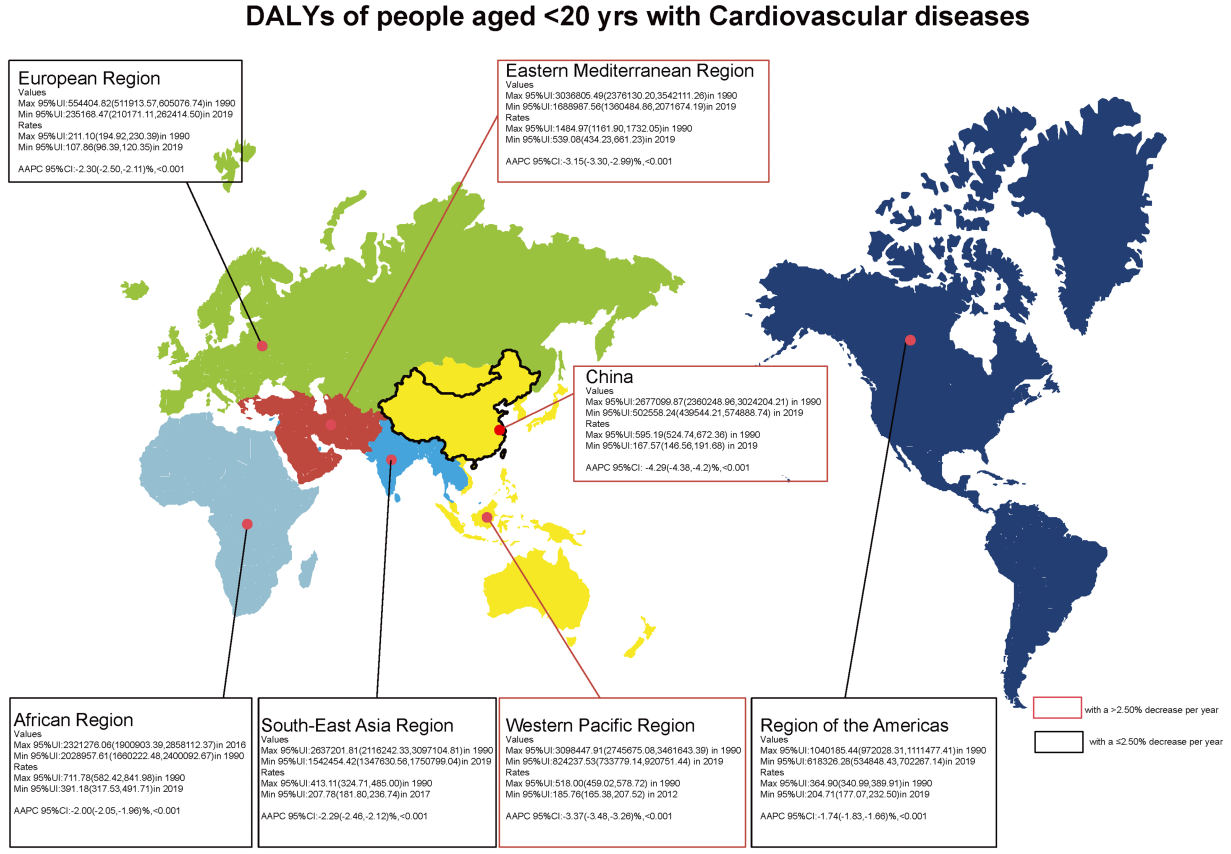


FIGURE 1
Number, rate, and average annual percentage change (AAPC) of DALYs among people with CVD 20 years.

(all $p < 0.001$). In China and the Western Pacific Region, the AAPC in DALYs for endocarditis between 1990 and 2019 was the largest, which was −8.65% (95% CI: −9.40% to −7.89%) and −6.40% (95% CI: −7.05% to −5.74%), respectively.

Figure 4 illustrates the long-term trend of CVD-related DALYs attributable to risk factors from 1990 to 2019 among people under 20 years of age. We focused on three major risk factors for CVD: behavioral risks, environmental/occupational risks, and metabolic risks. A decline in the DALY rate for all CVD risk factors was observed in China, the Western Pacific Region, and the world from 1990 to 2019, with a significant decrease in environmental/occupational risk factors. China had the largest AAPC values in all CVD risk factors (AAPC = −5.27, 95% CI: −5.41% to −5.14%).

Discussion

CVD remains the leading cause of premature mortality and rising healthcare costs and is a significant global health problem. Epidemiological studies in terms of the incidence, prevalence, deaths, YLLs, YLDs, and DALYs in CVD burden are sparse because of the overall low incidence of overt CVD among children and adolescents. To our knowledge, this is the first comprehensive and comparative report on the disease burden of CVD and its trends among people under 20 years of age in China, the Western Pacific Region, and the world over a 30-year period from 1990 to 2019. Our results provided several key messages. Globally in 2019, there were 2.37 million incidences of CVD, 16.85 million prevalence of CVD, and 74386.73 deaths due to CVD among people under 20 years of age. The burden and trends of CVD in China, the Western Pacific Region, and the global scale generally showed a downward trend among people younger than 20 years. The decrease in CVD burden is consistent with previous findings and may be attributed to the enforcement of life-saving health policies and interventions, rapid development of medical standards and essential treatment, as well as maternal education (13–15). Pathological evidence of atherosclerosis in young individuals was first identified in young male casualties from the Korean and Vietnam Wars and then further characterized by the Bogalusa Heart Study (16). CVD could begin in childhood and may progressively worsen without any appropriate intervention. Therefore, it is critical to pay attention to the burden of CVD and trends in childhood and actively implement effective interventions.

Findings from this study found that at the global level, the AAPC in the incidence and prevalence of CVD was observed to increase from 1990 to 2019. Chen Huang et al. (17) also revealed that the prevalence of CVD has been increasing in children, adolescents, and young adults in recent decades in developed countries. However, opposite results were observed for the incidence of APCC in China and the Western Pacific region. This discrepancy may be explained by the fact that many countries are included in the analysis of the global data, with different levels of development, medical conditions, distribution of health resources, and perception of CVD. We further observed that with the increase in age, the AAPC values of mortality, YLLs, and DALYs showed a notable downward trend. We speculated that this change was largely related to the global decline in fertility or increased awareness of healthy living in childhood. Comparatively, although there was a decline in the CVD burden, the increase in the absolute incidence of cases of CVD could not be ignored.

10.3389/fcvm.2023.1067072

TABLE 2 Average annual percentage change (AAPC) of incidence, prevalence, deaths, YLLs, YLDs, and DALYs due to CVD among people younger than 20 years for 1990–2019 in China, Western Pacific Region, and the world.

	<5years old		5–9years old		10–14years old		15–19years old	
	AAPC 95%CI (%)	*P*	AAPC 95%CI (%)	*P*	AAPC 95%CI (%)	*P*	AAPC 95%CI (%)	*P*
China								
Incidence	−1.81(−1.95, −1.66)	<0.001	−0.82(−1.03, −0.62)	<0.001	−0.41(−0.68, −0.15)	0.003	−0.57(−0.75, −0.38)	<0.001
Mortality	−6.82(−7.11, −6.53)	<0.001	−4.42(−4.89, −3.94)	<0.001	−3.45(−3.93, −2.97)	<0.001	−2.85(−2.95, −2.74)	<0.001
Prevalence	−0.04(−0.37,0.29)	0.811	0.27(−0.00,0.54)	0.052	0.41 (0.10,0.72)	0.012	0.00(−0.38,0.39)	0.983
YLLs	−6.82(−7.11, −6.52)	<0.001	−4.41(−4.89, −3.94)	<0.001	−3.46(−3.94, −2.98)	<0.001	−2.85(−2.95, −2.75)	<0.001
YLDs	−0.16(−0.31, −0.02)	0.028	0.10(−0.09,0.28)	0.288	0.18(−0.04,0.39)	0.108	−0.09(−0.34,0.17)	0.486
DALYs	−6.69(−6.97, −6.42)	<0.001	−3.47(−3.81, −3.12)	<0.001	−2.22(−2.50, −1.94)	<0.001	−2.35(−2.48, −2.23)	<0.001
Western Pacific Region								
Incidence	−1.45(−1.58, −1.31)	<0.001	−0.62(−0.80, −0.44)	<0.001	−0.27(−0.47, −0.07)	0.009	−0.39(−0.55, −0.24)	<0.001
Mortality	−5.74(−5.90, −5.58)	<0.001	−3.32(−3.64, −3.00)	<0.001	−2.06(−2.38, −1.74)	<0.001	−1.96(−2.10, −1.82)	<0.001
Prevalence	0.28 (0.01,0.56)	0.040	0.31 (0.08,0.53)	0.009	0.39 (0.16, 0.63)	0.002	0.17(−0.14, 0.48)	0.279
YLLs	−5.75(−5.91, −5.58)	<0.001	−3.33(−3.65, −3.01)	<0.001	−2.06(−2.38, −1.74)	<0.001	−1.97(−2.11, −1.83)	<0.001
YLDs	0.02(−0.09, 0.12)	0.767	0.16 (0.02,0.31)	0.025	0.20 (0.05, 0.36)	0.014	0.05(−0.15, 0.26)	0.590
DALYs	−5.64(−5.78, −5.49)	<0.001	−2.61(−2.84, −2.38)	<0.001	−1.35(−1.55, −1.16)	<0.001	−1.61(−1.77, −1.45)	<0.001
Global								
Incidence	0.20 (0.15, 0.24)	<0.001	0.69 (0.57, 0.81)	<0.001	0.89 (0.73, 1.05)	<0.001	0.52 (0.45, 0.60)	<0.001
Mortality	−3.40(−3.49, −3.31)	<0.001	−2.49(−2.58, −2.39)	<0.001	−1.47(−1.58, −1.36)	<0.001	−1.44(−1.51, −1.37)	<0.001
Prevalence	0.98 (0.90, 1.05)	<0.001	0.97 (0.86, 1.08)	<0.001	0.98 (0.83, 1.12)	<0.001	0.92 (0.80, 1.05)	<0.001
YLLs	−3.40(−3.49, −3.31)	<0.001	−2.49(−2.58, −2.39)	<0.001	−1.47(−1.58, −1.36)	<0.001	−1.44(−1.51, −1.37)	<0.001
YLDs	0.48 (0.44, 0.51)	<0.001	0.62 (0.55, 0.70)	<0.001	0.64 (0.54, 0.75)	<0.001	0.61 (0.51, 0.71)	<0.001
DALYs	−3.33(−3.42, −3.24)	<0.001	−1.87(−1.93, −1.80)	<0.001	−0.90(−0.98, −0.83)	<0.001	−1.09(−1.14, −1.04)	<0.001

DALYs, disability-adjusted life years; YLDs, years lived with disability; YLLs, years of life lost; UI, uncertainty interval; CI, confidence interval.

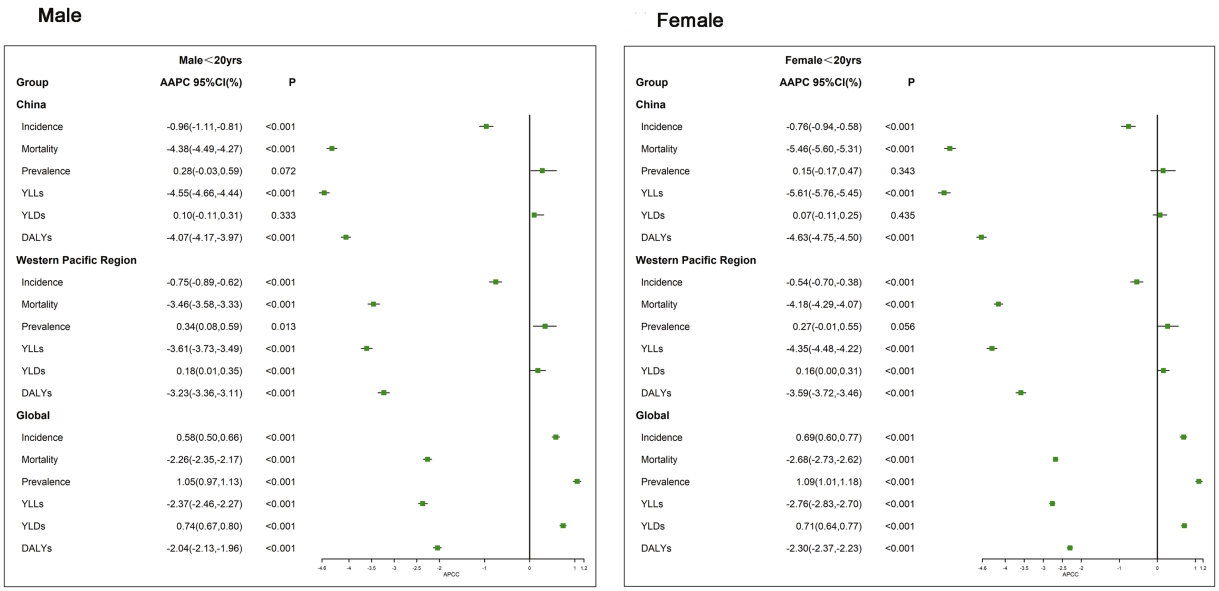


FIGURE 2
Average annual percentage change (AAPC) of incidence, prevalence, deaths, YLLs, YLDs, and DALYs of CVD in people younger than 20 years stratified by gender for 1990–2019 in China, the Western Pacific Region, and the world.

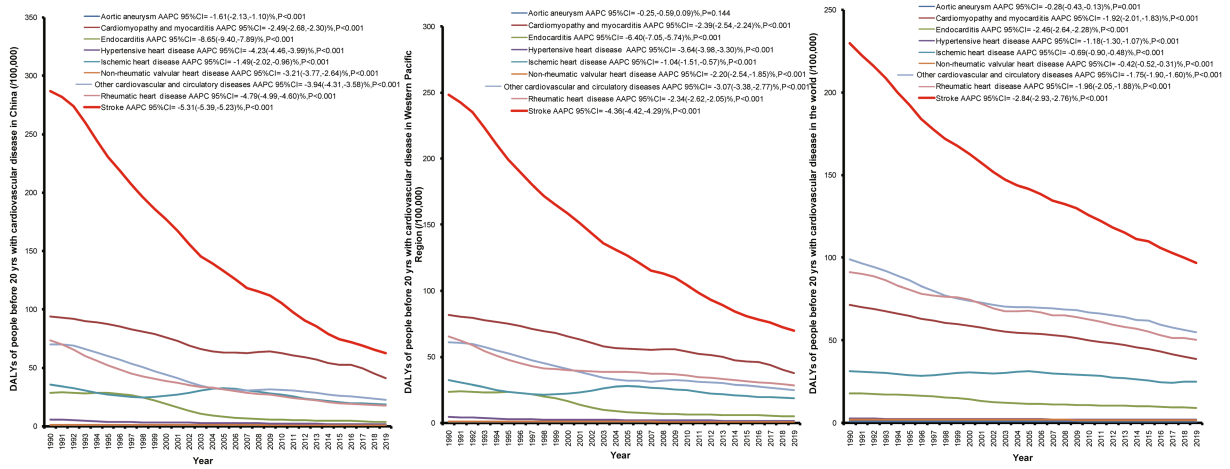


FIGURE 3
Long-term trends and AAPC values of DALYs among people before 20 years for all subtypes of CVD from 1990 to 2019 in China, the Western Pacific Region, and the world.

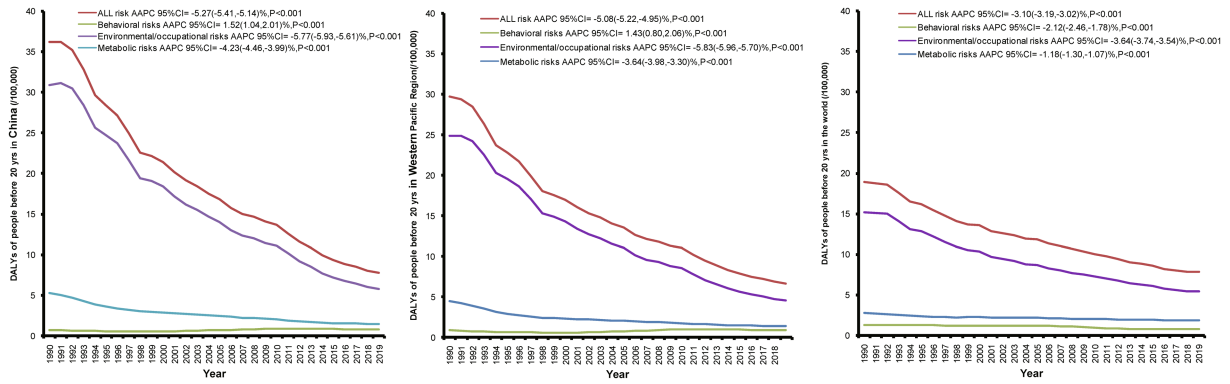


FIGURE 4
Long-term trends and AAPC values of CVD-related DALYs attributable to risk factors among people under 20years from 1990 to 2019 in China, the Western Pacific Region, and the world.

Furthermore, our results found that the CVD burden showed heterogeneity by gender in China, the Western Pacific Region, and the world. A decrease in the AAPC of mortality, YLLs, and DALYs was significantly higher in female patients than in male patients. This difference may be related to physiological differences, estrogen levels, and lifestyle between male patients and female patients (18). This gender difference should be taken into account by policymakers when planning future strategies and implementing interventions. There were marked differences in the trends of DALYs in terms of its main subcategories, including ischemic heart disease, stroke, endocarditis, and hypertensive heart disease. The AAPC values showed a downward trend, with the greatest decline in stroke. As for CVD subcategories, in clinical settings, stroke has been increasingly recognized as the main single type of atherosclerotic CVD in China, the Western Pacific Region, and the world (5). Although previous studies had reported a substantial increase in the burden of stroke (19), an obvious decline in the AAPC value and trend of stroke were observed in this study. Our results are consistent with a temporal trend in ischemic stroke incidence in younger adults in the Framingham study (20). A population study also observed that stroke due to small vessel occlusion and cardiac embolism may be on the decline (21). Long-term trends in stroke are controversial and may result from differences in the availability and affordability of medications, patient adherence to treatment, quality of healthcare, and appropriate management of post-discharge secondary prevention provided by professionals.

Behavioral, environmental/occupational, and metabolic risk factors are major drivers of CVD. Traditional risk factors such as high blood pressure (22), elevated lipid levels (23), smoking (24), a sedentary lifestyle (25), and being overweight (26) are well known; however, it is important to recognize that these risk factors often develop and begin to detrimentally affect health during childhood (27). In our study, a decline in the DALY rate for all CVD risk factors was observed over the past 30 years among people younger than 20 years, with a significant decrease in environmental/occupational risk factors. During this period of rising metabolic risk exposure, the burden of CVD has been declining, a seemingly paradoxical phenomenon that can be largely explained by the impact of access to care, social determinants of health, cohort effects, and other behavioral, occupational, and environmental risks not quantified here (7, 28, 29). There is growing evidence that environmental influences on an individual's cardiovascular health begin in childhood and even in the womb (30). As is well known, the early years of life, when behaviors

are still being learned, are a great opportunity to educate children about cardiovascular health. It is much easier to teach children healthy habits than to change well-established unhealthy behaviors in adults.

This study is based on the largest epidemiological dataset to date and is the first to provide systematic estimates of the CVD burden and trend of people under 20 years, stratified by gender and subtypes, as well as CVD-related DALYs attributable to risk factors in China, the Western Pacific Region, and the world from 1990 to 2019. However, it has some limitations. First, as part of the GBD study, all limitations of the GBD methodology affected this study, which have been described previously (31–33). Second, within the age range of the analysis, we did not make age-standardized adjustments for the corresponding indicators. Third, we have only roughly estimated three main risk factors for CVD-related DALYs. In addition, a comprehensive assessment of the burden of disease should also include economic, family, and social aspects, so multidimensional analysis can be considered to improve the accuracy of the results.

Conclusion

This study has evaluated the burden of CVD and its trends among people under 20 years, stratified by gender and subtypes in China, the Western Pacific Region, and the world from 1990 to 2019. Overall, the CVD burden saw a substantial decline among children and adolescents, although variability across countries was present. Targeted considerations were needed to integrate primary prevention and take effective measures in childhood to reduce the future burden of CVD in adults.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number (s) can be found at: https://vizhub.healthdata.org/gbd-results/.

Author contributions

YZ, XL, and ZL conceived and designed the experiment. YZ, CL, ML, and XL analyzed the data. ML, XX, JW, and ZL provided significant advice and consultation. YZ wrote the manuscript. All authors contributed to the article and approved the submitted version.

Funding

This study was supported by the Basic Research Program of Shanxi Province (Free exploration) project (20210302123216 to YZ), the Science and Technology Innovation Project of Higher Education Institutions in Shanxi Province (2021L221 to YZ), the Special Disease Construction Project of Pudong Health and Family Planning Commission of Shanghai (Grant No. PWZzb2022-20 to ZL), Discipline Construction Project of Pudong Health and Family Planning Commission of Shanghai (Grant No. PWYts2021-02 to ZL); the General Program of Health Bureau of the Shanghai Pudong New Area (PW2021A-68 to ZL), the Shanghai Health Medical College Faculty Teaching Project (ZPJXKT-21-11 to ZL), the General Program of Health Bureau of the Shanghai (202150015 to ZL), and the Shanghai Science and Technology Development Foundation (53310000501772180D to CL). The funder had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all data in the study and had responsibility for the decision to submit for publication.

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the article reported in this study.

Publisher's note

References

1. Roth, GA, Mensah, GA, and Fuster, V. The global burden of cardiovascular diseases and risks: a compass for global action. *J Am Coll Cardiol*. (2020) 76:2980–1. doi: 10.1016/j.jacc.2020.11.021

2. The Writing Committee of the Report on Cardiovascular Health and Diseases in China. Report on cardiovascular health and diseases burden in China: an updated summary of 2020. *Chin Circ J*. (2021) 36:521–45.

3. The State Council of the People's Republic of China. *State council issues plan to prevent chronic diseases* (2018). Available at: http://english.gov.cn/policies/latest_releases/2017/02/14/content_281475567482818.htm

4. Andersson, C, and Vasan, RS. Epidemiology of cardiovascular disease in young individuals. *Nat Rev Cardiol*. (2018) 15:230–40. doi: 10.1038/nrcardio.2017.154

5. Benjamin, EJ, Blaha, MJ, Chiuve, SE, Cushman, M, Das, SR, Deo, R, et al. Heart disease and stroke Statistics-2017 update: a report from the American Heart Association. *Circulation*. (2017) 135:e146–603. doi: 10.1161/CIR.0000000000000485

6. GBD 2017 Congenital Heart Disease collaborators. Global, regional, and national burden of congenital heart disease, 1990-2017: a systematic analysis for the global burden of disease study 2017. *Lancet Child Adolesc Health*. (2020) 4:185–200. doi: 10.1016/S2352-4642(19)30402-X

7. GBD 2019 Diseases and Injuries Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the global burden of disease study 2019. *Lancet*. (2020) 396:1204–22. doi: 10.1016/S0140-6736(20)30925-9

8. GBD 2019 Risk factors collaborators. Global burden of 87 risk factors in 204 countries and territories, 1990-2019: a systematic analysis for the global burden of disease study 2019. *Lancet*. (2020) 396:1223–49. doi: 10.1016/S0140-6736(20)30752-2

9. GBD 2019 Ageing collaborators. Global, regional, and national burden of diseases and injuries for adults 70 years and older: systematic analysis for the global burden of disease 2019 study. *BMJ*. (2022) 376:e068208. doi: 10.1136/bmj-2021-068208

10. Stevens, GA, Alkema, L, Black, RE, Boerma, JT, Collins, GS, Ezzati, M, et al. Guidelines for accurate and transparent health estimates reporting: the GATHER statement. *PLoS Med*. (2016) 13:e1002056. doi: 10.1371/journal.pmed.1002056

11. Clegg, LX, Hankey, BF, Tiwari, R, Feuer, EJ, and Edwards, BK. Estimating average annual per cent change in trend analysis. *Stat Med*. (2009) 28:3670–82. doi: 10.1002/sim.3733

12. GBD 2019 Stroke Collaborators. Global, regional, and national burden of stroke and its risk factors, 1990-2019: a systematic analysis for the global burden of disease study 2019. *Lancet Neurol*. (2021) 20:795–820. doi: 10.1016/S1474-4422(21)00252-0

13. Zhou, M, Wang, H, Zeng, X, Yin, P, Zhu, J, Chen, W, et al. Mortality, morbidity, and risk factors in China and its provinces, 1990-2017: a systematic analysis for the global burden of disease study 2017. *Lancet*. (2019) 394:1145–58. doi: 10.1016/S0140-6736(19)30427-1

14. Wang, Y, Li, X, Zhou, M, Luo, S, Liang, J, Liddell, CA, et al. Under-5 mortality in 2851 Chinese counties, 1996-2012: a subnational assessment of achieving MDG 4 goals in China. *Lancet*. (2016) 387:273–83. doi: 10.1016/S0140-6736(15)00554-1

15. Liu, S, Li, Y, Zeng, X, Wang, H, Yin, P, Wang, L, et al. Burden of cardiovascular diseases in China, 1990-2016: findings from the 2016 global burden of disease study. *JAMA Cardiol*. (2019) 4:342–52. doi: 10.1001/jamacardio.2019.0295

16. Berenson, GS, Srinivasan, SR, Bao, W, Newman, WP 3rd, Tracy, RE, and Wattigney, WA. Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults. The Bogalusa heart study. *N Engl J Med*. (1998) 338:1650–6. doi: 10.1056/NEJM199806043382302

17. Huang, C, Li, J, Qin, G, Liew, Z, Hu, J, László, KD, et al. Maternal hypertensive disorder of pregnancy and offspring early-onset cardiovascular disease in childhood, adolescence, and young adulthood: a national population-based cohort study. *PLoS Med*. (2021) 18:e1003805. doi: 10.1371/journal.pmed.1003805

18. Mauvais-Jarvis, F, Bairey Merz, N, Barnes, PJ, Brinton, RD, Carrero, JJ, DeMeo, DL, et al. Sex and gender: modifiers of health, disease, and medicine. *Lancet*. (2020) 396:565–82. doi: 10.1016/S0140-6736(20)31561-0

19. George, MG, Tong, X, and Bowman, BA. Prevalence of cardiovascular risk factors and strokes in younger adults. *JAMA Neurol*. (2017) 74:695–703. doi: 10.1001/jamaneurol.2017.0020

20. Aparicio, HJ, Himali, JJ, Satizabal, CL, Pase, MP, Romero, JR, Kase, CS, et al. Temporal trends in ischemic stroke incidence in younger adults in the Framingham study. *Stroke*. (2019) 50:1558–60. doi: 10.1161/STROKEAHA.119.025171

21. Wafa, HA, Wolfe, CDA, Rudd, A, and Wang, Y. Long-term trends in incidence and risk factors for ischaemic stroke subtypes: prospective population study of the South London stroke register. *PLoS Med*. (2018) 15:e1002669. doi: 10.1371/journal.pmed.1002669

22. Wang, Z, Chen, Z, Zhang, L, Wang, X, Hao, G, Zhang, Z, et al. Status of hypertension in China: results from the China hypertension survey, 2012–2015. *Circulation*. (2018) 137:2344–56. doi: 10.1161/CIRCULATIONAHA.117.032380

23. Tall, AR, Thomas, DG, Gonzalez-Cabodevilla, AG, and Goldberg, IJ. Addressing dyslipidemic risk beyond LDL-cholesterol. *J Clin Invest*. (2022) 132:e148559. doi: 10.1172/JCI148559

24. Jeong, SM, Jeon, KH, Shin, DW, Han, K, Kim, D, Park, SH, et al. Smoking cessation, but not reduction, reduces cardiovascular disease incidence. *Eur Heart J*. (2021) 42:4141–53. doi: 10.1093/eurheartj/ehab578

25. Bellettiere, J, LaMonte, MJ, Evenson, KR, Rillamas-Sun, E, Kerr, J, Lee, IM, et al. Sedentary behavior and cardiovascular disease in older women: the objective physical activity and cardiovascular health (OPACH) study. *Circulation*. (2019) 139:1036–46. doi: 10.1161/CIRCULATIONAHA.118.035312

26. Khan, SS, Ning, H, Wilkins, JT, Allen, N, Carnethon, M, Berry, JD, et al. Association of Body Mass Index with Lifetime Risk of cardiovascular disease and compression of morbidity. *JAMA Cardiol*. (2018) 3:280–7. doi: 10.1001/jamacardio.2018.0022

27. Baker Smith, CM, and Peterson, A. Preventing premature atherosclerotic disease. *Curr Hypertens Rep*. (2020) 22:87. doi: 10.1007/s11906-020-01097-3

28. Measuring performance on the healthcare access and quality index for 195 countries and territories and selected subnational locations: a systematic analysis from the global burden of disease study 2016. *Lancet*. (2018) 391:2236–71. doi: 10.1016/S0140-6736(18)30994-2

29. Li, Y, and Zhang, J. Disease burden and risk factors of ischemic heart disease in China during 1990-2019 based on the global burden of disease 2019 report: a systematic analysis. *Front Public Health*. (2022) 10:973317. doi: 10.3389/fpubh.2022.973317

30. Perak, AM, Lancki, N, Kuang, A, Labarthe, DR, Allen, NB, Shah, SH, et al. Associations of maternal cardiovascular health in pregnancy with offspring cardiovascular health in early adolescence. *JAMA*. (2021) 325:658–68. doi: 10.1001/jama.2021.0247

31. GBD 2017 Mortality collaborators. Global, regional, and national age-sex-specific mortality and life expectancy, 1950-2017: a systematic analysis for the global burden of disease study 2017. *Lancet*. (2018) 392:1684–735. doi: 10.1016/S0140-6736(18)31891-9

32. GBD 2017 Risk Factor Collaborators. Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks for 195 countries and territories, 1990-2017: a systematic analysis for the global burden of disease study 2017. *Lancet*. (2018) 392:1923–94. doi: 10.1016/S0140-6736(18)32225-6

33. GBD 2019 Viewpoint collaborators. Five insights from the global burden of disease study 2019. *Lancet*. (2020) 396:1135–59. doi: 10.1016/S0140-6736(20)31404-5

frontiers | Frontiers in Cardiovascular Medicine

TYPE Original Research
PUBLISHED 16 February 2023
DOI 10.3389/fcvm.2023.1051677

OPEN ACCESS

EDITED BY
Zhen-Yu Zhang,
KU Leuven, Belgium

REVIEWED BY
Jesus Melgarejo,
KU Leuven, Belgium
Oswin Grollmuss,
Université Paris-Sud, France
Shikai Yu,
Tongji University, China
Shohreh Naderimagham,
Tehran University of Medical Sciences, Iran

*CORRESPONDENCE
Cheng Wang
✉ wangcheng2nd@csu.edu.cn

SPECIALTY SECTION
This article was submitted to Pediatric Cardiology, a section of the journal Frontiers in Cardiovascular Medicine

RECEIVED 23 September 2022
ACCEPTED 27 January 2023
PUBLISHED 16 February 2023

CITATION
Liu P, Mei W, Zhou M, Zhao T, Wang Y, Zou R and Wang C (2023) Application of mind map can promote the health education effect of children with vasovagal syncope. *Front. Cardiovasc. Med.* 10:1051677. doi: 10.3389/fcvm.2023.1051677

Application of mind map can promote the health education effect of children with vasovagal syncope

Ping Liu[1,2], Wanzhen Mei[1,2], Mengying Zhou[1], Ting Zhao[2], Yuwen Wang[2], Runmei Zou[2] and Cheng Wang[2*]

[1]Clinical Nursing Teaching and Research Section, The Second Xiangya Hospital, Central South University, Changsha, Hunan, China, [2]Department of Pediatric Cardiovasology, Children's Medical Center, The Second Xiangya Hospital, Central South University, Changsha, Hunan, China

Objective: To explore the effect of mind map on health education in children with vasovagal syncope (VVS).

Methods: In this prospective controlled study, 66 children with VVS (29 males, 10.38 ± 1.80 years) and their parents (12 males, 39.27 ± 3.74 years) who were hospitalized in the Department of Pediatrics, The Second Xiangya Hospital, Central South University from April 2020 to March 2021 were set as the control group. 66 children with VVS (26 males, 10.29 ± 1.90 years) and their parents (9 males, 38.65 ± 1.99 years) who were hospitalized in the same hospital from April 2021 to March 2022 were set as the research group. Traditional oral propaganda method was applied in the control group, and the health education method based on mind map was applied in the research group. The self-designed VVS health education satisfaction questionnaire and comprehensive health knowledge questionnaire were used to conduct on-site return visits to the children and their parents who had been discharged from the hospital for 1 month.

Results: There was no significant difference in age, sex, hemodynamic type of VVS, and the parental age, sex, education level between the control group and the research group ($P > 0.05$). Health education satisfaction score, health education knowledge mastery score, compliance score, subjective efficacy and objective efficacy in the research group were higher than those in the control group ($P < 0.05$). If the satisfaction score, knowledge mastery score, and compliance score increase by 1 point, the risk of poor subjective efficacy is reduced by 48, 91, and 99%, respectively, and the risk of poor objective efficacy is reduced by 44, 92, and 93%, respectively.

Conclusions: Application of mind map can improve the health education effect of children with VVS.

KEYWORDS

children, vasovagal syncope, health education, effect, mind map

1. Introduction

Vasovagal syncope (VVS) is a common type of neurally mediated syncope in children, and the incidence is higher in females than males (1–4). It is characterized by transient loss of consciousness, inability to maintain an upright posture of the body and falling to the ground. Clinically, some patients may have recurrent syncope episodes or pre-syncope symptoms,

and even syncope-related physical accidental injury (5, 6), or anxiety and depression, loss of appetite, increased somatic symptoms and loss of confidence, resulting in a decrease in the quality of life of the child and seriously affecting the patient's learning and life (7). Taking effective intervention measures for VVS as early as possible can avoid or reduce the onset of these symptoms. Clinically, the treatment of VVS mainly based on non-drug treatment such as health education (8), including avoiding predisposing factors, anti-resistance training and increasing water and salt intake (8–10), etc. Syncope and pre-syncope symptoms can be effectively reduced through health education and some lifestyle changes (e.g., recognizing syncope prodromal symptoms, increasing water intake, anti-resistance training and physical exercise, etc.), thereby improving the quality of life and learning for children with VVS (11). It can be seen that effective health education and lifestyle guidance are crucial in VVS rehabilitation. At present, the health education methods for children with VVS are mostly dependent on traditional oral education. Children with VVS who were hospitalized for treatment were short in hospital, and the communication and expression skills of the mission nurses were different, the effective health education information received by children and their parents was limited, resulting in the failure of health education. In order to explore effective ways to improve the quality and efficiency of health education for children with VVS, this study introduced the health education method of mind map.

The mind map is a thinking tool that concretizes divergent thinking. It uses lines, symbols, vocabulary and images to form divergent and node-like structural forms, and turns cumbersome text information into a visual diagram with clear layers and rich pictures and texts. It not only omits the tedious and complicated oral communication process, but also intuitively provides visual stimulation to children and their parents, deepens the impression of key content, and eliminates the inefficient information dissemination caused by hearing fatigue, and allows learners to store and extract information more effectively, and improve work and learning efficiency (12, 13). Some studies have shown that mind maps can improve the health education effect of patients (14–16). Li et al. (17) has found that the combined communication mode of SBAR (namely Situation, Background, Assessment, Recommendation) standard and mind map used in the emergency department can improve the quality of handover, reduce adverse events and handover problems, and get higher patient satisfaction. In this study, mind map was introduced to the health education of children with VVS and their parents, and the effect of mind mapping on VVS children's health education was observed.

2. Study population and methods

2.1. Study population and data collection

A prospective controlled study was conducted. The inclusion criteria and exclusion criteria were shown in Figure 1. Children with VVS and their parents were divided into control group and research group. The study subjects returned to the hospital for follow-up visits 1 month after discharge.

The sample size was calculated by using the formula $n1 = n2 = [(Z\alpha + Z\beta)^2 \times 2\sigma^2]/\delta^2$. The outcome index of this study was compliance score. The average compliance score of the control group was expected to be 3.00 ± 1.3 points, and the compliance score of the study group was expected to be increased by 1.0 points. Bilateral test, α was 0.05, the sample size ratio of the two groups was 1:1, and the test efficacy was $1 - \beta = 90\%$. The sample size calculated was 41. Consider a 25% shedding rate, the required minimum total number of participants was 51 in our study. We selected a sample size of 66 cases in each group.

2.2. Implementer of health education

The health education of the research group and the control group were implemented by pediatric specialist nurses, aged 26–45 years old, with an average age of 33.00 ± 5.03 years old.

2.3. Methods of health education

The control group received the conventional health education method, namely the oral education method, which lasted about 15–30 min. After the diagnosis was confirmed, the nurses explain VVS-related knowledge to the children and their parents, including common predisposing factors for syncope, increasing intake of water and salt, methods of taking oral rehydration salts, and instructing children on autonomic nerve function exercises, emphasizing that exercises should be performed as required. The research group received the mind map health education method, about 10–15 min. First of all, the nurses in our hospital would be trained on the knowledge of mind map. The training content was based on the medical knowledge of VVS, focusing on the background and usage of mind map. A total of 4 h of training would be conducted. After passing the real-life operation assessment, they would participate in this study. On the basis of evidence-based nursing and clinical experience, the members of the research team made a mind map, based on the content of traditional VVS health education and guided by the general information of children and their parents, to select the key points of pediatric VVS health education, from the perspective of patients, consult the literature and design a mind map of pediatric VVS self-prevention management based on peer practices. The drawing follows the principles of reasonable logic, clear fonts, and rich pictures and texts, and uses the mind map software X Mind 8 to draw (Figure 2). After the diagnosis was confirmed, the children and their parents were given health education by using mind maps. The nurses emphasized the key points one by one according to the mind maps, and guided the children to exercise their autonomic nerve function. After the teaching, hand over the mind map to the children and their parents, and guide them to consolidate knowledge and improve compliance as shown in the picture. Nurses supervise their implementation in their daily work, and carry out targeted health education as appropriate.

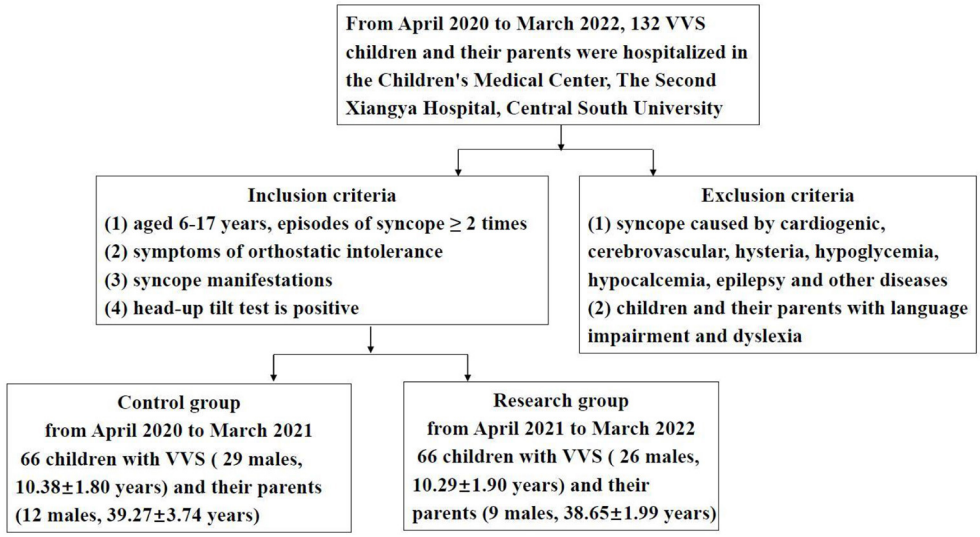


FIGURE 1
Inclusion criteria and exclusion criteria.

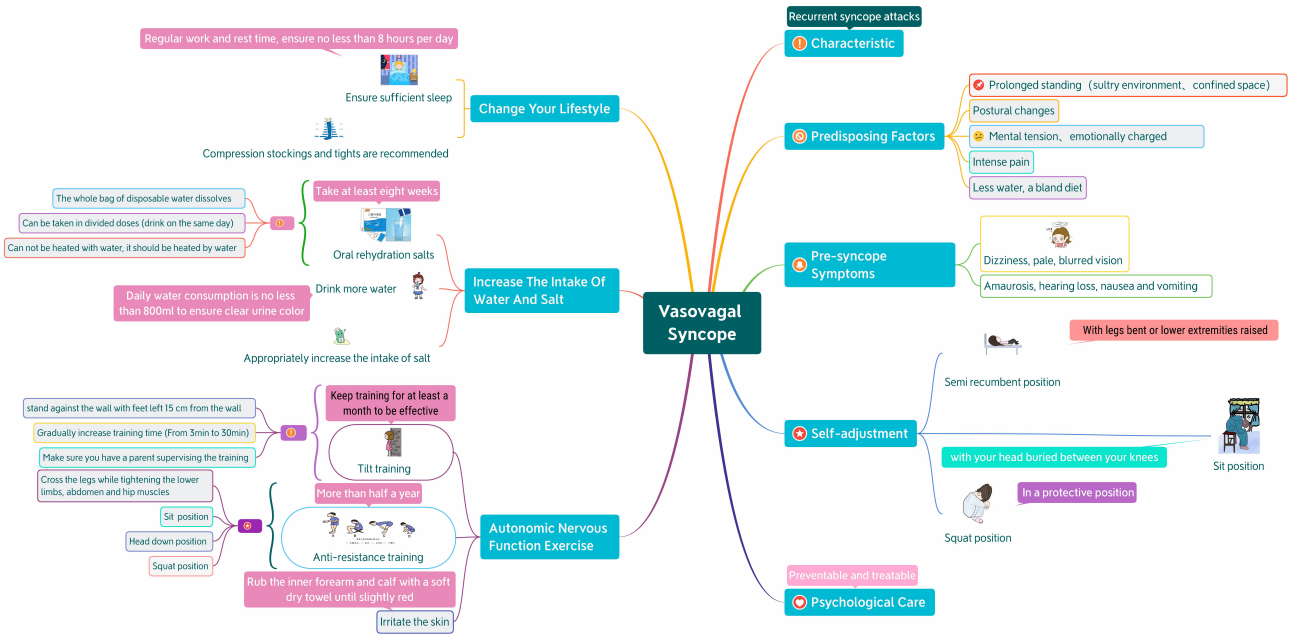


FIGURE 2
Mind map of health education for children with vasovagal syncope and their parents.

2.4. Evaluation method

2.4.1. General information questionnaire

The research team asked children and their parents to complete the questionnaire. The contents of the questionnaire included the child's name, sex, date of birth, academic performance, place of residence and parents' age, education level, and telephone number.

2.4.2. Health education satisfaction questionnaire (for children and their parents)

A self-designed health education satisfaction questionnaire was used. The contents include nurses' introduction of disease-related knowledge, guidance on eating and living habits, guidance on autonomous function exercise, guidance on drugs and psychological counseling. The score calculation standard was as follows: 2, satisfaction; 1, general; 0, dissatisfaction. The full

score is 16 scores. The higher the score, the higher the satisfaction. The assessment was performed by the patient and the parents before the patient was discharged from the hospital. We collected 66 valid questionnaires from the research group and the control group respectively, and the recovery rate and effective rate were both 100%.

2.4.3. Health education knowledge questionnaire

The self-designed VVS health education knowledge questionnaire was used to conduct on-site return visits to the children and their parents who had been discharged from the hospital for 1 month, and understand their mastery of VVS health education knowledge, syncope frequency, compliance and re-examination of head-up tilt test (HUTT) results, etc. The specific content is as follows: (1) What are the predisposing factors for syncope? (At least answer 3 or more predisposing factors, such as prolonged standing, postural changes, strenuous exercise, etc.). (2) What to do if fainting occurs? (For example, keep your supine position with your legs slightly elevated; in a sitting position, bury your head between your knees; in a squat position, clasp your hands tightly and hold your legs tightly in a protective position). (3) What are the precautions for oral rehydration salts? (The daily amount is dissolved at one time and can be taken in divided doses; it cannot be mixed with water in the middle; it can be warmed with water; drink it up on the same day). (4) How is the autonomic nervous system exercise performed? (Such as stand training, anti-resistance training, etc. Answer at least one of them and be absolutely correct). (5) Are you taking oral rehydration salts as prescribed by your doctor? (6) Do you do autonomic nervous system exercise every day? (7) Are you guaranteed three meals a day and enough sleep? (Sleep at least 8 h per day). (8) Do you use compression stockings or tights pants? In the questionnaires survey, "know" is scored as 1, "don't know" is scored as 0; if the answer is "yes," it is scored as 1, and the answer of "no" is scored as 0. 66 valid questionnaires were collected from the research group and the control group, respectively, and the recovery rate and effective rate were both 100%.

2.4.4. Evaluation of efficacy

(1) Subjective efficacy: after training, the number of syncope or the occurrence of syncope premonitory in the child was reduced compared with that before treatment or had no episodes, which was regarded as improvement; after the training, the number of syncope or the occurrence of syncope is increased or no change, which was regarded as noimprovement. Efficiency (Improvement rate) = number of improved cases/total number of cases. (2) Objective efficacy: according to the HUTT results of the patient's re-examination, the HUTT induced syncope time was longer than the previous once, or the result change from positive to negative, which was regarded as improved; shortened time to induction of syncope, or no change in HUTT results was considered no improvement.

2.4.5. Head-up tilt test (HUTT)

2.4.5.1. Preparations before the test

Children fasted for at least 4 h before the testing, any vasoactive medication was stopped for at least five half-lives, and drink that could affect autonomic nervous system function (e.g., coffee) was avoided. The test was performed ata suitable temperature, dim light, and quiet environment. Detailed instructions and risks should be described to children and their legal guardians/parents. Signed informed consent should be obtained before the test (9, 18, 19).

2.4.5.2. Basic HUTT (BHUT)

The test was performed using Head-up Tilt Test Mornitoring System (SHUT-100) of Jiangsu Standard Medical Technology Co., Ltd. after overnight fasting between 8:00 a.m. and 12:00 p.m. The subjects were asked to lay still for 10 min, and then baseline heart rate (HR), blood pressure (BP), and ECG were recorded. Subjects were tilted at 60° with head upward, and HR, BP, and ECG were recorded continuously until either 45 min duration, or the development of syncope or intolerable near syncope symptoms. If syncope occurred, patients were rapidly placed in the supine position.

2.4.5.3. Sublingual nitroglycerin HUTT (SNHUT)

If the subjects did not develop syncope or pre-syncope, they underwent SNHUT. A tilted posture was maintained, subjects were medicated with nitroglycerin 4–6 μg/kg (maximum ≤ 300 μg), and HR, BP, and ECG were recorded for 20 min or until syncope or pre-syncope occurred.

2.4.5.4. Diagnosis of VVS and response types

VVS was defined as the development of syncope or pre-syncope accompanied by hypotension (systolic BP ≤ 80 mmHg and/or diastolic BP ≤ 50 mmHg, or over 25% decrease in mean BP), bradycardia (HR < 75 bpm for children at 4–6 years of age, <65 bpm for children at 6–8 years of age, and <60 bpm for children at 8 years of age and older), or cardiac arrest >3 s. VVS was further classified into three responses: vasoinhibitory type VVS (VVS-VI) (significant reduction in BP but insignificant change in HR), cardioinhibitory type VVS (VVS-CI) (significant reduction in HR but insignificant change in BP), and mixed type VVS (VVS-M) (significant reduction both in BP and HR).

2.5. Statistical analysis

The continuous variables were characterized by mean ± standard deviation, or as median and interquartile range, as appropriate. The categorical variables were presented as a number (n) and percentages (%). The Student's t-test, Chi-square test, Fisher's exact test, or Mann–Whitney U test were conducted to compare factors between two groups, as appropriate. Univariate binary Logistic regression was used to briefly evaluate the approximate effects of factors on the efficacy and direction of both subjective efficacy and objective efficacy. Multifactor Logistic regression to analyze the possible association between subjective efficacy and objective efficacy and many factors was used and constructed two models to illustrate the stability of this relationship: Model 1 adjusted for sociodemographic data (sex, age); Mode 2 adjusted for sociodemographic data and parental sex and age and education level, hemodynamic type of VVS. All the analyses were performed with the statistical software packages

TABLE 1 General data of the study population and description of questionnaire data [Mean ± SD/*n* (%)].

Group	Control group ($n = 66$)	Research group ($n = 66$)	Standardize diff.	*P*-value
Comparison of general data between the research group and the control group				
Age (years)	10.38 ± 1.80	10.29 ± 1.90	0.05 (−0.29, 0.39)	0.778
Sex			0.09 (−0.25, 0.43)	0.596
Male	29 (43.94%)	26 (39.39%)		
Female	37 (56.06%)	40 (60.61%)		
Parents' age (years)	39.27 ± 3.72	38.65 ± 1.99	0.21 (−0.13, 0.55)	0.234
Parents' sex			0.12 (−0.22, 0.47)	0.475
Male	12 (18.18%)	9 (13.64%)		
Female	54 (81.82%)	57 (86.36%)		
Parents' education level			0.22 (−0.12, 0.56)	0.453
Middle school and below	36 (54.55%)	29 (43.94%)		
Senior middle school	20 (30.30%)	26 (39.39%)		
Undergraduate and above	10 (15.15%)	11 (16.67%)		
Comparison of satisfaction with health education between the research group and the control group				
The nurse explained to me how syncope happens			0.54 (0.19, 0.89)	0.008
Dissatisfaction	8 (12.12%)	0 (0.00%)		
General	17 (25.76%)	16 (24.24%)		
Satisfaction	41 (62.12%)	50 (75.76%)		
The nurse introduced me to pre-syncope symptoms			0.74 (0.39, 1.09)	<0.001
Dissatisfaction	6 (9.09%)	0 (0.00%)		
General	25 (37.88%)	11 (16.67%)		
Satisfaction	35 (53.03%)	55 (83.33%)		
The nurse explained to me what to do if I have fainting			0.90 (0.54, 1.26)	<0.001
Dissatisfaction	8 (12.12%)	0 (0.00%)		
General	20 (30.30%)	5 (7.58%)		
Satisfaction	38 (57.58%)	61 (92.42%)		
The nurse taught me how to take oral rehydration salts			0.45 (0.11, 0.80)	0.037
Dissatisfaction	4 (6.06%)	0 (0.00%)		
General	15 (22.73%)	9 (13.64%)		
Satisfaction	47 (71.21%)	57 (86.36%)		
The nurse instructed me on how to exercise the autonomic nervous function			0.53 (0.18, 0.88)	0.009
Dissatisfaction	8 (12.12%)	0 (0.00%)		
General	12 (18.18%)	12 (18.18%)		
Satisfaction	46 (69.70%)	54 (81.82%)		
The nurse guided me on my life and hygiene habits			0.50 (0.15, 0.84)	0.016
Dissatisfaction	7 (10.61%)	0 (0.00%)		

(Continued)

TABLE 1 (Continued)

Group	Control group ($n = 66$)	Research group ($n = 66$)	Standardize diff.	*P*-value
General	11 (16.67%)	10 (15.15%)		
Satisfaction	48 (72.73%)	56 (84.85%)		
The nurse guided my diet			0.57 (0.23, 0.92)	0.004
Dissatisfaction	8 (12.12%)	0 (0.00%)		
General	6 (9.09%)	12 (18.18%)		
Satisfaction	52 (78.79%)	54 (81.82%)		
The nurse eased my anxiety about the disease			0.56 (0.21, 0.91)	0.007
Dissatisfaction	5 (7.58%)	0 (0.00%)		
General	21 (31.82%)	12 (18.18%)		
Satisfaction	40 (60.61%)	54 (81.82%)		
Comparison of the health education knowledge mastery between the research group and the control group				
What are the predisposing factors for syncope?			0.55 (0.20, 0.89)	0.002
Don't know	11 (16.67%)	1 (1.52%)		
Know	55 (83.33%)	65 (98.48%)		
What to do if fainting occurs?			0.77 (0.41, 1.12)	<0.001
Don't know	15 (22.73%)	0 (0.00%)		
Know	51 (77.27%)	66 (100.00%)		
What are the precautions for oral rehydration salts?			0.63 (0.28, 0.98)	<0.001
Don't know	11 (16.67%)	0 (0.00%)		
Know	55 (83.33%)	66 (100.00%)		
How is the autonomic nervous system exercise performed?			0.92 (0.57, 1.28)	<0.001
Don't know	22 (33.33%)	1 (1.52%)		
Know	44 (66.67%)	65 (98.48%)		
Comparison of compliance with health education between the research group and the control group				
Are you taking oral rehydration salts as prescribed by your doctor?			0.87 (0.51, 1.22)	<0.001
No	18 (27.27%)	0 (0.00%)		
Yes	48 (72.73%)	66 (100.00%)		
Do you do autonomic nervous system exercise every day?			0.74 (0.39, 1.09)	<0.001
No	24 (36.36%)	5 (7.58%)		
Yes	42 (63.64%)	61 (92.42%)		
Are you guaranteed three meals a day and enough sleep?			0.67 (0.32, 1.02)	<0.001
No	12 (18.18%)	0 (0.00%)		
Yes	54 (81.82%)	66 (100.00%)		
Do you use compression stockings or tights pants?			0.52 (0.18, 0.87)	0.004
No	16 (24.24%)	4 (6.06%)		
Yes	50 (75.76%)	62 (93.94%)		

(Continued)

TABLE 1 (Continued)

Group	Control group ($n = 66$)	Research group ($n = 66$)	Standardize diff.	*P*-value
Comparison of satisfaction scores, knowledge mastery scores, and compliance scores between the research group and the control group				
Satisfaction scores	12.44 ± 3.08	14.68 ± 1.60	0.91 (0.56, 1.27)	<0.001
Knowledge mastery scores	3.09 ± 1.09	3.97 ± 0.17	1.12 (0.76, 1.49)	<0.001
Compliance scores	2.91 ± 1.17	3.86 ± 0.46	1.07 (0.71, 1.44)	<0.001
Comparison of subjective and objective efficacy between the research group and the control group				
Subjective efficacy			0.59 (0.25, 0.94)	0.001
Improved	48 (72.73%)	62 (93.94%)		
No improved	18 (27.27%)	4 (6.06%)		
Objective efficacy			0.61 (0.26, 0.96)	<0.001
Improved	36 (54.55%)	54 (81.82%)		
No improved	30 (45.45%)	12 (18.18%)		
Comparison of hemodynamic type of VVS between the research group and the control group				
VVS hemodynamic types			0.17 (-0.17, 0.52)	0.639
Vasoinhibitory type	52 (78.79%)	49 (74.24%)		
Cardioinhibitory type	2 (3.03%)	1 (1.52%)		
Mixed type	12 (18.18%)	16 (24.24%)		

R (version 3.6.1) (http://www.R-project.org, The R Foundation) and EmpowerStats (http://www.empowerstats.com, X & Y Solutions, Inc, Boston, MA). *P*-values < 0.05 (two-sided) were considered statistically significant.

3. Results

3.1. General data and questionnaire data analysis

There were no significant differences in age and sex of the children and their parents between the research group and the control group ($P > 0.05$). The satisfaction on health education, the awareness rate of health education, the compliance of health education, the satisfaction score, the knowledge score, the compliance score, the subjective efficacy and the objective efficacy of the research group were higher than those of the control group ($P < 0.01$). There was no statistical difference in hemodynamic types of VVS and parental education between the research group and the control group ($P > 0.05$) (Table 1).

3.2. Univariate analysis of subjective efficacy and objective efficacy

The research group was the protective factor of subjective efficacy and objective efficacy. The ages of the children and their parents were the risk factors of subjective efficacy, the education level of the parents in high school was the protective factor of subjective efficacy and objective efficacy, the satisfaction score and the knowledge mastery score and the compliance score were the protective factor of subjective efficacy and objective efficacy ($P > 0.05$) (Table 2).

3.3. Comparison of multifactor regression equations of subjective efficacy and objective efficacy

In order to further clarify whether satisfaction score, knowledge mastery score and compliance score had independent and stable influences on subjective and objective efficacy in univariate analysis, we conducted a comparison of multifactor binary Logistic regression equations. After adjusting different confounding factors, the model still showed good stability and small fluctuation of effect value. The satisfaction score, knowledge mastery score, and compliance score increased by 1 point, the risk of poor subjective efficacy was reduced by 48, 91, and 99%, respectively, and the risk of poor objective efficacy was reduced by 44, 92, and 93%, respectively (Table 3).

4. Discussion

VVS is a common neurally mediated syncope in clinical practice, and health education is the basic measure for intervention of VVS (8). Although the prognosis of VVS is good, due to the

TABLE 2 Univariate analysis of subjective efficacy and objective efficacy [$n = 132$, Mean ± SD/n (%)].

	Statistics	Subjective efficacy		Objective efficacy	
		OR (95%CI)	*P*-value	OR (95%CI)	*P*-value
Group					
Control group	66 (50.00%)	1.0		1.0	
Research group	66 (50.00%)	0.17 (0.05, 0.54)	0.003	0.27 (0.12, 0.59)	0.001
Age (years)	10.33 ± 1.84	1.39 (1.08, 1.79)	0.012	1.26 (1.02, 1.55)	0.029
Sex					
Male	55 (41.67%)	1.0		1.0	
Female	77 (58.33%)	1.04 (0.41, 2.63)	0.937	1.67 (0.78, 3.59)	0.187
Parents' age (years)	38.96 ± 2.99	1.20 (1.03, 1.40)	0.022	1.12 (0.98, 1.27)	0.088
Parents' sex					
Male	21 (15.91%)	1.0		1.0	
Female	111 (84.09%)	0.42 (0.14, 1.25)	0.118	0.56 (0.22, 1.47)	0.240
Parents' education level					
Middle school and below	65 (49.24%)	1.0		1.0	
Senior middle school	46 (34.85%)	0.88 (0.31, 2.48)	0.810	0.47 (0.20, 1.12)	0.090
Undergraduate and above	21 (15.91%)	1.16 (0.33, 4.10)	0.824	1.05 (0.38, 2.90)	0.923
Hemodynamic type of VVS					
Vasoinhibitory type	101 (76.52%)	1.0		1.0	
Cardioinhibitory type	3 (2.27%)	2.87 (0.24, 33.63)	0.402	1.18 (0.10, 13.55)	0.892
Mixed type	28 (21.21%)	1.56 (0.54, 4.50)	0.407	1.53 (0.64, 3.66)	0.337
Satisfaction scores	13.56 ± 2.69	0.71 (0.60, 0.85)	0.000	0.67 (0.56, 0.79)	0.000
Knowledge mastery scores	3.53 ± 0.89	0.21 (0.12, 0.40)	0.000	0.12 (0.05, 0.27)	0.000
Compliance scores	3.39 ± 1.01	0.04 (0.01, 0.15)	0.000	0.10 (0.05, 0.23)	0.000

Data in table: OR, odds ratio; CI, confidence interval.
Result variable: subjective efficacy, objective efficacy.
Exposure variable: group, sex, parents' sex, hemodynamic type of VVS, parents' education level, age, parents' age, satisfaction scores, knowledge mastery scores, compliance scores.
Adjusted variable: none.

lack of knowledge of the disease and health education of the children and their parents, the compliance of the intervention and the rehabilitation effect are affected, which can lead to the recurrence of syncope or pre-syncope. In addition to seriously affecting the physical and mental health and quality of life of the children, the parents are also under great psychological pressure. Therefore, paying attention to the psychological feelings and service requirements of children with VVS and their parents, especially the health education of children and their parents, and improving their compliance, are the key links to promoting the rehabilitation of children (20, 21).

The purpose of health education is not only to "educate knowledge," but also to establish "medical compliance behavior or healthy behavior" through guidance. Its effect is closely related to factors such as health educators, health education methods and health education objects. In order to avoid the omission of information or unclear expression due to the differences in theoretical knowledge and language expression ability of health educators, the health education practitioners in this study are all highly educated nurses who have undergone unified training and have worked in clinical practice for at least 3 years. Individuals have different abilities to understand and accept information, and people have limited short-term memory, and the content of oral education is easy to forget, which may lead to children and their parents lack of information acceptance or lack of understanding, resulting in reduced compliance. The mind map used in this study can make up for this deficiency. Mind map can turn boring information into colorful and well-organized diagrams to help understand memory (13, 22) (Figure 2).

4.1. Health education method based on mind map can improve the satisfaction of children with VVS and their parents with health education

The results of this study showed that the research group's satisfaction score for health education was increased compared with the control group ($P < 0.01$), and the risk of poor subjective efficacy was decreased by 48% and the risk of poor objective efficacy was decreased by 44% for each point increase of satisfaction score of health education in clinical nursing work in the research

TABLE 3 Comparison of multifactor regression equations of subjective efficacy and objective efficacy.

Exposure	Model 1		Model 2	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Subjective efficacy				
Satisfaction scores	0.66 (0.54, 0.82)	0.000	0.52 (0.36, 0.74)	0.000
Knowledge mastery scores	0.18 (0.09, 0.36)	0.000	0.09 (0.03, 0.27)	0.000
Compliance scores	0.02 (0.00, 0.15)	0.000	0.01 (0.00, 0.13)	0.000
Objective efficacy				
Satisfaction scores	0.65 (0.54, 0.79)	0.000	0.56 (0.43, 0.73)	0.000
Knowledge mastery scores	0.12 (0.05, 0.29)	0.000	0.08 (0.03, 0.23)	0.000
Compliance scores	0.09 (0.03, 0.21)	0.000	0.07 (0.03, 0.19)	0.000

Data in table: OR, odds ratio; CI, confidence interval.
Result variable: subjective efficacy, objective efficacy.
Exposure variable: satisfaction scores, knowledge mastery scores, compliance scores.
Model 1 adjusted for: sex, age.
Model 2 adjusted for: sex, age, parents' sex, parents' age, hemodynamic type of VVS, parents' education level.

group. It is suggested that the health education method based on mind mapping can improve the satisfaction of health education and intervention effect of children with VVS and their parents. Zhang et al. (23) applied mind map to the health education of parents of children with infectious mononucleosis, and found that the research group was significantly higher than the control group in terms of nursing satisfaction in nurse-patient communication, health education, and nursing technology ($P < 0.01$). This may be related to the simplicity and clarity of the mind map, focusing on prominent features, which is more conducive to the transmission of information. Targeted health education can promote emotional communication between nurses and patients, increase the trust between nurses and patients, and thus improve the satisfaction of children and their parents with clinical nursing work. Gakhal et al. (13) also reported that the use of audiovisual presentations and mind map exercises to improve the information recall ability of orthodontic patients and their parents and found that the use of audiovisual presentations and written information can improve the information recall rate of orthodontic patients and their parents, and thought mind map is a better form than written information. It can be seen that the health education method based on mind mapping can improve the health education effect of children with VVS and their parents.

4.2. The health education method based on mind map can improve the mastery of health education knowledge and compliance in children with VVS and their parents

Through the health education knowledge questionnaire, it was found that the research group had significantly higher scores on the mastery of health education knowledge and compliance than the control group ($P < 0.01$). And in research group, the risk of poor subjective efficacy was decreased by 91 and 99% for each point increase of the score of mastery knowledge and compliance, respectively. The risk of poor objective efficacy was decreased by 92 and 93% for each point increase of the score of mastery knowledge and compliance, respectively. The above results suggested that the health education based on mind map can improve the compliance of children with VVS and their parents to health education, avoid possible clinical inducements and triggers, effectively increase the intake of water and salt, and ensure the effectiveness of the intervention. Studies have shown that the application of mind map in pediatric VVS health education can improve the compliance of children and their parents. Sesanelvira et al. (24) reported the educational effect of using mind map method on school-age children's food safety behavior, and found that the use of mind map method has a significant impact on school-age children's food safety knowledge, attitudes and skills. It is believed that the mind map method can be applied to improve the clean and healthy living behaviors of school-age children. Yang et al. (25) reported the application of mind map health education in extended care for children with caries, and found that the use of mind map health education method could significantly improve the caries knowledge of children with caries and their parents, and improve their compliance to health education. Therefore, mind mapping is an appropriate health education tool that can be used for extended care of children with dental caries. In conclusion, health education based on mind map can carry out effective cognitive and behavioral intervention for children and their parents, thereby significantly improving the cognitive level of children and their parents in dealing with disease-related knowledge, and effectively improving the compliance and quality of life of children.

4.3. The health education method based on mind map can improve the subjective efficacy and objective efficacy of VVS children

In this study, both the subjective efficacy and objective efficacy of the research group and the control group were improved, and

the subjective and objective efficacy of the research group were better than those of the control group ($P < 0.01$). And the research group was the protective factor of subjective efficacy and objective efficacy, the satisfaction score, the knowledge mastery score and the compliance score were the protective factor of subjective efficacy and objective efficacy, which was related to the improvement of patient compliance behavior with mind map (26). The mind map is easy to understand and can make up for the unclear explanations and understandings in oral health education. It can carefully let children with VVS and their parents clarify the rehabilitation knowledge of VVS, and provide guidance for effective rehabilitation and improved prognosis. This study shows that the parents' education level in high school is a protective factor for both subjective efficacy and objective efficacy, indicating that the group with higher education levels has a higher acceptance level and understanding ability of health education, which is conducive to improving compliance. The ages of the children and their parents were risk factors for subjective efficacy, which may be related to the obvious anxiety about syncope or pre-syncope episodes in older age.

It can be seen that the application of a mind map in the health education of children with VVS and their parents can increase the clinical intervention effect.

5. Shortcomings and prospects

However, this study had certain limitations. It was a single-center-based research, the subjects were younger and the sample size was not large enough. At the same time, due to the impact of the COVID-19 epidemic, the research group did not recruit the research subjects at the same time, which needs to be avoided in the future research. Therefore, further large sample and multi-center studies can be conducted in the future, and the outcome indicators can be added to verify the educational program. It is recommended to promote and establish patient health records in pediatric cardiovascular outpatient clinics, record the progress of health education during patient follow-up, and lay a foundation for follow-up research.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of The Second Xiangya Hospital, Central South University. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

PL and WM had primary responsibility for the protocol development, patient enrollment, data collecting preliminary data analysis, and writing the manuscript. MZ was responsible for the drawing. TZ was responsible for language polishing. YW and RZ completed the head-up tilt test. PL and CW assisted with critical revision for important content and edited the draft. CW supervised the design, execution of the study, checked the data analysis, and contributed to a final approval of the manuscript submitted. All authors have read and approved the final manuscript and assumed full responsibility for its contents.

Funding

This work was supported by grants from National High Level Hospital Clinical Research Funding (Multi-Center Clinical Research Project of Peking University First Hospital) (2022CR59) and Hunan Province Clinical Medical Technology Innovation Guidance Project (2020SK53405 and 2020SK53406).

Acknowledgments

Thanks to Dr. Shuo Wang from the Department of Neonatology, Xiangya Hospital, Central South University for the help in statistical work of this article.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Li HX, Gao L, Yuan Y. Advance in the understanding of vasovagal syncope in children and adolescents. *World J Pediatr.* (2021) 17:58–62. doi: 10.1007/s12519-020-00367-z

2. Wang Y, Wang Y, He B, Tao C, Han Z, Liu P, et al. Plasma human growth cytokines in children with vasovagal syncope. *Front Cardiovasc Med.* (2022) 9:1030618. doi: 10.3389/fcvm.2022.1030618

3. Hu E, Liu X, Chen Q, Wang C. Investigation on the incidence of syncope in children and adolescents aged 2–18 years in Changsha. *Front Pediatr.* (2021) 9:638394. doi: 10.3389/fped.2021.638394

4. Xu WR, Du JB, Jin HF. Can pediatric vasovagal syncope be individually managed? *World J Pediatr.* (2022) 18:4–6. doi: 10.1007/s12519-021-00495-0

5. Jorge JG, Pournazari P, Raj SR, Maxey C, Sheldon RS. Frequency of injuries associated with syncope in the prevention of syncope trials. *Europace.* (2020) 22:1896–903. doi: 10.1093/europace/euaa246

6. Hino S, Yamada M, Araki R, Kaneko T, Horie N. Effects of loss of consciousness on maxillofacial fractures in simple falls. *Dent Traumatol.* (2019) 35:48–53. doi: 10.1111/edt.12452

7. Ng J, Sheldon RS, Ritchie D, Raj V, Raj SR. Reduced quality of life and greater psychological distress in vasovagal syncope patients compared to healthy individuals. *Pacing Clin Electrophysiol.* (2019) 42:180–8. doi: 10.1111/pace.13559

8. Wang C, Li Y, Liao Y, Tian H, Huang M, Dong X, et al. 2018 Chinese Pediatric Cardiology Society (CPCS) guideline for diagnosis and treatment of syncope in children and adolescents. *Sci Bull.* (2018) 63:1558–64. doi: 10.1016/j.scib.2018.09.019

9. Chu W, Wang C, Wu L, Lin P, Li F, Zou R. Oral rehydration salts: an effective choice for the treatment of children with vasovagal syncope. *Pediatr Cardiol.* (2015) 36:867–72. doi: 10.1007/s00246-015-1097-5

10. Wen C, Wang S, Zou R, Wang Y, Tan C, Xu Y, et al. Duration of treatment with oralrehydration salts for vasovagal syncope in children and adolescents. *Turk J Pediatr.* (2020) 62:820–5. doi: 10.24953/turkjped.2020.05.014

11. Aghajani F, Tavolinejad H, Sadeghian S, Bozorgi A, Jalali A, Vasheghani-Farahani A, et al. Implementation of supervised physical training to reduce vasovagal syncope recurrence: a randomized controlled trial. *J Cardiovasc Electrophysiol.* (2022) 33:1863–70. doi: 10.1111/jce.15578

12. Tony B. *Mind Map*. Beijing: China Citic Press (2009). p. 15–61.

13. Gakhal MK, Kwon O. Improving orthodontic patients' and parents' information recall with use of audio-visual presentation and mind mapping exercises. *Evid Based Dent.* (2020) 21:34–5. doi: 10.1038/s41432-020-0073-y

14. Michelini CA. Mind map: a new way to teach patients and staff. *Home Healthc Nurse.* (2000) 18:318–22. doi: 10.1097/00004045-200005000-00012

15. Farrand P, Hussain F, Hennessy E. The efficacy of the 'mind map' study technique. *Med Educ.* (2002) 36:426–31. doi: 10.1046/j.1365-2923.2002.01205.x

16. Walker D, Adebajo A, Heslop P, Hill J, Firth J, Bishop P, et al. Patient education in rheumatoid arthritis: the effectiveness of the ARC booklet and the mind map. *Rheumatology.* (2007) 46:1593–6. doi: 10.1093/rheumatology/kem171

17. Li X, Zhao J, Fu S. SBAR standard and mind map combined communication mode used in emergency department to reduce the value of handover defects and adverse events. *J Healthc Eng.* (2022) 2022:8475322. doi: 10.1155/2022/8475322

18. Zou R, Wang S, Li F, Lin P, Zhang J, Wang Y, et al. The application of head-up tilt test to diagnose hemodynamic type of orthostatic intolerance in children aged between 3 and 5 years old. *Front Pediatr.* (2021) 9:623880. doi: 10.3389/fped.2021.623880

19. Zou R, Wang S, Wen W, Cai H, Wang Y, Liu P, et al. Risk factors and prognostic follow-up of vasovagal syncope children with seizure-like activities during head-up tilt test induced-syncope. *Front Cardiovasc Med.* (2022) 9:916542. doi: 10.3389/fcvm.2022.916542

20. Liu P, Zeng X, Mei W, Wang Y, Zou R, Wang C. The predictive value of urine specific gravity in the diagnosis of vasovagal syncope in children and adolescents. *Ital J Pediatr.* (2021) 47:93. doi: 10.1186/s13052-021-01043-2

21. Zhao T, Wang S, Wang M, Cai H, Wang Y, Xu Y, et al. Research progress on the predictive value of electrocardiographic indicators in the diagnosis and prognosis of children with vasovagal syncope. *Front Cardiovasc Med.* (2022) 9:916770. doi: 10.3389/fcvm.2022.916770

22. Liu T, Yuizono T. Mind mapping training's effects on reading ability: detection based on Eye Tracking Sensors. *Sensors.* (2020) 20:4422. doi: 10.3390/s20164422

23. Zhang B, Xie A, Wang C, Yang Y, Sun Y. Application of mind mapping in health education for parents of children with infectious mononucleosis. *J Nurs Admin.* (2021) 21:757–60. doi: 10.3969/j.jssn.1671-315x.2021.10.015

24. Sesanelvira ADIM, Mulyono S, Sukihananto S. Improving food safety behavior through mind map methods in school-age children. *Compr Child Adolesc Nurs.* (2019) 42:97–107. doi: 10.1080/24694193.2019.1578301

25. Yang H, Gao XB Li MH, Ye Q, Sun Y, Huang Y. The use of mind mapping in health education in extended care for children with caries. *J Int Med Res.* (2020) 48:300060519898053. doi: 10.1177/0300060519898053

26. Zhao Y,Guo Q, Qi H, Li H. Effects of mind mapping health education on compliance behavior and self-perceived burden in patients with intra-articular fracture of extremities. *Chin J Mod Nur.* (2021) 27:2083–6. doi: 10.3760/cma.j.cn115682-20200925-05533

frontiers | Frontiers in Cardiovascular Medicine

TYPE Mini Review
PUBLISHED 08 March 2023
DOI 10.3389/fcvm.2023.1131967

OPEN ACCESS

EDITED BY
Shikai Yu,
Tongji University, China

REVIEWED BY
Oksana Boyarchuk,
Ternopil State Medical University, Ukraine

*CORRESPONDENCE
Junbao Du
junbaodu1@126.com
Hongfang Jin
jinhongfang51@126.com
Xueqin Liu
101811liu@163.com

SPECIALTY SECTION
This article was submitted to Pediatric Cardiology, a section of the journal Frontiers in Cardiovascular Medicine

RECEIVED 26 December 2022
ACCEPTED 20 February 2023
PUBLISHED 08 March 2023

CITATION
Wang J, Liu X, Jin H and Du J (2023) Markers for predicting the efficacy of beta-blockers in vasovagal syncope management in children: A mini-review.
Front. Cardiovasc. Med. 10:1131967.
doi: 10.3389/fcvm.2023.1131967

Markers for predicting the efficacy of beta-blockers in vasovagal syncope management in children: A mini-review

Jing Wang[1], Xueqin Liu[1]*, Hongfang Jin[1]* and Junbao Du[1,2]*

[1]Department of Pediatrics, Peking University First Hospital, Beijing, China, [2]Key Laboratory of Molecular Cardiovascular Sciences, Ministry of Education, Beijing, China

Vasovagal syncope (VVS) is a common subtype of neurally mediated syncope. It is prevalent in children and adolescents, and critically affects the quality of life of patients. In recent years, the management of pediatric patients with VVS has received extensive attention, and β-blocker serves as an important choice of the drug therapy for children with VVS. However, the empirical use of β-blocker treatment has limited therapeutic efficacy in patients with VVS. Therefore, predicting the efficacy of β-blocker therapy based on biomarkers related to the pathophysiological mechanism is essential, and great progress has been made by applying these biomarkers in formulating individualized treatment plans for children with VVS. This review summarizes recent advances in predicting the effect of β-blockers in the management of VVS in children.

KEYWORDS

vasovagal syncope, beta-adrenergic receptor blockers, individualized management, children, prediction

1. Introduction

Syncope is a common clinical symptom caused by transient cerebral blood supply reduction or interruption. It mainly manifests as transient loss of consciousness followed by decreased muscle tone and fall due to inability to maintain autonomous posture. The process is mostly temporary and self-limited (1). Neurally mediated syncope (NMS) is a very prevalent condition and accounts for a large proportion of pediatric syncopal cases, of which VVS is one of the most common forms (73%). In patients with VVS, sudden postural change from supine to upright, stuffy environments, and psychological stress lead to hypotension and/or bradycardia, which causes pre-syncope or syncope due to the inability to maintain posture. The physical and mental health of children with VVS is often affected (2, 3). In recent years, ample research has been conducted on individualized treatment of children with VVS (4). Currently, known therapeutic methods of VVS include pharmacological and non-pharmacological therapies. Beta-blockers, α1-adrenergic receptor agonist, sertraline, fludrocortisone, and oral rehydration salts are commonly used pharmacological treatments for VVS (1, 5, 6). This review summarizes the latest advances of biomarkers that can predict the therapeutic efficacy of β-blocker in children with VVS, and points out the advantages and disadvantages of these biomarkers. The aim of the present review is to describe the characteristics of VVS children who had a positive response to the treatment of β-blocker and to help the effective clinical use of β-blocker in the treatment of children with VVS.

2. Hypercatecholamine and hypersympathetic nerve function in children with VVS

The pathophysiology of VVS is very complex, involving a variety of potential mechanisms, such as hypercatecholamine and hypersympathetic nerve function, excessive vasorelexation or relatively low blood volume, etc (7–9). and the pathophysiology varies greatly among VVS individuals. In healthy children, when they stand for a long time or undergo sudden position changes from supine to upright, the decrease of the venous return results in a trend of declining blood pressure and heart rate; however by stimulating baroreceptors, they can be reflexively raised without causing obvious hypotension and symptoms. Previous studies have shown that the level of basal catecholamines in circulation of some VVS children is increased and they show hypersympathetic nerve function due to the imbalance of autonomic nervous function regulation. Therefore, in these children with VVS, due to the hypercatecholamine status and hypersympathetic nerve function, under the inducement factors such as sudden posture change, the Bezold-Jarisch reflex of the heart is initiated by the enhancement of compensatory myocardial contractility, which leads to the increase of vagus nerve activity and the heart rate and blood pressure continue to drop (10, 11). This causes insufficient blood supply to the brain, resulting in chest tightness, pallor, sweating, dizziness, blurred vision, and then fainting due to inability to maintain posture (12).

3. Treatment of beta-blockers in VVS of children

Patients with VVS are often treated with non-pharmacological and pharmacological therapies. Non-pharmacological therapy includes health education, fluid and salt supplementation, exercise of autonomic nervous function, and physical counter-pressure maneuvers. Pharmacological therapy includes β-blockers, α1-adrenergic receptor agonists, neurohormones, sertraline, fludrocortisone, and oral rehydration (13, 14). In clinical practice, the beta-blocker treatment for VVS was often prescribed empirically and non-selectively, and the efficacy of empirical treatment was often unsatisfactory. Previous studies have shown that the recurrence rate of syncope in children with VVS after 20 months of empirically non-selective metoprolol treatment was up to 34%, and the recurrence rate after 3 years was 43% (15, 16). Sheldon et al. found that there was no difference between metoprolol and placebo in preventing syncope in VVS patients (17).

4. Individualized beta-blocker therapy for children with VVS: biomarkers and therapeutic efficacy prediction

The empirical therapeutic effect of beta-blockers is often unsatisfactory because of the diversity of pathogenesis of VVS. According to recent studies, the pathogenesis of VVS includes increased sympathetic nerve activity and hypercatecholamine, a relatively insufficient central volume, peripheral vasodilation, neurohormonal disturbance, and the loss of baroreflex integrity. Therefore, the pathogenesis-based biological indicators should be determined to predict the therapeutic effect of drugs to implement individualized treatment to increase therapeutic efficacy (18). In some children with VVS, hypersympathetic nerve function and hypercatecholamine levels are the main mechanism, which can be antagonized by beta-blockers. Therefore, we should determine the stable biomarkers reflecting hypersympathetic nerve function and hypercatecholamine status as the main mechanism of VVS and direct β-blocker use as an individualized treatment to increase the therapeutic level (13). We summarizes the currently known biomarkers that can predict the efficacy of β-blockers on VVS in children (**Table 1**).

4.1. Changes in heart rate during the head-up tilt test (HUTT)

During the HUTT, some children with VVS develop reflective tachycardia after tilting from the supine position because of postural changes or long-term standing likely due to the sympathetic nerve activation (25, 26). Zhang et al. observed the hemodynamic changes of VVS children during HUTT and found that β-blockers were more effective for patients with significant heart rate increase before positive reaction during HUTT. A heart rate increase by 30 bpm before the positive response at HUTT as a cut-off value yielded a sensitivity of 81% and specificity of 80% to predict the responsiveness to β-blockers in VVS children (19).

4.2. Left ventricular ejection fraction (LVEF) and left ventricular fractional shortening fraction (LVFS)

Left ventricular ejection fraction (LVEF) and left ventricular fractional shortening fraction (LVFS) measured by echocardiography can reflect plasma catecholamine level and sympathetic nerve activity to some extent, although they are influenced by several other factors, such as cardiac function (27, 28). Based on the above correlations, Song et al. speculated that the VVS children with increased LVEF or LVFS might be in a status of high catecholamine level or sympathetic overexcitation, thereby exhibiting a better responsiveness to β-blocker (20). They followed up the VVS children treated with β-blocker for 6 months to explore the role of baseline LVEF and LVFS in the prediction of therapeutic efficacy of β-blocker in the children with VVS. As they expected, the results of follow-up at 6 months showed that the VVS children with baseline LVEF > 70.5% or LVFS > 37.5% responded better to β-blocker than those without, suggesting that the baseline LVEF and LVFS are meaningful and useful predictors of therapeutic response to β-blocker in children with VVS.

TABLE 1 Markers in predicting the therapeutic efficacy of beta-blockers in children with VVS.

References	Markers	Cut-off values	Sensitivity (%)	Specificity (%)
(19), Zhang et al.	ΔHR	30 bpm	81.0	80.0
(20), Song et al.	LVEF	70.5% (2 months after treatment)	80	100
		70.5% (6 months after treatment)	81.3	88.9
	LVFS	38.5% (2 months after treatment)	90.0	90.0
		37.5% (6 months after treatment)	93.8	66.7
(21), Tao et al.	BRS	10 ms/mmHg	71.0	83.0
	ΔBRS	4 ms/mmHg	81.3	88.9
(22), Kong et al.	24-h urinary NE	34.84 μg/24 h	70.0	100
(23, 24), Yuan et al.	L/T of Poincaré plot	2.7	88.2	82.8

ΔHR, the change of heart rate from supine to positive response occurrence during HUTT; LVEF, left ventricular ejection fraction; LVFS, left ventricular fractional shortening fraction; HUTT, head-up tilt test; BRS, baroreflex sensitivity; ΔBRS, the change of baroreflex sensitivity from supine to positive response occurrence during HUTT; NE, norepinephrine.

4.3. Baroreflex sensitivity

Baroreceptor reflex, as one of the important neuroregulatory reflexes to maintain blood pressure homeostasis, plays a key role in the regulation of hemodynamics when the body position changes. Abnormal changes in baroreceptors are one of the important pathogeneses of VVS. Measurements of baroreflex sensitivity (BRS) can evaluate the response to baroreceptors in the process of arterial pressure changes and reflect sympathetic nerve activity (6). The pre-treatment supine BRS of children with VVS to whom β-blockers are effective is much higher than that of children to whom β-blockers are ineffective. The change of BRS (ΔBRS) from supine position to positive response during the HUTT before treatment was more obvious in the effective patients than in the ineffective patients. Therefore, both BRS and ΔBRS can predict the response of VVS patients to β-blockers, and both indicators are non-invasive with good safety. However, the acquisition of these two indicators requires the use of specific instruments with relatively high cost, so they have not been widely used in clinics. Using pre-treatment BRS of 10 ms/mmHg as a cut-off value, the predicted sensitivity and specificity of β-blocker response in children with VVS were 82% and 83%, respectively. Pre-treatment ΔBRS of 4 ms/mmHg as a cut-off value yielded a sensitivity and specificity of 71% and 83%, respectively, to predict the efficacy of β-blockers in children with VVS (21).

4.4. Twenty four-hour urinary norepinephrine

Norepinephrine (NE) is released from adrenergic nerve endings mainly as a neurotransmitter and reflects the sympathetic nerve activity to some extent. NE is excreted through urine. Therefore, the measurement of NE at 24-h would reflect sympathetic nerve activity to some extent (9). The 24-h urinary NE concentration has the advantages of being relatively stable and inexpensive. Studies have shown that VVS patients with high 24-h urinary NE levels before treatment exhibit better β-blocker treatment effects. Pre-treatment 24-h urinary NE of 34.84 μg/24 h as a cut-off value yielded a sensitivity and specificity of 70% and 100%, respectively, to predict the responsiveness to β-blockers in children with VVS (22).

4.5. L/T of poincaré plot

The Lorenz-RR scatterplot, also called the Poincaré plot, is converted from 24-h dynamic electrocardiogram monitoring data and used to evaluate autonomic nervous function (29). The longitudinal axis (L) of the Poincaré plot represents the 24-h heart rate variation and reflects the sympathetic tension to some extent. The longer the longitudinal axis is, the stronger is the sympathetic nerve activity. The transverse axis (T) reflects the difference among adjacent RR segments, which represents the instantaneous heart rate change and mainly reflects vagal tone (24). According to previous studies, the L/T of the Poincaré plot is also called the "cardiac sympathetic index" because it reflects cardiac sympathetic function. The L/T value is stable, intuitive, and non-invasive. Although it is time-consuming in detection, it is easier to obtain than the 24-h urinary NE concentration. Studies have shown that when children with VVS were treated with β-blockers, the L/T in patients of the effective group before treatment was higher than that in the ineffective group. A pre-treatment L/T of 2.7 as a cut-off value yielded a sensitivity and specificity of 88.2% and 82.8%, respectively, to predict the efficacy of β-blockers in children with VVS (23).

4.6. Beta-1 receptor gene polymorphism

Adrenergic receptors (ARs) are targeted by epinephrine and norepinephrine in the sympathetic nervous system. They are expressed on almost all types of cells and are important parts of the sympathetic nervous system. Therefore, they play an important role in maintaining homoeostasis. The abnormal changes of structural and functional ARs are closely related to the pathogenesis of many diseases. There are nine subtypes of human ARs: α1A, α1B, α1D, α2A, α2B, α2C, β1, β2, and β3 (30). Stimulation of the cardiac β1 receptor can produce positive chronotropic, inotropic, and dromotropic effects through

G protein coupled signaling pathways. Adenylate cyclase is a second messenger in the G-protein coupled signaling pathway. Mason et al. found that nine adrenergic genes have polymorphisms (31). β1 adrenocepter gene (ADBR1) encodes a functional protein with 477 amino acids, in which there are multiple single nucleotide polymorphism (SNPs). According to the nucleotide variant #1165, the amino acid position of 389 can encode arginine and glycine. The Arg389 variant is more effective in stimulating adenylate cyclase than Gly389 variant, and has a better response to catecholamine. Therefore, the signal transduction ability of Arg389 variant is more stronger than Gly389 variant (32). The imbalance of autonomic nervous system regulation is one of an important pathogenesis of patients with VVS, and ADBR1 polymorphism may lead to changes in the structure and function of β1 adrenoceptor, and then result in autonomic nervous system imbalance. Beta-blockers can antagonize the binding of catecholamines to β1 adrenoceptor and block signal transduction, thus playing a role in the treatment of VVS children. In recent years, in the study of the role of β1 adrenoceptor gene polymorphism in VVS, it was found that the patients of VVS with positive HUTT had a higher frequency of Gly389 variant than VVS patients with negative HUTT (33.33% vs. 14.58%) (33). Atici et al. found that patients of VVS with Arg389Arg variant had a higher frequency of syncope episodes before β-blocker treatment than those with Arg389Gly variant (7.9 ± 3.7 vs. 6.4 ± 3.0). After 18 months of beta-blocker treatment, the number of syncope episodes of VVS patients with Arg389Arg variant was significantly lower than that of Arg389Gly variant (3.0 ± 1.4 vs. 6.8 ± 3.2) (32). However, the detection of β1 receptor gene polymorphism is a complex and costly process, and it is mainly used for research, as its wide application in clinical practice is not viable.

5. Conclusion and perspective

In summary, the markers including hemodynamic data during HUTT, characteristics of electrocardiogram, echocardiographic parameters, genetic information, and laboratory biochemistry index were successively found to have the ability to predict the therapeutic response to β-blocker in children with VVS. The facts that the above baseline clinical indices were collected before the treatment made it possible to help the pediatricians early identify the VVS children responding to β-blocker and then select the effective therapy. However, most of markers discovered so far have their own limitations such as unstability, unworkability, and expensiveness. In the future, the ability of markers to predict therapeutic response to β-blocker still needs to be improved. Moreover, it is worthy of paying great attention to the external validation study. Finally, the more novel, convenient, inexpensive, and readily available markers are still expected.

Author contributions

JW and XL: conceptualized, prepared, and wrote the manuscript. JD and HJ: reviewed, edited, and revised the manuscript. All authors contributed to the article and approved the submitted version.

Funding

The manuscript was supported by the National High Level Hospital Clinical Research Funding (Multi-center Clinical Research Project of Peking University First Hospital, China) (2022CR59).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Wang C, Li YQ, Tian H, Huang M, Dong XY, Shi L, et al. Chinese Pediatric Cardiology Society (CPCS) guideline for diagnosis and treatment of syncope in children and adolescents. *Sci Bull.* (2018) 63:1558–64. doi: 10.1016/j.scib.2018.09.019

2. Lin J, Jin H, Du J. Assessment of therapeutic biomarkers in the treatment of children with postural tachycardia syndrome and vasovagal syncope. *Cardiol Young.* (2014) 24(5):792–6. doi: 10.1017/S1047951114000316

3. Zavala R, Metais B, Tuckfield B, Delvecchio M, Aronoff S. Pediatric syncope: a systematic review. *Pediatr Emerg Care.* (2020) 36(9):442–5. doi: 10.1097/PEC.0000000000002149

4. Xu WR, Du JB, Jin HF. Can pediatric vasovagal syncope be individually managed? *World J Pediatr.* (2022) 18(1):4–6. doi: 10.1007/s12519-021-00495-0

5. Flevari P, Livanis EG, Theodorakis GN, Zarvalis E, Mesiskli T, Kremastinos DT. Vasovagal syncope: a prospective, randomized, crossover evaluation of the effect of propranolol, nadolol and placebo on syncope recurrence and patients' well-being. *J Am Coll Cardiol.* (2002) 40(3):499–504. doi: 10.1016/s0735-1097(02)01974-5

6. Mitro P, Aimurda M, Muller E. Improvement in low upright baroreflex sensitivity is associated with positive clinical effect of orthostatic training. *Pacing Clin Electrophysiol.* (2018) 41(1):42–9. doi: 10.1111/pace.13238

7. Du X, Tao C, Wang Y, Sun Y, Zhang Q, Zhang C, et al. Twenty-four-hour urinary sodium excretion predicts therapeutic effectiveness of oral rehydration saline in pediatric vasovagal syncope. *Children.* (2022) 9(7):992. doi: 10.3390/children9070992

8. Santini L, Capria A, Brusca V, Violo A, Smurra F, Scarfò I, et al. An increased endothelial-independent vasodilation is the hallmark of the neurally mediated syncope. *Clin Cardiol.* (2012) 35(2):107–10. doi: 10.1002/clc.20990

9. Vaddadi G, Guo L, Esler M, Socratous F, Schlaich M, Chopra R, et al. Recurrent postural vasovagal syncope. *Circ Arrhythm Electrophysiol*. (2011) 4(5):711–8. doi: 10.1161/CIRCEP.111.962332

10. Iwase S, Nishimura N, Mano T. Role of sympathetic nerve activity in the process of fainting. *Front Physiol*. (2014) 5:343. doi: 10.3389/fphys.2014.00343

11. Dilip Chand Raja S, Rajasekaran S, Sri Vijayanand KS, Shetty AP, Kanna RM. Bezold–jarisch reflex causing bradycardia and hypotension in a case of severe dystrophic cervical kyphotic deformity: a case report and review of literature. *Eur Spine J*. (2020) 29(Suppl 2):188–92. doi: 10.1007/s00586-020-06619-w.

12. Wang Y, Du J, Jin H, Liao Y. Comorbidity of neurally mediated syncope and allergic disease in children. *Front Immunol*. (2020) 11:1865. doi: 10.3389/fimmu.2020.01865

13. Chen LY, Shen WK. Neurocardiogenic syncope: latest pharmacological therapies.. *Expert Opin Pharmacother*. (2006) 7(9):1151–62. doi: 10.1517/14656566.7.9.1151

14. Sheldon RS, Grubb BP 2nd, Olshansky B, Shen WK, Calkins H, Brignole M, et al. 2015 Heart Rhythm Society expert consensus statement on the diagnosis and treatment of postural tachycardia syndrome, inappropriate sinus tachycardia, and vasovagal syncope. *Heart Rhythm*. (2015) 12(6):e41–63. doi: 10.1016/j.hrthm.2015.03.029

15. Zhang Q, Jin H, Wang L, Chen J, Tang C, Du J. Randomized comparison of metoprolol versus conventional treatment in preventing recurrence of vasovagal syncope in children and adolescents. *Med Sci Monit*. (2008) 14(4):CR199–203. doi: 10.12659/MSM.938647

16. Tao C, Cui Y, Zhang C, Liu X, Zhang Q, Liu P, et al. Clinical efficacy of empirical therapy in children with vasovagal syncope. *Children*. (2022) 9(7):1065. doi: 10.3390/children9071065

17. Sheldon R, Connolly S, Rose S, Klingenheben T, Krahn A, Morillo C, et al. Prevention of syncope trial (POST): a randomized, placebo-controlled study of metoprolol in the prevention of vasovagal syncope. *Circulation*. (2006) 113(9):1164–70. doi: 10.1161/CIRCULATIONAHA.105.535161

18. Liao Y, Du J. Pathophysiology and individualized management of vasovagal syncope and postural tachycardia syndrome in children and adolescents: an update. *Neurosci Bull*. (2020) 36(6):667–81. doi: 10.1007/s12264-020-00497-4

19. Zhang Q, Du J, Zhen J, Li W, Wang Y. Hemodynamic changes during head-up tilt test and predictive value there of in predicting the efficacy of metoprolol therapy in children with vasovagal syncope. *Zhonghua Yi Xue Za Zhi*. (2007) 18:1260–2. doi: 10.3760/j:issn:0376-2491.2007.18.011

20. Song J, Li H, Wang Y, Liu P, Li X, Tang C, et al. Left ventricular ejection fraction and fractional shortening are useful for the prediction of the therapeutic response to metoprolol in children with vasovagal syncope. *Pediatr Cardiol*. (2018) 39(7):1366–72. doi: 10.1007/s00246-018-1904-x

21. Tao C, Li X, Tang C, Jin H, Du J. Baroreflex sensitivity predicts response to metoprolol in children with vasovagal syncope: a pilot study. *Front Neurosci*. (2019) 13:1329. doi: 10.3389/fnins.2019.01329

22. Kong Q, Yang X, Cai Z, Pan Y, Wang M, Liu M, et al. Twenty-four-hour urine NE level as a predictor of the therapeutic response to metoprolol in children with recurrent vasovagal syncope. *Ir J Med Sci*. (2019) 188(4):1279–87. doi: 10.1007/s11845-019-01979-9

23. Yuan P, Li X, Tao C, Du X, Zhang C, Du J, et al. Poincare plot can be a useful tool to select potential responders to metoprolol therapy in children with vasovagal syncope. *Int J Gen Med*. (2022b) 15:2681–93. doi: 10.2147/IJGM.S352928

24. Yuan P, Lian Z, Wang Y, Wang Y, Zhang C, Du J. Poincaré plot is useful for distinguishing vasovagal syncope from postural tachycardia syndrome in children. *Front Pediatr*. (2022a) 10:758100. doi: 10.3389/fped.2022.758100

25. Gielerak G, Makowski K, Cholewa M. Prognostic value of head-up tilt test with intravenous beta-blocker administration in assessing the efficacy of therapy in patients with vasovagal syncope. *Ann Noninvasive Electrocardiol*. (2005) 10(1):65–72. doi: 10.1111/j.1542-474X.2005.00603.x

26. Kolarczyk E, Szydlowski L, Skierska A, Markiewicz-Loskot G. The differences in the diagnostic profile in children with vasovagal syncope between the result of head-up tilt table test. *Int J Environ Res Public Health*. (2020) 17(12):4524. doi: 3390/ijerph17124524

27. Pfeffer MA, Shah AM, Borlaug BA. Heart failure with preserved ejection fraction in perspective. *Circ Res*. (2019) 124(11):1598–617. doi: 10.1161/CIRCRESAHA.119.313572

28. Støylen A, Dalen H, Molmen HE. Left ventricular longitudinal shortening: relation to stroke volume and ejection fraction in ageing, blood pressure, body size and gender in the HUNT3 study. *Open Heart*. (2020) 7(2):e001243. doi: 10.1136/openhrt-2020-001243

29. Romito G, Guglielmini C, Poser H, Baron Toaldo M. Lorenz plot analysis in dogs with sinus rhythm and tachyarrhythmias. *Animals*. (2021) 11(6):1645. doi: 10.3390/ani11061645

30. Small KM, Rathz DA, Liggett SB. Identification of adrenergic receptor polymorphisms. *Methods Enzymol*. (2002) 343:459–75. doi: 10.1016/s0076-6879(02)43152-7

31. Mason DA, Moore JD, Green SA, Liggett SB. A gain-of-function polymorphism in a G-protein coupling domain of the human beta1-adrenergic receptor. *J Biol Chem*. (1999) 274(18):12670–4. doi: 10.1074/jbc.274.18.12670

32. Atici A, Rasih-Sonsoz M, Ali-Barman H, Durmaz E, Demirkiran A, Gulsen K, et al. The role of beta-1 receptor gene polymorphism in beta-blocker therapy for vasovagal syncope. *Rev Invest Clin*. (2020) 72(5):300–7. doi: 10.24875/RIC.20003319

33. Huang YJ, Wang JY, Li J, Shen J, Xu M, Huang M. Association between polymorphism of β1-adrenergic receptor gene and vasovagal syncope in children. *J Clin Pediatr*. (2010) 28(2):156–9. doi: 1000-3606(2010)02-0156-04

frontiers | Frontiers in Cardiovascular Medicine

TYPE Original Research
PUBLISHED 08 March 2023
DOI 10.3389/fcvm.2023.1099115

OPEN ACCESS

EDITED BY
Zhen-Yu Zhang,
KU Leuven, Belgium

REVIEWED BY
Régis Guieu,
Aix Marseille Université, France
Julian Mark Stewart,
New York Medical College, United States

*CORRESPONDENCE
Xiaohui Li
✉ lxhmaggie@126.com

†These authors have contributed equally to this work and shared first authorship

SPECIALTY SECTION
This article was submitted to Pediatric Cardiology, a section of the journal Frontiers in Cardiovascular Medicine

RECEIVED 15 November 2022
ACCEPTED 17 February 2023
PUBLISHED 08 March 2023

CITATION
Sun R, Kang Y, Zhang M, Wang H, Shi L and Li X (2023) Development of prognostic nomogram model to predict syncope recurrence in children with vasovagal syncope.
Front. Cardiovasc. Med. 10:1099115.
doi: 10.3389/fcvm.2023.1099115

Development of prognostic nomogram model to predict syncope recurrence in children with vasovagal syncope

Rui Sun[1,2†], Yingying Kang[2,3†], Mingming Zhang[2], Hongmao Wang[2], Lin Shi[2] and Xiaohui Li[1,2,3*]

[1]Department of Cardiology, Capital Institute of Pediatrics-Peking University Teaching Hospital, Beijing, China, [2]Department of Cardiology, Children's Hospital Capital Institute of Pediatrics, Beijing, China, [3]Graduate School of Peking Union Medical College, Capital Institute of Pediatrics, Beijing, China

Backgrounds: Vasovagal syncope (VVS) is a common form of syncope. In children with VVS, recurrent syncope or presyncope can affect the physical and mental health of both children and parents, which markedly impairs quality of life.
Objectives: We aimed to identify factors at baseline that can predict the recurrence of syncope or presyncope over a 5-year follow-up period, and further to develop a prognostic nomogram model.
Methods: This cohort is bidirectional in design. From July 2017 to August 2022, children with VVS were included and followed up every 3 to 6 months. Head-up Tilt Test (HUTT) was performed for diagnosing VVS. Data were analyzed using STATA software, and risk estimates are presented as hazard ratio (HR) and 95% confidence interval (CI).
Results: Total 352 children with VVS who had complete information were included in this study. Median follow-up time was 22 months. Overall, supine mean arterial pressure (MAP-supine) in HUTT and baseline urine specific gravity (USG) were associated with the significant risk of syncope or presyncope recurrence (HR: 0.70 and 3.00, respectively; both $P < 0.05$). Calibration and discrimination analyses revealed that the addition of MAP-supine and USG can result in a better fit. A prognostic nomogram model based on significant factors annexed with five traditional promising factors was finally constructed, with strong discriminative and predictive abilities (C-index approaching 0.700, $P < 0.05$).
Conclusions: Our findings indicated that MAP-supine and USG can independently predict the significant risk of syncope recurrence in children with VVS, and the prediction was more obvious in a nomogram model.

KEYWORDS
vasovagal syncope, children, recurrence of syncope, prognosis, nomogram model

1. Introduction

Syncope is a major public health concern with approximately 17% of children 2 to 18 years of age experiencing at least one episode of syncope (1). As a common form of syncope, vasovagal syncope (VVS) accounts for about 60 to 80% of all pediatric cases (2). VVS tends to have a good prognosis, yet its recurrent episodes can affect the physical and mental health of children, as well as their parents, which markedly impairs the quality of life (3). As the development of syncope is a complex process, it is of clinical and healthcare importance to identify potential factors attributable to the recurrence of syncope in children affected with VVS.

Currently, research on the risk profiles of recurrent syncope or presyncope in children with VVS has been less conducted in medical literature. For example, some investigators have reported that the number of previous episodes of syncope (4, 5), onset age of syncope, and family history (6) were identified as promising predictors for recurrent syncope in VVS. In addition, others revealed that venous blood routine hemoglobin concentration and mean corpuscular hemoglobin were candidate biomarkers in predisposition to syncope recurrence (7). Further, heart rate variability (HRV), body mass index (BMI), and therapeutic regimens can also affect the prognosis of VVS (8–10). Thus far, no consensus has been attained which and how many factors actually precipitate the development of recurrent syncope in children with VVS, likely due to differences in genetic underpinnings, statistical power or participant characteristics. Given that VVS etiology is complex and usually involve a multistep, multifactorial process, the impact of any single factors is believed to be small, but may be more evident when assessed in combination. However, a literature search did not trace any hints concerning the joint contribution of various factors to recurrent syncope in VVS.

To fill this gap in knowledge and yield more references for future studies, we, in a large cohort of children with VVS, aimed to identify factors at baseline that can predict the recurrence of syncope over a 5-year follow-up period, and meanwhile for clinical application, to develop a prognostic nomogram model based on promising significant attributes.

2. Methods

2.1. Ethical approval and informed consent

The conduct of this study was approved by the Ethics Committee of Children's Hospital Capital Institute of Pediatrics (SHERLLM2021025), and written informed consent was obtained from parents or supervisors of participating children.

2.2. Study children

The present cohort is bidirectional in design. From July 2017 to August 2022, children diagnosed with VVS were hospitalized for the first time at the Department of Cardiology, Children's Hospital Capital Institute of Pediatrics, and after discharge they were followed up at the Out-Patient Department every 3–6 months. The latest follow-up was competed on October 7, 2022. In case of no-show at the scheduled time, we reached out to their parents or supervisors through phone. The minimal follow-up time was set at 1 month.

2.3. Inclusion and exclusion criteria

Children were included if all of the following criteria were satisfied simultaneously: (i) <18 years of age; (ii) hospitalized children; (iii) confirmed diagnosis of VVS. The clinical diagnostic criteria of VVS refer to the expert consensus on the diagnosis of syncope in children (11).

Children were excluded if they complicated any of the following criteria: (i) cardiovascular diseases, such as hypertension, arrhythmias, and congenital heart disease; (ii) neuropsychological diseases, such as anxiety and depression; (iii) metabolic diseases, such as hyperthyroidism and metabolic syndrome; (iv) convulsant syncope confirmed as seizure based on their medical histories as well as electroencephalograph and brain magnetic resonance imaging examination.

2.4. Follow-up assessment

The details of treatment regimens for children with VVS can be found in the Supplementary Materials (Appendix A.1). During each follow-up, autonomic exercises, oral rehydration salts, and drug regimens were recorded. Disease-specific survival was calculated from the date of diagnosis to the date of syncope or presyncope recurrence or the date of the last follow-up visit, whichever came first. Presyncope is defined as symptoms before syncope, and it includes extreme lightheadedness, visual sensations (such as tunnel vision and graying out), and variable degrees of altered consciousness without complete loss of consciousness. If the child had a transient loss of consciousness associated with inability to maintain postural tone with rapid and spontaneous recovery, syncope was confirmed. Recurrence information was obtained from either parents or supervisors. Children with VVS were divided into two groups: children with syncope or presyncope recurrence and children free of syncope or presyncope recurrence.

2.5. Head-up tilt test

Participating children were requested to lie on the electric tilting bed (SHUT -100A, STANDARD, Beijing, China) in the supine position for 10 min. A baseline head-up tilt test (HUTT) was conducted with the child tilted for 45 min without medication. If syncope did not develop, the child was given a sublingual nitroglycerin (4–6 μg/kg, maximum ≤0.3 mg) to provoke syncope within 20 min. Automatic cuff blood pressure, heart rate, and electrocardiograph were recorded continuously by electric tilting instrument. If syncope occurred during the test, the tilt table would be quickly lowered to the supine position. Positive responses to HUTT involve syncope or presyncope in addition to four key factors, including (i) drops in blood pressure (systolic blood pressure [SBP] ≤80 mmHg diastolic blood pressure [DBP] ≤50 mmHg; (ii) a sinus arrest with junctional escape rhythm; (iii) an atrioventricular (AV) conduction block no less than II° or a cardiac arrest for three seconds; (iv) a decrease in heart rate of <75 beats per minute(bpm) in children aged 4–6 years, <65 bpm in those aged 7–8 years, and <60 bpm in those aged 8 years (11–13). In addition, VVS is divided into three types according to the changes in blood pressure and heart

rate. The cases with lower blood pressure were defined as the vaso inhibitive type, the cases with significantly lower heart rate were defined as the VVS cardiac inhibitory type, and the cases with both lower heart rate and lower blood pressure as the VVS mixed type.

2.6. Data collection

For children admitted for the first time to our hospital, a standardized questionnaire was adopted to glean demographic information at baseline, including age, sex, BMI, medical history, number of syncope, and family history of syncope. Routine blood tests, cardiac enzymes, urine routine, 24-hour urine output and electrolytes, cardiac function, and 24-hour Holter during hospitalization were also recorded. All above tests were completed prior to the HUTT test. The first morning urine specimens were measured using an automatic urinary sediment analyzer (AX-4030, Arkray, Kyoto, Japan). Heart rate and arterial pressure were measured twice after affected children had stayed in a supine position for 10 min and again at 60-degree tilting when stable within the first 1 min.

In addition, the following indicators were also collected. Mean arterial pressure in the supine position for 10 min (MAP-supine), and mean arterial pressure in the first 1 min at 60 degrees of inclination (MAP-tilt) were calculated SBP and DBP in tilt position. MAP was calculated as DBP plus $0.333 \times$ (SBP - DBP). Change-SBP was calculated as SBP in tilt immediately minus SBP in supine, and Change-DBP as DBP in tilt immediately minus DBP in supine. Change-HR was calculated as heart rate in tilt immediately minus heart rate in supine.

2.7. Statistical analysis

Continuous parameters are presented as mean ± standard deviation (SD) or as median (interquartile range) depending on whether the parameter was deviated from the Gaussian distribution. Where appropriate, the *t*-test or Mann-Whitney test was used to compare differences of continuous parameters between groups. Categorical parameters are presented as percentage (count) and compared using the χ^2 test or Fisher's exact test. Potential factors related to recurrence were initially identified by the univariate Cox proportional hazards regression analyses. Then, the multivariate Cox proportional hazards regression analyses were undertaken to control for covariates, including age, sex, BMI, medical history, number of syncope, family history of syncope, and therapeutic regimens.

A series of discrimination and calibration statistics were used to evaluate prediction accuracy. To justify the improvement in prediction accuracy, net reclassification improvement (NRI) and integrated discrimination improvement (IDI) (14, 15) were calculated. If the outcome is less than 0.05, adding significant risk factors might greatly increase the model's ability in prediction. The area under the Harrell C-statistic is to examine whether the traditional model can distinguish between children who had presyncope or syncope recurrence when significant factors are added. To determine how closely the prediction probability for the addition of significant factors reflected actual observed risk and the overall fit of the improved risk model, the Akaike information criterion (AIC), Bayesian information criterion (BIC), and likelihood ratio test were utilized (16). For the AIC and BIC indices, smaller values indicate better models.

By using decision curve analysis (DCA), the net benefit of the addition of significant factors over the conventional model was clearly demonstrated (17). The DCA graph's X-axis represents the recurrence thresholds, while the Y-axis represents the net benefits for various thresholds. If the "model" curve is further from the solid curve line under all recurrence assumptions and the dotted horizontal line with none recurrence assumptions, a bigger net benefit is reported.

A predicted nomogram for the 1-year, 2-year, and 3-year recurrence rates from VVS was constructed among all research patients based on baseline demographic and clinical data with statistical significance, improving clinical interpretation. The predictive precision and discriminative power of this prognostic nomogram were assessed using the concordance index (C-index) and calibration curve. The area under the receiver operating characteristic curve and the C-index are equivalent. According to the calibration curve, the 45° line illustrates how far the prognostic nomogram's predicted probabilities differ from actual outcomes.

The regression modeling strategies (RMS) package (https://cran.r-project.org/web/packages/rms/index.html) in the R-language (version 4.2.1) was used to create the prognostic nomogram model. A nomogram is a graphic calculator that has been scaled and is used to determine an approximation of a function. In this study, a simple 10-point scale was used as the basis for the nomogram.

All of the aforementioned statistical analyses were conducted using STATA/SE software (version 14.0, Stata Corp, TX, USA). Probability less than 5% was considered statistically significant.

3. Results

3.1. Sample size

In total, 409 children were diagnosed with VVS during the study period, and 37 of them were excluded because of anxiety and depression ($n = 23$), hyperthyroidism ($n = 7$), arrhythmias ($n = 3$), hypertension ($n = 3$), and abnormal origin coronary artery ($n = 1$). Twenty children were lost during follow-up, leaving 352 patients with complete follow-up data in the final analysis. The median time to an endpoint (syncope or presyncope recurrence) event occurred was 22 months (from 1 day to 63 months).

3.2. Baseline characteristics

The baseline characteristics of study patients are showed in **Table 1**. Urine specific gravity (USG) before diagnosis and the

TABLE 1 Baseline characteristics of participating children by the presence and absence of recurrence of vasovagal syncope.

	No Recurrence ($n = 220$)	Recurrence ($n = 132$)	P
Demographic information			
Age (years)	12.00 (9.29, 13.34)	12.00 (9.90, 13.64)	0.068
Girls, *n* (%)	120 (54.5)	84 (63.6)	0.118
Body mass index (kg/m^2)	18.00 (15.76, 20.05)	18.00 (15.67, 19.89)	0.786
Medical history (months)	3.50 (0.75, 12.00)	6.00 (1.00, 24.00)	0.068
Number of syncope (*n*)	1.00 (0.00, 2.00)	1.00 (0.00, 2.00)	0.553
Family history of syncope (%)	22 (10.0)	18 (13.6)	0.303
Laboratory Examination			
Hemoglobin (g/L)	130.00 (124.00, 138.00)	130 (126.00, 137.25)	0.621
MCV (fL)	84.00 (81.85, 86.70)	84.00 (81.90, 87.32)	0.637
MCH (pg)	29.00 (27.80, 29.70)	29.00 (27.70, 29.80)	0.516
MCHC (g/L)	340.00 (332.50, 346.00)	340.00 (332.75, 346.00)	0.912
Creatine Kinase (U/L)	74.00 (60.00, 98.00)	70.00 (54.50, 91.50)	0.119
Creatine Kinase-MB (ng/ml)	0.54 (0.21, 0.90)	0.45 (0.20, 0.80)	0.135
Urine output (ml/24 h)	1300.00 (894.00, 1,755.00)	1300.00 (950.00, 1,748.00)	0.888
Total-Na (mmol/24 h)	120.00 (93.06, 170.13)	120.00 (78.57, 171.70)	0.728
Total-K (mmol/24 h)	31.00 (24.86, 39.90)	30.00 (22.36, 37.59)	0.309
Urine specific gravity	1.02 (1.01, 1.02)	1.02 (1.01, 1.03)	0.016
LVEF (%)	70.00 (67.00, 73.50)	70.00 (66.00, 73.00)	0.674
LVFS (%)	39.00 (36.00, 42.00)	39.00 (36.00, 42.00)	0.662
24-Hour Holter			
Average HR (bpm)	81.00 (75.00, 86.00)	80.00 (75.00, 87.00)	0.733
SDNN (ms)	150.00 (127.00, 175.00)	150.00 (132.00, 172.00)	0.878
SDANN (ms)	130.00 (110.00, 151.00)	120.00 (111.00, 148.00)	0.819
SDNN index (ms)	73.00 (60.00, 87.25)	72.00 (61.00, 88.00)	0.961
pnn50 (%)	24.00 (15.00, 33.00)	22.00 (16.00, 32.00)	0.493
DC	7.10 (6.27, 8.01)	7.20 (6.46, 7.95)	0.687
TP	4200.00 (3,049.80, 5,895.57)	3900.00 (2,994.78, 5,596.25)	0.172
LF/HF	1.50 (1.17, 2.06)	1.60 (1.24, 2.00)	0.367
Head-up Tilt Test			
MAP-supine (mm Hg)	81.00 (75.58, 86.00)	79.00 (75.33, 84.00)	0.188
MAP-tilt (mm Hg)	80.00 (74.67, 85.00)	78.00 (73.00, 83.00)	0.154
Change-SBP (mm Hg)	−1 (−7.00, 3.00)	0 (−6.00, 4.00)	0.398
Change-DBP (mm Hg)	−3 (−8.00, 1.00)	−5 (−9.00, 1.00)	0.06
Change-HR (bpm)	17.00 (11.00, 24.00)	16.00 (10.00, 24.25)	0.995
Positive reaction time (min)	35.00 (20.00, 35.00)	33.00 (18.00, 35.00)	0.332
Nitroglycerin (%)	140 (63.6)	78 (59.5)	0.515
Type (%)			
Type1	86 (39.1)	53 (40.2)	0.262
Type2	46 (20.9)	36 (27.3)	
Type3	88 (40.0)	43 (32.6)	
Sinus arrest (%)	9 (4.1)	9 (6.8)	0.319
Therapy			
Autonomic nerve function exercises (%)	144 (65.5)	76 (57.6)	0.142
ORS (months)	1.00 (0.25, 2.00)	1.00 (0.00, 3.50)	0.029
Drug therapy (%)			
Without	158 (71.8)	88 (66.7)	0.578
Metoprolol	46 (20.9)	32 (24.2)	
Sertraline hydrochloride	16 (7.3)	12 (9.1)	
Drug therapy duration (months)	0 (0.00, 1.00)	0 (0.00, 1.00)	0.292

SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, average arterial pressure; HR, heart rate; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; LVEF, left ventricular ejection fraction; LVFS, left ventricular fraction shortening; SDNN, standard deviation of RR intervals in milliseconds; SDANN, Standard deviation of the average RR intervals milliseconds; SDNN index, Mean score of the standard deviations of all RR intervals in 5-min segments in milliseconds; pnn50, Proportion of pairs of successive RR intervals differing by more than 50 ms divided by the total number of RR intervals (percentage); DC, deceleration capacity; TP, total power, the frequency components in heart rate variability; LF/HF, ratio between the low- and high frequency component; Type1, vasodepressor type; Type2, cardioinhibitory type; Type3, mixed type; ORS, oral rehydration salts. Sinus arrest means the children had syncope with sinus arrest during an inspection in the hospital. "Autonomic nerve function exercises" doesn't involve the use of MSNA.

time used oral rehydration salts (ORS) during follow-ups differed significantly between children with or without recurrence ($P < 0.05$). No significance was noted for the rest characteristics.

Comparison of baseline characteristics between children analyzed and lost to follow-ups is provided in **Supplementary Table S1**.

3.3. Identification of significant factors

The two factors, MAP-supine and USG, were associated with the significant risk of syncope or presyncope recurrence in VVS patients before adjustment at a 5% level of significance (**Table 2**). After adjusting for age, sex, BMI, medical history, number of syncope, family history of syncope, and therapeutic regimens, three factors were consistently and independently associated with the significant risk of recurrence in VVS, including MAP-supine (HR, 95% CI, *P*: 0.700, 0.567 to 0.869, 0.001), MAP-tilt (0.796, 0.654 to 0.969, 0.035), and USG (3.000, 1.03 to 8.741, 0.044).

3.4. Prediction accuracy assessment

Because MAP-supine had collinearity with MAP- tilt, MAP-tilt was removed from the following analyses. To evaluate the predictive power of the major factors identified, two models—the

TABLE 2 Identification of factors independently and significantly associated with the recurrence of vasovagal syncope.

Factors at baseline	Univariate model			Multivariable model		
	HR	95% CI	*P*	HR	95% CI	*P*
Age	1.005	0.999 to 1.011	0.090	NA	NA	NA
Sex	0.738	0.517 to 1.052	0.093	NA	NA	NA
BMI	0.993	0.943 to 1.047	0.801	NA	NA	NA
Medical history	1.064	0.986 to 1.149	0.111	NA	NA	NA
Number of syncope	1.013	0.926 to 1.109	0.778	NA	NA	NA
Family history of syncope	1.120	0.68 to 1.844	0.656	NA	NA	NA
Hemoglobin	1.001	0.987 to 1.016	0.899	1.004	0.988 to 1.021	0.601
MCV	1.000	0.997 to 1.002	0.750	1.000	0.996 to 1.003	0.769
MCH	1.042	0.953 to 1.14	0.365	1.026	0.937 to 1.123	0.580
MCHC	0.991	0.976 to 1.006	0.226	0.991	0.976 to 1.007	0.285
Creatine Kinase	0.995	0.989 to 1.000	0.067	0.996	0.99 to 1.002	0.250
Creatine Kinase-MB	0.908	0.7 to 1.178	0.469	0.951	0.756 to 1.195	0.665
LVEF	0.999	0.958 to 1.042	0.969	1.008	0.966 to 1.052	0.705
LVFS	0.997	0.948 to 1.049	0.912	1.007	0.957 to 1.06	0.778
Urine output of 24h	1.000	1.0 to 1.0	0.889	1.0	1.0 to 1.0	0.901
Total-Na	1.000	0.998 to 1.002	0.857	1.000	0.998 to 1.002	0.990
Total-K	1.000	1.0 to 1.001	0.298	1.000	1.0 to 1.001	0.258
Urine specific gravity (+0.05)	3.455	1.232 to 9.691	0.018	3.000	1.03 to 8.741	0.044
Average heart rate	0.999	0.982 to 1.018	0.952	1.001	0.979 to 1.024	0.912
SDNN	0.999	0.996 to 1.003	0.638	1.000	0.996 to 1.003	0.957
SDANN	1.000	0.994 to 1.005	0.943	1.000	0.994 to 1.006	0.919
SDNN index	0.998	0.992 to 1.003	0.421	0.999	0.993 to 1.005	0.710
pnn50	0.997	0.983 to 1.011	0.684	1.000	0.987 to 1.014	0.988
DC	0.998	0.977 to 1.02	0.863	0.994	0.882 to 1.121	0.925
TP	1.000	1.0 to 1.0	0.343	1.000	1.0 to 1.0	0.154
LF/HF	1.093	0.874 to 1.367	0.435	1.123	0.885 to 1.424	0.339
MAP-supine (+10 mmHg)	0.775	0.633 to 0.948	0.013	0.700	0.567 to 0.869	0.001
MAP-tilt (+10 mmHg)	0.879	0.734 to 1.053	0.161	0.796	0.654 to 0.969	0.035
Change-SBP (+10 mmHg)	1.050	0.879 to 1.254	0.589	1.096	0.911 to 1.319	0.332
Change-DBP (+10 mmHg)	0.876	0.714 to 1.076	0.207	0.863	0.71 to 1.048	0.138
Change-HR (+10 bpm)	0.863	0.71 to 1.048	0.138	0.876	0.714 to 1.076	0.207
Positive reaction time (min)	0.991	0.976 to 1.007	0.272	0.993	0.977 to 1.009	0.407
Nitroglycerin	0.816	0.592 to 1.125	0.214	0.800	0.578 to 1.109	0.181
Type	0.820	0.671 to 1.004	0.054	0.820	0.663 to 1.015	0.068
Sinus arrest	1.354	0.688 to 2.666	0.380	0.778	0.296 to 2.046	0.611

HR, hazard ratio; 95% CI, 95% confidence interval; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, average arterial pressure; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; LVEF, left ventricular ejection fraction; LVFS, left ventricular fraction shortening; SDNN, standard deviation of RR intervals in milliseconds; SDANN, Standard deviation of the average RR intervals milliseconds; SDNN index, Mean score of the standard deviations of all RR intervals in 5-min segments in milliseconds; pnn50, Proportion of pairs of successive RR intervals differing by more than 50 ms divided by the total number of RR intervals (percentage); DC, deceleration capacity; TP, total power, the frequency components in heart rate variability; LF/HF, ratio between the low- and high frequency component; ORS, oral rehydration salts, NA, not available. Sinus arrest means that children had syncope with sinus arrest during an inspection in the hospital. In multivariable model, adjusted factors included age, sex, body mass index, medical history, number of syncope, family history of syncope, and therapeutic regimens.

basic model and the full model—were built. The basic model includes general characteristics (age, sex, BMI, medical history, family history of syncope), and the full model includes general characteristics and the two significant factors (MAP-supine and USG).

The prediction accuracy gained by adding the two major factors to the basic model was assessed using both calibration and discrimination statistics (Table 3). Compared with the basic model, the prediction accuracy of the full model was significantly improved. The AIC and BIC in full model were smaller, and as revealed by the likelihood ratio test, both models differed significantly in prediction performance ($P = 0.001$). NRI and IDI statistics showed significant improvement after adding MAP-supine and USG to the basic model from the aspect of reclassification performance. Harrell's C-statistic indicated that the addition of MAP-supine and USG can improve the predictive ability of the basic model.

Furthermore, DCA graph indicated the obvious net benefits gained by adding the two significant factors to the basic model (Figure 1).

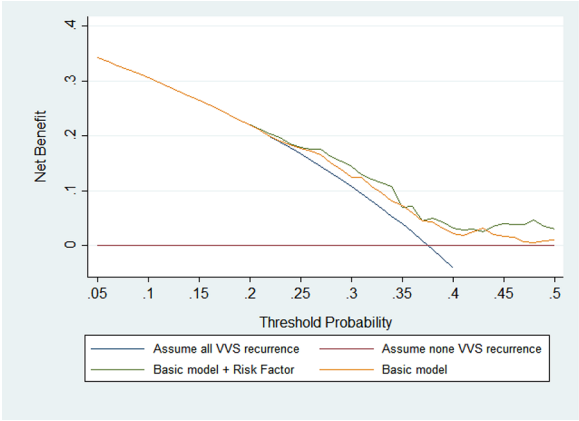


FIGURE 1
Prognostic decision curves for the basic model and the addition of MAP-supine and urine specific gravity in vasovagal syncope patients. The basic model included age, sex, body mass index, medical history, and family history.

3.5. Risk prognostic nomogram model

To facilitate clinical interpretation, a prognostic nomogram model was constructed on the basis of the two significant factors aforementioned and some acknowledged conventional factors (Figure 2). For an example of clinical usefulness of this nomogram, assuming a girl (1.5 points) aged ten years (3.5 points), with a family history of syncope (1.8 points), BMI of 16 kg/m^2 (1 points), MAP-supine 90 mmHg (2.9 points), and USG 1.025 (2.8 points), she would have an estimated 71% chance to experience no-recurrence of syncope or presyncope at 1st year and 65% chance at 2nd year, and 58% chance at 3rd year. Thus, the recurrence rate in 1st year, 2nd year, and 3rd year were estimated to be 29%, 35%, and 42%, respectively.

TABLE 3 Predictive accuracy of risk model with and without MAP-supine or USG for the prediction of VVS recurrence.

Statistics	Basic model	Full model
Calibration		
AIC	1,432.398	1,217.030
BIC	1,455.580	1,246.897
LR test (χ^2)	13.670	
LR test (P value)	0.001	
Discrimination		
NRI (P value)	0.043	
IDI (P value)	0.000	
Harrell's C	0.589	0.651

VVS, vasovagal syncope; MAP, average arterial pressure; USG, urine specific gravity; AIC, Akaike information criterion; BIC, Bayesian information criteria; LR test, likelihood ratio test; NRI, net reclassification improvement; IDI, integrated discrimination improvement. Basic model included age, sex, body mass index, medical history, number of syncope, and family history, and full model additionally included MAP-supine and USG.

This nomogram had a good prediction accuracy, with the C-index approaching 70%. In addition, the calibration curves for the probabilities of no-recurrence at 1-year, 2-year, and 3-year diagnosed showed the best possible agreement between this prognostic nomogram's forecast and the actual observations (Figure 3).

4. Discussion

The aim of this cohort study was to identify factors at baseline that can predict the recurrence of syncope or presyncope in children with VVS and develop a prognostic nomogram model based on promising significant attributes. It is worth noting that MAP-supine and USG can independently predict the significant risk of syncope or presyncope recurrence in VVS, especially in a nomogram model annexed with 5 other established factors. As far as we know, this is thus far the largest study that has examined factors in a joint manner associated with syncope or presyncope recurrence in children with VVS in the literature.

It is widely recognized that age is a promising factor for syncope recurrence among adults with VVS, and the recurrence rates increase with aging (18, 19). Similarly in this study, our findings supported the contribution of age to syncope recurrence in children with VVS. A possible explanation is that the epinephrine (Epi)/norepinephrine (NE) ratio increases to a greater extent in younger fainters (20). Other factors, such as number of previous syncope and family history, also played a contributory role in the recurrence of syncope or presyncope in VVS. For example, in a Canadian study of 51 children with VVS the higher number of previous syncope was linked to the greater likelihood of syncope or presyncope recurrence (4). Another study from Turkey showed that age, family history, and several prior syncope onsets were factors attributable to syncope recurrence (6). Yet, in the present study, we failed to detect

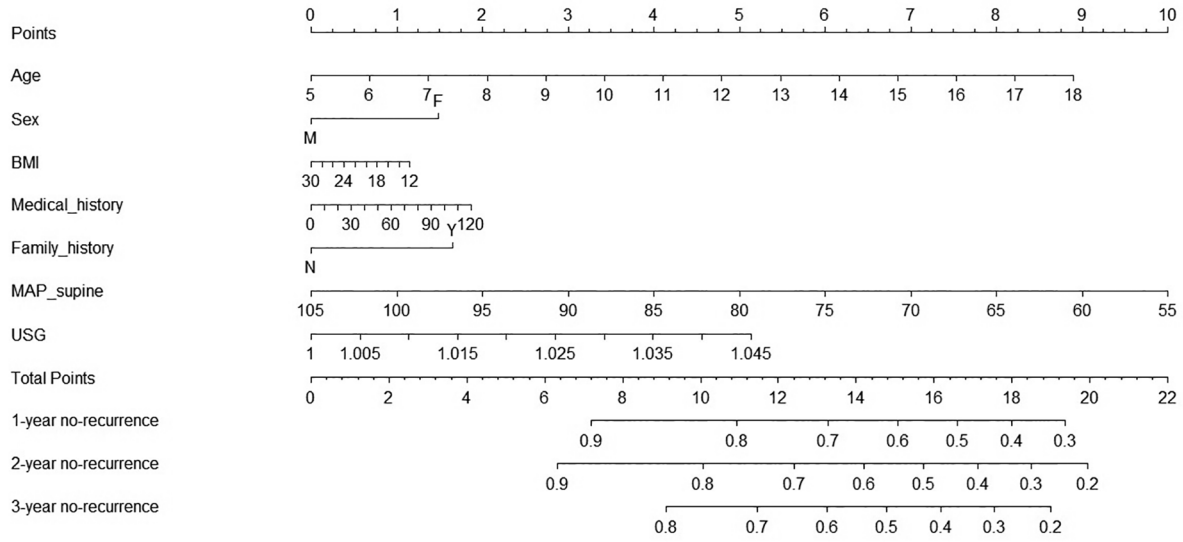


FIGURE 2
Prognostic nomogram of the prediction of significant parameters for 1-year, 2-year, and 3-year no-recurrence of vasovagal syncope among all study children. Abbreviations: F, female; M, male; Y, with family history of syncope; N, without family history of syncope; BMI, body mass index; MAP, average arterial pressure; USG, urine specific gravity.

statistical significance for above demographic factors, and instead we focused on laboratory indicators by taking these factors as confounders. After a careful analysis among 352 children with VVS, our findings indicated that MAP-supine and USG were independently and significantly associated with the risk of syncope or presyncope recurrence in children with VVS, differing from the results of a previous study (21) of 63 children with VVS, which identified hemoglobin and MCH as two recurrence-predisposition factors. Given the complex nature of syncope recurrence, we agree that identification of more promising factors that can accurately predict VVS prognosis is still in the process of exploration, perfection and renewal.

In fact, USG, a non-invasive biomarker and objective substitutability for water homeostasis, are widely used in clinical practice (22). The USG fluctuates depending on the amount of fluids consumed, and it reflects the total amount of water consumed and lost (23, 24). An increase in USG indicates low water intake or excessive water loss. Prior studies have shown that USG had a specific predictive value in diagnosing VVS in children and adolescents (25). However, there is a paucity of data on its role in predicting syncope of presyncope recurrence. Our study showed that elevated USG was a statistically significant risk factor for syncope or presyncope recurrence in VVS, and for practical reasons, USG can be routinely monitored for the early identification of possible recurrence. Moreover, MAP is the average of arterial blood pressure during a cardiac cycle. The median or mean MAP was regularly higher than MAP of 65 mmHg (range 70–114 mmHg) (26, 27). Considering the fact that children are in a period of growth and development, blood pressure is determined based on age, gender, BMI, and so there is currently no uniform value for MAP. In the present study, lower the MAP-supine and MAP-tilt, were found to be associated with the greater likelihood of syncope or presyncope recurrence in VVS. Previous studies showed that children with VVS usually had high levels of catecholamine, which can cause excessive contraction of the heart and abnormal Bezold-Jarish reflex (10). Then, the imbalance of sympathetic impulses and vagal impulses may reduce MAP, which is commonly seen in our recurrence group. Lower MAP in the recurrence group in this study indicated that BP can be easily decreased in the presence of triggering factors, causing the symptoms of pre-syncope. Further decrease in BP annexed with sudden falls in cerebral blood flow can lead to syncope eventually (28, 29). Both USG and MAP were for the first time identified as predisposing factors for syncope or presyncope recurrence in children with VVS, and more large-scale, well-designed studies are warranted to confirm or refute our findings.

Besides the obvious advantages, including large sample size, extended follow-up, and effective calibration/discrimination assessment, some possible limitations should be acknowledged. Firstly, because this study was conducted at a single site, our conclusions would be broadly applied pending consistently validated in other independent cohorts. Secondly, all assessable children with VVS were enrolled between July 2017 and August 2022, and during the 5-year period remarkable advances in techniques and deepened knowledge about this disease can introduce a potential bias that understates the influence of factors on the recurrence of syncope or presyncope. Thirdly, the findings presented here were based merely on children with VVS free of comorbidities and thereby cannot be extrapolated to all VVS populations. Last but not the least, only baseline biomarkers were assayed in this cohort, and frequently monitoring of these

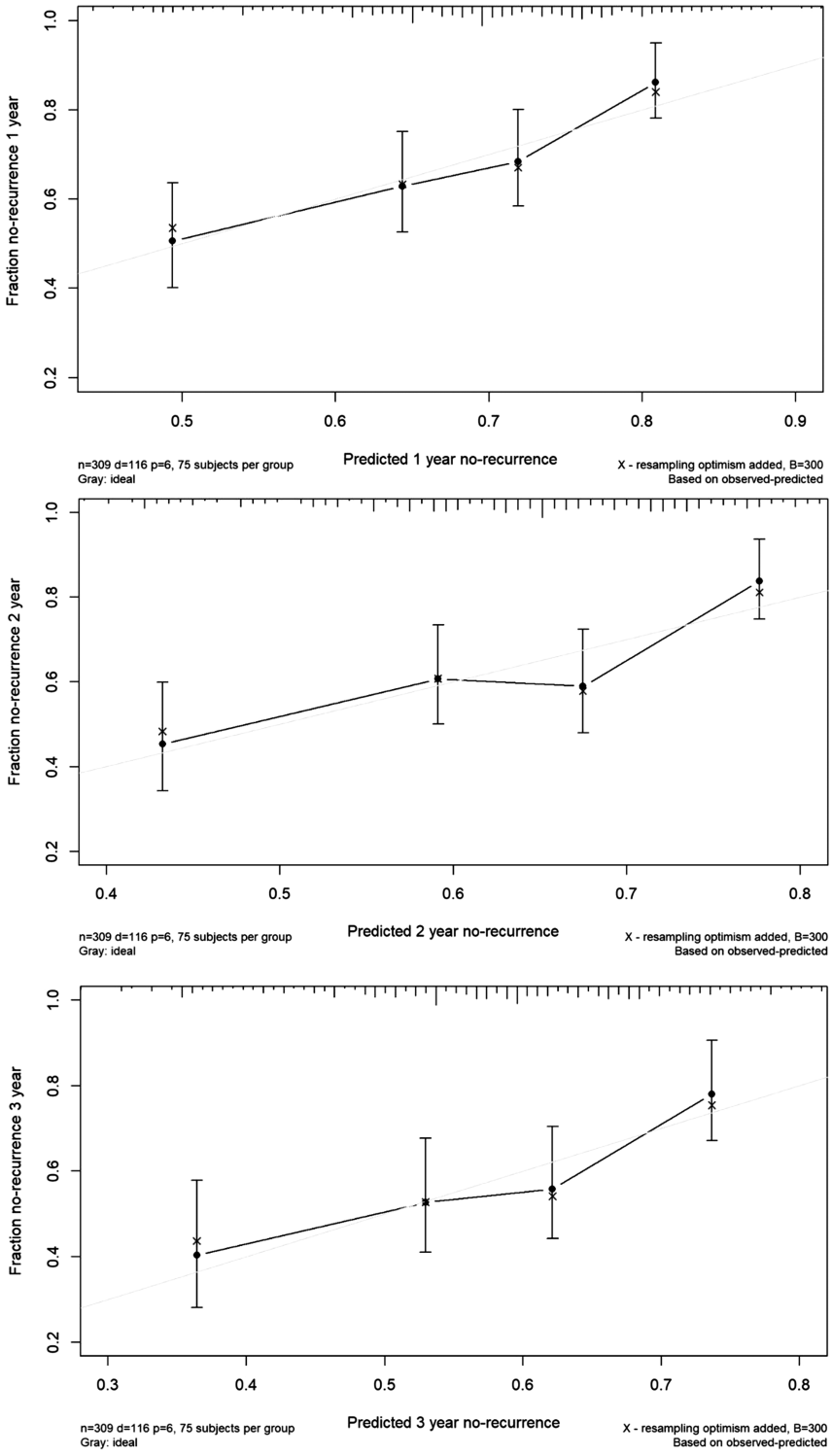


FIGURE 3
The calibration curves for predicting the risk of no-recurrence of vasovagal syncope at 1-year (the upper panel), 2-year (the middle panel) and 3-year (the lower panel) among all study children. Nomogram-predicted probability of no-recurrence is plotted on the X-axis, and actual no-recurrence is plotted on the Y-axis.

biomarkers and analyzing their dynamic variations may be of added interest. We agree that more investigations are warranted to confirm or refute the factors associated with VVS recurrence in this study.

Conclusions

Taken together, our findings indicated that MAP-supine and USG can independently predict the significant risk of syncope or

presyncope recurrence in VVS, and the prediction was more obvious in a nomogram model. For practical reasons, we hope that this study will not only serve as an endpoint but also a new beginning for future large, well-designed studies to explore the risk profiles of syncope or presyncope recurrence in children with VVS.

Data availability statement

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

Ethics statement

The studies involving human participants were reviewed and approved by Ethics Committee of Children's Hospital Capital Institute of Pediatrics Beijing, China. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

XL and RS designed the study. RS, YK collected and analyzed the data. RS drafted the manuscript and MZ, HW revised the paper. LS, XL contributed to the interpretation of the results and critical revision of the manuscript. All authors contributed to the article and approved the submitted version.

Funding

This work was supported by the "Peak Climbing" Talents Development Program of Beijing Hospital Authority (DFL20181301).

Acknowledgments

We thank the parents, guardians, and children who participated in this study.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2023.1099115/full#supplementary-material.

References

1. Hu E, Liu X, Chen Q, Wang C. Investigation on the incidence of syncope in children and adolescents aged 2–18 years in Changsha. *Front Pediatr.* (2021) 9:638394. doi: 10.3389/fped.2021.638394

2. Jin H, Du J. Pediatric syncope: where are we now? *Chin Med J Publishing House.* (2014) 127(21):3681–3. doi: 10.3760/cma.j.issn.0366-6999.20132944

3. Kenny RA, Bhangu J, King-Kallimanis BL. Epidemiology of syncope/collapse in younger and older western patient populations. *Prog Cardiovasc Dis.* (2013) 55 (4):357–63. doi: 10.1016/j.pcad.2012.11.006

4. Díaz JF, Tercedor L, Moreno E, García R, Álvarez M, Sánchez J, et al. Vasovagal syncope in pediatric patients: a medium-term follow-up analysis. *Rev Esp Cardiol.* (2002) 55(5):487–92. doi: 10.1016/S0300-8932(02)76640-2

5. Kouakam C, Vaksmann G, Pachy E, Lacroix D, Rey C, Kacet S. Long-term follow-up of children and adolescents with syncope; predictor of syncope recurrence. *Eur Heart J.* (2001) 22(17):1618–25. doi: 10.1053/euhj.2000.2577

6. Yılmaz ST, Binnetoğlu K, Babaoğlu K, Altun G. Predictors of vasovagal syncope recurrence in children and adolescents and value of head-up tilt table test. *Anadolu Kardiyol Derg.* (2013) 13(7):688–94. doi: 10.5152/akd.2013.250

7. Yan H, Wang S, Cai H, Zhang J, Liu P, Wang Y, et al. Prognostic value of biomarkers in children and adolescents with orthostatic intolerance. *Front Pediatr.* (2021) 9:752123. doi: 10.3389/fped.2021.752123

8. Tao C-Y, Chen S, Li X-Y, Tang C-S, Du J-B, Jin H-F. Body mass index is a promising predictor of response to oral rehydration saline in children with vasovagal syncope. *Chin Med J.* (2021) 134(04):463–8. doi: 10.1097/CM9.0000000000001168

9. Zhao T, Wang S, Wang M, Cai H, Wang Y, Xu Y, et al. Research progress on the predictive value of electrocardiographic indicators in the diagnosis and prognosis of children with vasovagal syncope. *Front Cardiovasc Med.* (2022) 9:916770. doi: 10.3389/fcvm.2022.916770

10. Li H-X, Gao L, Yuan Y. Advance in the understanding of vasovagal syncope in children and adolescents. *World J Pediatr.* (2021) 17(1):58–62. doi: 10.1007/s12519-020-00367-z

11. Pediatric Cardiovascular Group CMA. Guideline for diagnosis of syncope in children (updated in 2016). *Chin J Pediatr.* (2016) 54(4):246–50. doi: 10.3760/cma.j.issn.0578-1310.2016.04.003

12. Brignole M, Moya A, de Lange FJ, Deharo J-C, Elliott PM, Fanciulli A, et al. 2018 ESC guidelines for the diagnosis and management of syncope. *Eur Heart J.* (2018) 39 (21):1883–948. doi: 10.1093/eurheartj/ehy037

13. Shen W-K, Sheldon RS, Benditt DG, Cohen MI, Forman DE, Goldberger ZD, et al. 2017 ACC/AHA/HRS guideline for the evaluation and management of patients with syncope: a report of the American college of cardiology/American heart association task force on clinical practice guidelines and the heart rhythm society. *J Am Coll Cardiol.* (2017) 70(5):e39–e110. doi: 10.1016/j.jacc.2017.03.003

14. Pencina MJ, D'Agostino RB Sr, D'Agostino RB Jr, Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC

curve to reclassification and beyond. *Stat Med*. (2008) 27(2):157–72. doi: 10.1002/sim.2929

15. Pencina MJ, D'Agostino RB, Vasan RS. Statistical methods for assessment of added usefulness of new biomarkers. *Clin Chem Lab Med*. (2010) 48(12):1703–11. doi: 10.1515/CCLM.2010.340

16. Aho K, Derryberry D, Peterson T. Model selection for ecologists: the worldviews of AIC and BIC. *Ecology*. (2014) 95(3):631–6. doi: 10.1890/13-1452.1

17. Vickers AJ, Elkin EB. Decision curve analysis: a novel method for evaluating prediction models. *Med Decis Making*. (2006) 26(6):565–74. doi: 10.1177/0272989X06295361

18. Guo Y, Chen X, Zeng T, Wang L, Cen L. Age is a predictor for the syncope recurrence in elderly vasovagal syncope patients with a positive head-up tilt test. *Front Cardiovasc Med*. (2021) 8:609. doi: 10.3389/fcvm.2021.667171

19. Pournazari P, Sahota I, Sheldon R. High remission rates in vasovagal syncope: systematic review and meta-analysis of observational and randomized studies. *JACC: Clin Electrophysiol*. (2017) 3(4):384–92. doi: 10.1016/j.jacep.2016.10.012

20. Benditt DG, Detloff BL, Adkisson WO, Lu F, Sakaguchi S, Schussler S, et al. Age-dependence of relative change in circulating epinephrine and norepinephrine concentrations during tilt-induced vasovagal syncope. *Heart Rhythm*. (2012) 9(11):1847–52. doi: 10.1016/j.hrthm.2012.07.028

21. Song J, Li H, Li X, Wang Y, Jin H, Du J. Relationship between blood routine test parameters and syncopal recurrence of vasovagal syncope in children. *Chin J Pediatr*. (2017) 55(1):59–63. doi: 10.3760/cma.j.issn.0578-1310.2017.01.012

22. Vanhaecke T, Dolci A, Fulgoni VL, Lieberman HR. Associations between urinary hydration markers and metabolic dysfunction: a cross-sectional analysis of NHANES data, 2008–2010. *Eur J Nutr*. (2021) 60(8):4229–41. doi: 10.1007/s00394-021-02575-3

23. Khan NA, Westfall DR, Jones AR, Sinn MA, Bottin JH, Perrier ET, et al. A 4-d water intake intervention increases hydration and cognitive flexibility among preadolescent children. *J Nutr*. (2019) 149(12):2255–64. doi: 10.1093/jn/nxz206

24. Zhang J, Ma G, Du S, Zhang N. The relationships between water intake and hydration biomarkers and the applications for assessing adequate total water intake among young adults in Hebei, China. *Nutrients*. (2021) 13(11):3805. doi: 10.3390/nu13113805

25. Liu P, Zeng X, Mei W, Wang Y, Zou R, Wang C. The predictive value of urine specific gravity in the diagnosis of vasovagal syncope in children and adolescents. *Ital J Pediatr*. (2021) 47(1):1–7. doi: 10.1186/s13052-020-00935-z

26. Sekhon MS, Gooderham P, Menon DK, Brasher PM, Foster D, Cardim D, et al. The burden of brain hypoxia and optimal mean arterial pressure in patients with hypoxic ischemic brain injury after cardiac arrest. *Crit Care Med*. (2019) 47(7):960–9. doi: 10.1097/CCM.0000000000003745

27. Rikhraj KJ, Wood MD, Hoiland RL, Thiara S, Griesdale DE, Sekhon MS. Determining optimal mean arterial pressure after cardiac arrest: a systematic review. *Neurocrit Care*. (2021) 34(2):621–34. doi: 10.1007/s12028-020-01027-w

28. Liao Y, Du J. Pathophysiology and individualized management of vasovagal syncope and postural tachycardia syndrome in children and adolescents: an update. *Neurosci Bull*. (2020) 36(6):667–81. doi: 10.1007/s12264-020-00497-4

29. Jardine DL, Wieling W, Brignole M, Lenders JWM, Sutton R, Stewart J. The pathophysiology of the vasovagal response. *Heart Rhythm*. (2018) 15(6):921–9. doi: 10.1016/j.hrthm.2017.12.013

frontiers | Frontiers in Pediatrics

TYPE Original Research
PUBLISHED 15 March 2023
DOI 10.3389/fped.2023.1121905

OPEN ACCESS

EDITED BY
Zhen-Yu Zhang,
KU Leuven, Belgium

REVIEWED BY
Hafize Emine Sönmez,
Kocaeli University, Türkiye
Satoshi Yasukochi,
Aizawa Hospital, Japan

*CORRESPONDENCE
Chodchanok Vijarnsorn
✉ cvijarnsorn@yahoo.com

SPECIALTY SECTION
This article was submitted to Pediatric Cardiology, a section of the journal Frontiers in Pediatrics

RECEIVED 12 December 2022
ACCEPTED 14 February 2023
PUBLISHED 15 March 2023

CITATION
Wongbundit C, Vijarnsorn C, Pornprasertchai V, Somkittitham P, Bositthipichet D, Tongbunnum T and Chanthong P (2023) Coronary changes and cardiac events in children diagnosed with kawasaki disease without initial coronary aneurysm: A multicenter retrospective cohort study. Front. Pediatr. 11:1121905. doi: 10.3389/fped.2023.1121905

Coronary changes and cardiac events in children diagnosed with kawasaki disease without initial coronary aneurysm: A multicenter retrospective cohort study

Chanikarn Wongbundit[1], Chodchanok Vijarnsorn[1]*, Varisara Pornprasertchai[2], Pimonrat Somkittitham[3], Densiri Bositthipichet[3], Tikamporn Tongbunnum[4] and Prakul Chanthong[1]

[1]Division of Pediatric Cardiology, Department of Pediatrics, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand, [2]Department of Pediatrics, Phrapokklao Hospital, Chanthaburi, Thailand, [3]Department of Pediatrics, Nakhon Pathom Hospital, Nakhon pathom, Thailand, [4]Department of Pediatrics, Chao Phraya Yommarat Hospital, Suphanburi, Thailand

Background: Kawasaki disease (KD) is a systemic vasculitis affecting young children, which may lead to coronary artery aneurysm (CAA). The optimal timing of serial echocardiography in patients with uncomplicated KD is debated.
Objectives: To assess changes in coronary artery Z-scores from the initial diagnosis, two weeks, eight weeks, and one year following diagnosis and adverse cardiac events in children diagnosed with KD without initial CAA.
Methods: Retrospective chart reviews of four referral centers in Thailand were conducted of all children who were diagnosed with KD without initial CAA (coronary artery Z-score < 2.5) between 2017 and 2020. Eligibility criteria included the absence of congenital heart disease and patients with available echocardiographic evaluations at baseline and at eight weeks of illness. The two-week and one-year echocardiographies were reported. Adverse cardiac events at one year from diagnosis were explored. The primary outcome was a maximal coronary Z-score on the follow-up echocardiography at eight weeks and one year.
Results: Of 200 patients diagnosed with KD, 144 patients (72%) did not have CAA. A total of 110 patients were included in the study. The median age was 23 months (IQR, 2–39 months) and 60% were male. Fifty patients (45.5%) had incomplete KD, and four (3.6%) received a second intravenous immunoglobulin treatment. Of 110 patients, 26 patients (23.6%) had coronary ectasia (Z-score of 2–2.49) on their initial echocardiographic examination. Sixty-four patients were evaluated in two-week echocardiographic studies, which showed four new small CAAs and five coronary ectasia. At 8 weeks, 110 patients had undergone complete echocardiographic studies. No patient had residual CAAs. Only one patient had persistent coronary ectasia that regressed to normal within one year. At one-year follow-up ($n = 90$), no cardiac events were reported.
Conclusion: New CAA in-patients with KD who had no previous CAA in their initial echocardiography are rare. In addition, patients who had normal echocardiographic follow-up at two weeks or eight weeks mostly continued to be normal at one year. The optimal timing of the echocardiographic

follow-up should be at two to eight weeks in patients without initial CAA, who still have a coronary artery Z-score < 2 at the second echocardiography.
Trial registration: TCTR20210603001.

KEYWORDS

kawasaki disease (KD), coronary artery aneurysm (CAA), coronary ectasia, coronary artery *z* score, echocar diography, adverse cardiac events

Introduction

Kawasaki disease (KD) is an acute febrile illness with inflammation of medium-sized vessels, often affecting young children. Coronary artery involvement is common and varied in its severity from transient, mild coronary artery dilation (so called coronary ectasia) to severe forms such as giant coronary artery aneurysm (CAA). The incidence of CAA in untreated patients, especially in the era of pre-intravenous immunoglobulin (IVIG), has been reported to be as high as 25%, though it is significantly reduced to 4%–10% in patients who receive timely administration of IVIG (1–4). Coronary artery lesions (CAL) in children with KD (up to 80% of all cases), can be identified with an initial echocardiography, during the first week of illness (5). Changes in CALs from the initial echocardiography have been documented to regress in up to 75% of the cases, however 4%–5% of cases progress (6). In particular, over 80% of patients with coronary artery ectasia were reported to have an improved outcome. Baseline measurements of coronary artery diameter are realistic predictors of their involvement during early follow-up (7, 8). A major adverse cardiac event (MACE) has been shown to be correlated to higher CAA Z-scores at diagnosis, the presence of giant CAA, and the lack of IVIG treatment (9–11). Surveillance of myocardial stress tests and regular echocardiographies are warranted in the presence of CAA.

In contrast to the presence of CAA, the timing of follow-up echocardiography in patients with KD who do not have CAA at the initial echocardiography (coronary artery Z-score < 2.5) is still controversial. Based on 2017 American Heart Association guidelines, serial echocardiography is recommended at baseline, at one to two weeks, and at four to six weeks after diagnosis to detect coronary artery abnormalities. In patients without coronary artery involvement, discharge from cardiology service may reasonably take place at 4–6 weeks after KD onset, though extended follow-up to 12 months may be considered (1). The 2020 Japanese guidelines recommend serial echocardiography at the time of treatment initiation, 1–2 weeks later, and at follow-up assessments at 1, 2, 6, 12 months, and 5 years or yearly until 5 years for patients with KD and normal coronary artery or transient dilatation (2). In a large retrospective study from Boston and San Diego, new abnormalities in coronary arteries were found to be rare (1.7%), which suggests that the six-week echocardiographic imaging may not be needed in patients with uncomplicated KD and coronary artery Z-scores < 2.0 in the first two weeks of illness (12). In a recent study from the Post-RAISE registry in Japan; however, the optimal duration of echocardiographic follow-up is suggested to be one month in patients with no initial CAA and no CAL at one month (13). Based on these findings, new CAAs are assumed to develop frequently from the second week and then peak at the fourth week of illness in patients with no initial CAL (11, 14).

In low-income countries, frequent echocardiographic assessments can lead to high costs or risks for sedated patients. In a retrospective trial of the cost-effectiveness of echocardiography in 1999, all children with KD were recommended to have an echocardiography at the time of diagnosis with a follow-up study four to eight weeks after the onset of fever (15). We hypothesized that coronary arteries in patients without initial CAA and that remained normal at eight-weeks follow-up did not progress to CAA or require further intervention. Considering the prior studies that were conducted in different settings and among different ethnic groups, we undertook this multicenter retrospective study of patients diagnosed with KD without initial CAA (Z-score < 2.5). Our aim is to evaluate changes in the coronary artery Z-scores and occurrences of major adverse cardiac events from the initial diagnosis, to two weeks, eight weeks, and at one year following diagnosis.

Methods

The present study was a multicenter retrospective study using hospital databases from four cardiac centers in Thailand: (1) Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok; (2) Phrapokklao Hospital, Chanthaburi; (3) Nakhon Pathom Hospital, Nakorn Pathom; and (4) Chao Phraya Yommarat Hospital, Suphanburi, Thailand. Following approval from the institutional ethics committees of all institutes, patients who were diagnosed with KD without CAA between July 1, 2017 and December 31, 2020 were retrospectively reviewed. We restricted the analyses to patients who had no initial CAA, which was defined as having a coronary Z-score < 2.5 at the initial echocardiography (1). Patients were also required to have had a complete echocardiographic measurement of the proximal right coronary artery (RCA), the left main coronary artery (LCA), and the left anterior descending artery (LAD) at least twice: at baseline and at eight weeks from the diagnosis. The echocardiographic measurements that were recorded when possible at two weeks and at one year following diagnosis were in accordance with guidelines. Patients who had only a single echocardiography without any follow-up were considered as incomplete data, and patients with congenital heart disease that could lead to coronary dilation were excluded from the study. The requirement for informed consent from patients was waived and the process for protecting patient confidentiality was

guaranteed. Permission for the study protocol to waive the informed consent process was approved by the Siriraj Institutional Review Board, Faculty of Medicine, Siriraj Hospital, Mahidol University [Study number 244/2,564 (EC4), COA No Si 309/2021], Phrapokklao Hospital Chanthaburi [COA No. 034/65], Nakhon Pathom Hospital [Record No 028/2021, COA No. 029/2021], and Chao Phraya Yommarat Hospital, Suphanburi, Thailand [COA No. YM027/2565]. Demographic, clinical, initial laboratory, and echocardiographic findings of RCA, LCA, LAD, and treatment were explored. Demographic data was collected for gender, age at diagnosis of KD, and clinical presentation. The laboratory data included erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), hematocrit (Hct), white blood cell (WBC), and platelet count. The echocardiographic findings were collected at the time of diagnosis, and at two weeks, eight weeks, and at one year following diagnosis. The dimensions of the RCA, LCA and LAD with their Z-scores were recorded (7). The left circumflex artery (LCx) was reported as an absolute number and not evaluated in the analysis due to its anatomical variability and the difficulty in obtaining images. Normal coronary dimension was defined as coronary Z-score < 2.0 and coronary ectasia was defined as coronary Z-score 2.0–2.49. Small CAA was defined as coronary artery Z-score ≥2.5 and <5 (1). Treatment of KD included receiving IVIG, onset of fever that received IVIG (within 10 days or after 10 days), requirement for retreatment with IVIG, and receiving adjunctive anti-inflammation medications. The primary outcome was a maximal coronary artery Z-score at follow-up echocardiography at eight weeks and at one year. The secondary outcomes were clinical data and the report of MACE at a one-year follow-up. MACE was identified if the patients had a cardiovascular-related illness including total coronary artery occlusion, congestive heart failure, clinical or imaging evidence of myocardial ischemia (MI), the requirement for coronary artery bypass grafting (CABG), or percutaneous coronary intervention (PCI) (9).

Statistical methods

Statistical analyses were performed with SPSS 20.0 for Windows (SPSS Inc., Chicago, IL, United States). Demographic, clinical, laboratory, cardiac imaging, and KD treatment data were presented as frequencies with percentages for the categorical variables and mean ± SD or median with interquartile range for the continuous variables. The maximal coronary artery Z-score at initial, two weeks, eight weeks, and one year was expressed as median with interquartile range. Changes in the maximal coronary artery Z-score across the four time points were assessed using a non-parametric test (Friedman's test). Two-tailed *P* values were used, and values less than.05 were considered significant.

Results

Patient characteristics

A total of 200 patients had been diagnosed with KD in the 4 centers in 2017–2020. CAAs were noted in 56 patients (28%). Of the 144 patients without CAA, 33 patients had incomplete echocardiographic examinations and 1 patient had underlying congenital heart defect. Therefore, 110 patients were included in the study (**Figure 1**). Of these patients, 60% were male and the median age at diagnosis was 1.9 years (IQR 2 months, 3.2 years). Complete KD was diagnosed in 54.5% of the patients. No patients in this study had Kawasaki shock or ventricular

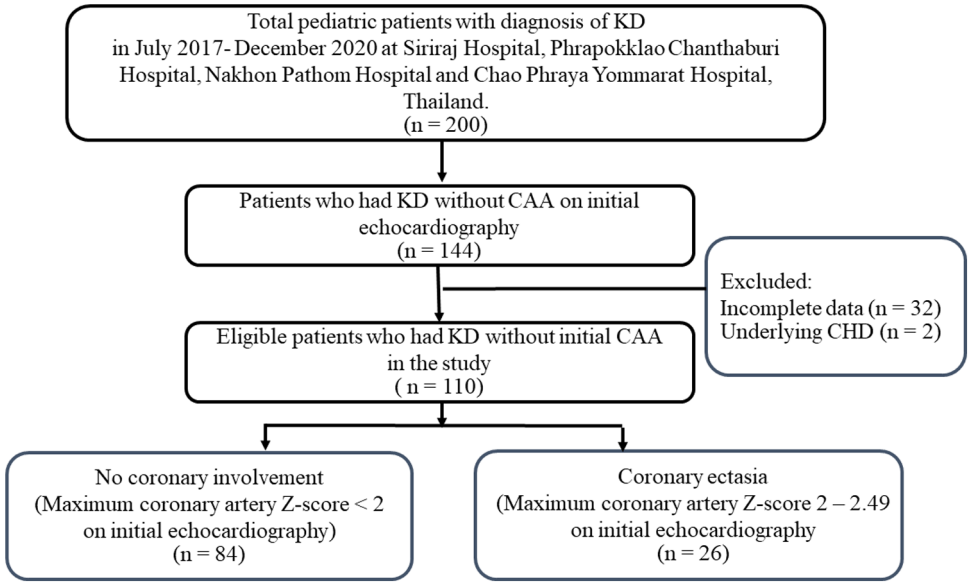


FIGURE 1
Flow diagram of pediatric patients that were included in the analysis (*n* = 110). KD, Kawasaki disease; CAA, coronary artery aneurysm.

dysfunction. Initial left ventricular ejection fraction was 68.4 ± 6.3%. Almost all of patients (90%) received IVIG as a standard treatment. IVIG-resistant KD presented in four patients, which responded to a second IVIG treatment plus steroids. Initial coronary artery Z-scores were normal (Z-score < 2) in 84 patients (76.4%). Of the remaining 26 patients, the maximal Z-score ranged from 2 to 2.47, which was consistent to coronary ectasia on initial echocardiography. The patients' demographics including clinical and laboratory data are described in Table 1.

TABLE 1 Baseline characteristics.

Variables	Total (n = 110)
Age at diagnosis (months)	23 (2, 39)
Weight at diagnosis (kg)	12.23 ± 5.01
BMI	16.10 ± 2.24
Male sex	66 (60%)
Incomplete KD	50 (45.5%)
Lack of IVIG treatment	4 (3.6%)
Timing of IVIG treatment	
≤10 days of fever	99 (90%)
>10 days of fever	7 (6.3%)
Onset of fever received IVIG (day)	6.60 ± 2.10
Retreatment with second IVIG	4 (3.6%)
Receiving adjunctive anti-inflammatory medication	4 (3.6%)
Hct (%)	30.99 ± 3.72
WBC (/mm^3)	17,064 ± 5,249
Platelet (/mm^3)	44,0411 ± 14,9018
ESR (mm/hr)	72.60 ± 29.28
CRP (mg/l)	111 ± 92
ALT	76 ± 107
Albumin	3.50 ± 0.51
Presence of sterile pyuria	12 (10.9%)
Initial Z-score of coronary artery	
RCA	0.81 (0.02, 1.64)
LCA	0.40 (−0.12, 1.14)
LAD	0.71 (−0.38, 1.40)
Presence of initial coronary ectasia (Z-score 2–2.49)	26 (23.6%)

Data presented as n (%), mean ± SD, and median (interquartile range).
KD, Kawasaki disease; IVIG, intravenous immunoglobulin; LCA, left main coronary artery; LAD, left anterior descending artery; RCA, right coronary artery; WBC, white blood cell; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; ALT, alanine aminotransferase.

Changes in the coronary artery on echocardiography and clinical outcomes

The echocardiographic measurements were performed at baseline and at 8 weeks following diagnosis in 110 patients, and used as the entry criteria. Overall, serial echocardiographic examinations were performed in 64 patients (58%) at 2.7 weeks (IQR 2.1, 3.2 weeks), in 110 patients (100%) at 8.1 weeks (IQR 7.2, 8.8 weeks), and in 51 patients (46.3%) at 1 year (IQR 0.7, 1.3 years) (Table 2). The median Z-score of all coronary arteries tended to decrease over time. At the 2-week echocardiography (n = 64), progressive changes were seen in coronary arteries with small CAA, and Z-scores between 2.6 and 4.28 were seen for the first time in 4 patients (6.2%). Two patients were noted as having initial coronary ectasia and two patients had normal coronary artery Z-scores at their baseline echocardiography. No additional antithrombotic treatment was given. Three patients had dilatation of the coronary artery that progressed from normal to ectasia. Two patients with initial ectasia of the coronary artery had mildly dilated coronary arteries that did not change. In contrast, regression of coronary ectasia to normal occurred in nine patients (14%).

Of the 110 echocardiographic evaluations at 8 weeks, 109 patients (99.1%) showed normal coronary artery Z-scores (<2). Only one patient (0.9%) who had initial coronary ectasia had persistent coronary ectasia with a maximal Z-score of 2.0 (Table 3). Overall, the left ventricular ejection fraction was preserved at 68.5 ± 6.1%. All four of the small CAA that were seen at two weeks, had regressed to normal at the eight-week follow-up. Moreover, 25 (96.1%) of the 26 patients with initial coronary ectasia regressed to normal within 4–8 weeks of illness. The remaining patient with initial coronary ectasia, that had an

TABLE 2 Echocardiographic findings and clinical data at each time point.

	Initial (N = 110)	2 weeks (N = 64)	4–8 weeks (N = 110)	1 year (N = 51)
Coronary artery Z-score				
RCA	0.81 (0.02, 1.64)	−0.11 (−0.80, 0.43)	−0.03 (−0.51, 0.51)	−0.10 (−0.76, 0.33)
LCA	0.40 (−1.23, 1.14)	−0.18 (−0.77, 0.31)	−0.20 (−0.74, 0.32)	−0.30 (−1.00, 0.16)
LAD	0.71 (−0.18, 1.40)	−0.53 (−1.21, 0.31)	−0.29 (−1.01–0.43)	−0.54 (−1.30, 0.31)
Maximal Coronary artery Z-score	2.47	4.28	2.00	1.90
Absolute number of coronary dimension (mm)				
RCA	2.00 (1.70, 2.21)	1.71 (1.41, 2.00)	1.80 (1.53, 1.94)	1.83 (1.57, 2.07)
LCA	2.30 (2.10, 2.60)	2.20 (1.80, 2.46)	2.10 (1.90–2.40)	2.20 (2.00, 2.40)
LAD	1.80 (1.60, 2.00)	1.70 (1.31, 1.90)	1.7 (1.50, 1.80)	1.60 (1.50, 1.90)
Presence of coronary ectasia	26 (23.6%)	5 (7.8%)	1 (0.9%)	0
Presence of coronary aneurysm	0	4 (6.2%)	0	0
MACE report	0	0	0	0
Functional class I		64 (100%)	110 (100%)	90 (100%)*

Data is shown as n (%), median (interquartile range).
*Number of patients who had clinical follow-up at 1 year, N = 90.
LCA, left main coronary artery; LAD, left anterior descending artery; RCA, right coronary artery; MACE, major adverse cardiac events.

TABLE 3 Maximal coronary artery Z-scores of the left main coronary artery, left anterior descending artery, or right coronary artery at the 8-week echocardiography, compared to baseline, 2-week, and 1-year.

Maximal coronary artery Z-score	Number of patients	Maximal coronary artery Z-score at 8-week echocardiography		
Baseline	110	<2	2–2.49	2.5–5
<2	84	84 (100%)	0	0
2–2.49	26	25 (96.2%)	1 (3.8%)	0
2-week echocardiography	64			
<2	55	55 (100%)	0	0
2–2.49	5	5 (100%)	0	0
2.5–5	4	4 (100%)	0	0
1-year echocardiography	51			
<2	51	50 (98%)	1 (2%)	0

Data is shown as *n* (% in the row).

unchanged risk level at eight weeks, resolved to normal at the one-year echocardiography. Of the 51 available one-year echocardiographies, all patients had coronary artery Z-score <2. The one-year clinical follow-up was conducted for 90 patients (81.8%). No MACE or mortalities were reported in this cohort study.

In the analysis of 55 patients who had normal coronary artery Z-scores at baseline and at 2 weeks, no patient had progressive dilation of the coronary artery to either ectasia or CAA at the 8-week echocardiographic examination (Table 3). Of the 55 patients, 48 patients visited a clinic and were asymptomatic at 1 year, and still showed a maximal coronary artery Z-score <2. Of the 84 patients who had normal coronary artery Z-scores at baseline and at 8 weeks, 37 patients had a fourth echocardiographic evaluation at 1 year that showed a normal coronary appearance. All patients with coronary ectasia or CAA at two weeks or at eight weeks underwent an echocardiography at the one-year follow-up, and showed resolution of all coronary lesions. If we consider the patients with coronary artery Z-score < 2 at two weeks or at eight weeks, who underwent an echocardiography at one year ($n = 30$ and $n = 50$, respectively), no evidence was found of worsening coronary dilatation at one year. These findings imply that progressive dilation of the coronary artery in patients who had been diagnosed with KD without CAA was rare, though it may have occurred at two to four weeks after illness. For most patients with dilation that included CAA and ectasia, their cases were benign and spontaneously resolved within four to eight weeks. No additional antithrombotic agents were given to this cohort. Patients who had normal coronary artery *Z* scores at their follow-up echocardiographies at two weeks or eight weeks continued to have normal *Z* scores at one year. Changes in the coronary artery Z-scores for RCA, LCA, and LAD for each patient are shown in Figure 2, Figures 3, 4, respectively.

Comparing patients with complete KD ($n = 60$) and incomplete KD ($n = 50$), the proportion of initial coronary ectasia was not statistically different (30% vs. 16%, $p = 0.08$). In the complete KD group ($n = 60$), 18 patients had initial coronary ectasia (30%), which regressed to a normal size in 17 patients (94%) at 8 weeks (Table 4). One patient who had residual coronary ectasia with a Z-score of two at eight weeks was resolved to normal at one-year follow-up (Table 4). Likewise, in the incomplete KD group ($n = 50$), initial coronary ectasia was noted in 8 patients (16%). All patients were resolved to normal at the eight-week echocardiography (Table 5). New findings of coronary aneurysms were detected by two-week echocardiography in three patients who had complete KD and in one patient who had incomplete KD. All coronary aneurysms were resolved to normal at eight-week and one-year echocardiography (Tables 4, 5). No cardiac events were reported.

Discussion

This multicenter retrospective study describes changes in coronary artery Z-scores in 110 children who were diagnosed

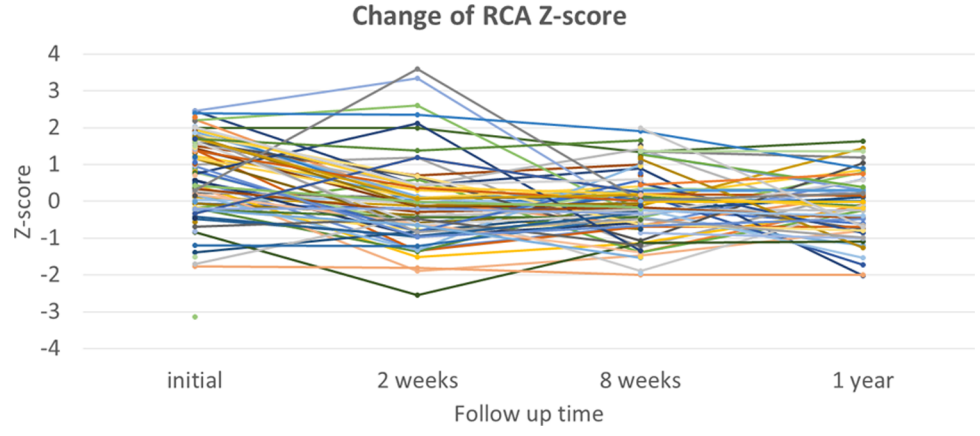


FIGURE 2
Changes in Z-scores for the right coronary artery (RCA) at each time point.

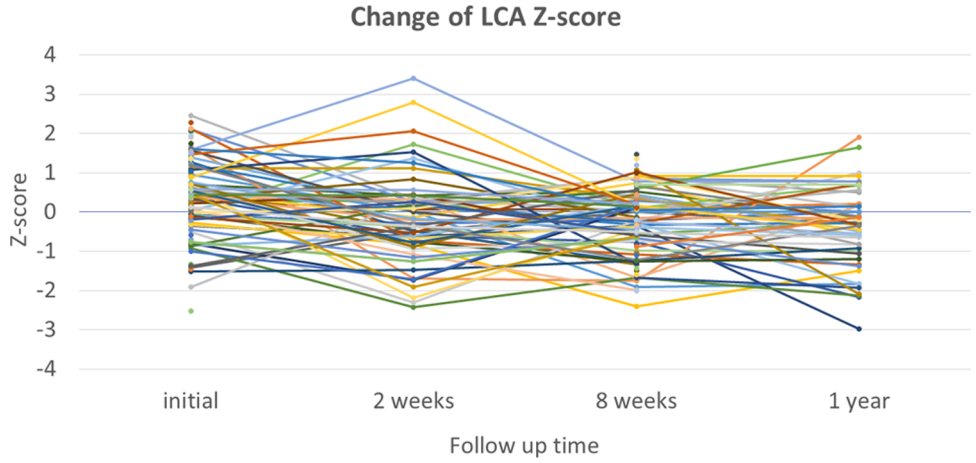


FIGURE 3
Changes in Z-scores for the left main coronary artery (LCA) at each time point.

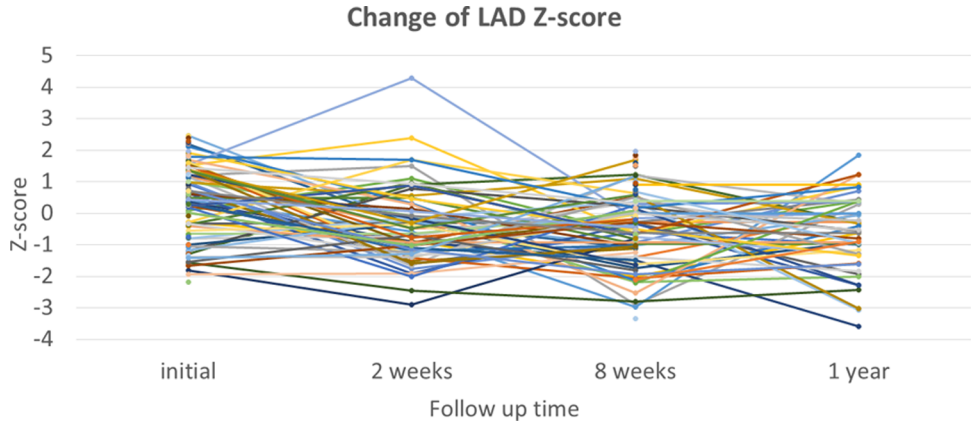


FIGURE 4
Changes in Z-scores for the left anterior descending artery (LAD) at each time point.

with KD without CAA (Z-score < 2.5) at the initial management. Eighty-four patients (76.4%) had initial coronary artery Z-scores < 2 and 26 patients had initial coronary ectasia with a maximal Z-score of 2–2.47. At the eight-week follow-up echocardiography, only one patient (0.9%) with initial coronary ectasia had persistent coronary ectasia with a maximal Z-score of 2.0. All four patients with small CAAs that were detected at the two-week echocardiographic follow-up were resolved to normal in the eight-week examination. Of the 51 patients who received a one-year echocardiographic evaluation, all patients had coronary artery Z-scores < 2, including 1 patient who had persistent coronary ectasia at the 8-week echocardiography. Patients who had normal coronary artery Z-scores at the two-week or eight-week follow-up echocardiography continued to be normal at one year. In clinical follow-ups at one year ($n = 90$; 81.8%), no MACE or mortality were reported in this cohort study. We proposed that the optimal timing of echocardiographic follow-up could be two to eight weeks in patients without initial CAA and who still had a normal coronary appearance (coronary artery Z-score < 2) at their second echocardiographic evaluation. This suggested timing for the echocardiographic examination in this group would reduce costs, parental anxiety, and risks of sedation to patients for at least two evaluations, which would be suitable for low-socioeconomic countries.

Most coronary abnormalities in children with KD can be identified at the initial echocardiography, during the first week of illness (5). Coronary dilations, as a consequence of inflammation, usually peak around two to four weeks after illness onset (14). Patients with persistent CAA, defined as a Z score ≥ 2.5 after six weeks are considered to be at least risk level 3, which requires long-term management and lifetime specialist management from cardiology services based on whether or not assessing coronary insufficiency is required (1, 2, 16). In contrast, the cohort study of 258 children initially found to have normal coronary arteries at the first coronary angiogram, who were followed for 10–21 years, did not show any cardiac symptoms at follow-up (3).

10.3389/fped.2023.1121905

TABLE 4 Maximal coronary artery Z-scores of the left main coronary artery, left anterior descending artery, or right coronary artery at the 8-week echocardiography, compared to baseline, 2-week, and 1-year of 60 patients with complete KD.

Maximal coronary artery Z-score	Number of patients	Maximal coronary artery Z-score at 8-week echocardiography		
Baseline	60	<2	2–2.49	2.5–5
<2	42	42 (100%)	0	0
2–2.49	18	17 (94.4%)	1 (5.6%)	0
2-week echocardiography	31			
<2	26	26 (100%)	0	0
2–2.49	2	2 (100%)	0	0
2.5–5	3	3 (100%)	0	0
1-year echocardiography	24			
<2	24	24 (100%)	0	0

Data is shown as *n* (% in the row).

TABLE 5 Maximal coronary artery Z-scores of the left main coronary artery, left anterior descending artery, or right coronary artery at the 8-week echocardiography, compared to baseline, 2-week, and 1-year of 50 patients with incomplete form of KD.

Maximal coronary artery Z-score	Number of patients	Maximal coronary artery Z-score at 8-week echocardiography		
Baseline	50	<2	2–2.49	2.5–5
<2	42	42 (100%)	0	0
2–2.49	8	8 (100%)	0	0
2-week echocardiography	33			
<2	29	29 (100%)	0	0
2–2.49	3	3 (100%)	0	0
2.5–5	1	1 (100%)	0	0
1-year echocardiography	27			
<2	27	27 (100%)	0	0

Data is shown as *n* (% in the row).

Hence, patients who have KD without CAA, or are at risk level 1 or 2 are widely accepted to have follow-ups by their general practitioner (1, 16). The recent 2017 AHA guideline recommends that assessment for coronary artery involvement in patients with KD is by serial transthoracic echocardiography, at diagnosis, and at two weeks and six weeks following onset of the disease, as a minimum. If abnormal, more frequent echocardiographies would be required to identify rapidly progressing CAA. In patients without coronary artery involvement, discharge from cardiology service would reasonably be at four to six weeks, but a follow-up at one year can be considered (1). The consensus recommendations from a UK group are similar to those of the AHA, with the recommendation of an additional echocardiographic evaluation at six months (16). Recent Japanese guidelines recommend the most frequent follow-up echocardiographies in patients without CAA to be at baseline, and at 1–2 weeks, 4 weeks, 8 weeks, 6 months, 12 months, and 5 years or yearly until 5 years (2). Undoubtably, frequent investigations would aid in the detection of new lesions, though the low incidence of new progressive coronary lesions and the needed therapy for this group should be weighed against the high cost of testing, the family's travel burden, and the added risk of sedation for most young children requiring echocardiographic evaluation.

The present study demonstrates that new CAA in-patients with KD with no previous CAA in their initial echocardiography are rare and all cases were resolved within eight weeks after illness without additional treatment. Furthermore, patients with normal echocardiographies at two weeks or eight weeks continued to be normal at one year, which implies the benign nature. Therefore, a second echocardiography may produce a high yield at two to eight weeks, and if the results show normal coronary arteries, further echocardiographic follow-up may not be indicated. This finding is comparable to prior reports (12, 13, 15). For example, a retrospective study of 67 patients with KD had follow-ups at 2–8 weeks and one patient had another follow-up. Scott et al. (15) found that 50 patients who had normal echocardiograms at 2–8 weeks after the onset of KD, continued to have normal coronary arteries at later follow-ups. Echocardiographic imaging beyond six to eight weeks appears to have little benefit (15). A recent report in Japan by Wang et al. (13) considered 386 children with KD who had no CAA at their baseline and had follow-ups at 1, 2, 4, and 8 weeks, and 1 year and 5 years. Nine patients (2.3%) were found to have new CAAs at one month with three of the nine patients (0.8%) having moderate CAA that required additional antithrombotic therapy. The remaining six of nine patients had coronary ectasia, which were resolved spontaneously at the subsequent follow-up. After four weeks, seven of nine patients developed new coronary artery lesions (Z-score > 2), three developed new lesions at eight weeks, and four developed new lesions at one year. In any case, their lesions were spontaneously resolved later. The authors concluded that the optimal timing for echocardiographic follow-up may be one month in patients with no initial CAA and coronary artery Z-scores < 2 at one month (13). de Ferranti et al. (12) reviewed a large database of 464 patients with KD who had coronary artery Z-scores < 2 at baseline and at 2 weeks following diagnosis. Their 6-week echocardiographic follow-ups showed that 456 patients (98.3%) continued to have normal Z-scores. Of the remaining eight patients (1.7%), five had coronary ectasia and three had CAAs. All coronary artery lesions subsequently regressed to normal. In this study, the authors suggested that the six-week echocardiographic imaging may be unnecessary in patients with uncomplicated KD and *Z* scores < 2.0 in the first two weeks of illness (12). From our study, and the above three studies, the follow-up timing of echocardiography differed slightly, but all of these studies provide evidence for a low incidence of new CAA in uncomplicated KD after the second echocardiography between two and eight weeks. All new cases of CAA tend to regress over time without the need for additional therapy. Therefore, we propose that subsequent echocardiographies in patients with KD who had no initial CAA and normal Z-scores at their second echocardiography that had been performed at two to eight weeks may not be necessary. In our study, a one-year clinical follow-up showed a good functional class without adverse cardiac symptoms, as was reported by previous authors (3, 12). In a

study of 166 adults with a history of KD, all patients without CAA had normal coronary calcium scores, though significantly increased calcium scores were found in the patients with CAA (17). Thus, patients with KD and no CAAs can be classified into a low cardiovascular risk group, without needing to have long-term cardiology testing and stress imaging surveillance. Nevertheless, general counseling about a healthy lifestyle and activity is recommended for these patients (1, 16).

Our study had several limitations in its retrospective nature, with selection bias, small sample size, significant loss to follow-up at two-weeks and at one year, and possible measurement bias due to the use of multicenter data. In any case, all investigators were certified cardiologists and trained at the same institute (Siriraj Hospital); thus, we expected the methods of measurement to have only a small deviation. Z-scores were calculated using the same standard reference (7). Because the entry criteria were patients without CAA who had complete baseline and follow-up echocardiography at eight weeks, the rate of no echocardiographic follow-up at two weeks was 41%, which could underpower the actual rates of new coronary artery lesions. Nonetheless, the results of eight-week follow-up were complete and clinically meaningful. The clinical follow-up at 1 year occurred with 81.8% of the patients and the echocardiographic follow-up occurred with 46.3% of the patients. Again, the results at the one-year follow-up could be an underestimation. Consequently, we analyzed the data carefully and identified the number of patients at each visit (**Table 3**).

Conclusion

New CAA in patients with KD who had no previous CAA in their initial echocardiography are rare. The patients who had a normal echocardiographic follow-up at two weeks or eight weeks mostly continued to have normal assessments at one year. The optimal timing for the echocardiographic follow-up should be at two to eight weeks in patients without initial CAA and still having a coronary artery Z-score < 2 in the second echocardiographic examination. While clinical follow-ups at one year may be considered, the decision should involve the physician and family counsellor.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by The Siriraj Institutional Review Board, Faculty of Medicine, Siriraj Hospital, Mahidol University [Study number 244/2,564 (EC4), COA No Si 309/2021], Phrapokklao Hospital Chanthaburi [COA No 034/65], Nakhon Pathom Hospital [Record No 028/2021, COA No. 029/2021], and Chao Phraya Yommarat Hospital, Suphanburi, Thailand [COA No. YM027/2565]. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Author contributions

CV conceptualized the study, collected and analyzed the data for this research and wrote the manuscript. CW collected and analyzed the data and prepared the initial reports. VP, PS, DB, and TB facilitated the data collection and edited the manuscript. PC provided critical feedback and edited the manuscript. All authors contributed to the manuscript, and read and approved the final submission. All authors contributed to the article and approved the submitted version.

Acknowledgments

The authors acknowledge Miss Kanokwan Sommai and Julaporn Pooliam, Clinical Epidemiology Unit, Office of Research and Development, Faculty of Medicine, Siriaj Hospital for their assistance with the statistical analysis. We also thank Glen Wheeler for his effective proofreading and editing.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. McCrindle BW, Rowley AH, Newburger JW, Burns JC, Bolger AF, Gewitz M, et al. Diagnosis, treatment, and long-term management of kawasaki disease: a scientific statement for health professionals from the American heart association. *Circulation*. (2017) 135(17):e927–e99. doi: 10.1161/CIR.0000000000000484

2. Fukazawa R, Kobayashi J, Ayusawa M, Hamada H, Miura M, Mitani Y, et al. JCS/JSCS 2020 guideline on diagnosis and management of cardiovascular sequelae in kawasaki disease. *Circ J*. (2020) 84(8):1348–407. doi: 10.1253/circj.CJ-19-1094

3. Kato H, Sugimura T, Akagi T, Sato N, Hashino K, Maeno Y, et al. Long-term consequences of kawasaki disease. A 10- to 21-year follow-up study of 594 patients. *Circulation*. (1996) 94(6):1379–85. doi: 10.1161/01.CIR.94.6.1379

4. Newburger JW, Takahashi M, Gerber MA, Gewitz MH, Tani LY, Burns JC, et al. Diagnosis, treatment, and long-term management of kawasaki disease: a statement for health professionals from the committee on rheumatic fever, endocarditis and kawasaki disease, council on cardiovascular disease in the young, American heart association. *Circulation*. (2004) 110(17):2747–71. doi: 10.1161/01.CIR.0000145143.19711.78

5. Dominguez SR, Anderson MS, El-Adawy M, Glodé MP. Preventing coronary artery abnormalities: a need for earlier diagnosis and treatment of kawasaki disease. *Pediatr Infect Dis J*. (2012) 31(12):1217–20. doi: 10.1097/INF.0b013e318266bcf9

6. Ae R, Abrams JY, Maddox RA, Schonberger LB, Nakamura Y, Kuwabara M, et al. Outcomes in kawasaki disease patients with coronary artery abnormalities at admission. *Am Heart J*. (2020) 225:120–8. doi: 10.1016/j.ahj.2020.04.019

7. McCrindle BW, Li JS, Minich LL, Colan SD, Atz AM, Takahashi M, et al. Coronary artery involvement in children with kawasaki disease: risk factors from analysis of serial normalized measurements. *Circulation*. (2007) 116(2):174–9. doi: 10.1161/CIRCULATIONAHA.107.690875

8. Baer AZ, Rubin LG, Shapiro CA, Sood SK, Rajan S, Shapir Y, et al. Prevalence of coronary artery lesions on the initial echocardiogram in kawasaki syndrome. *Arch Pediatr Adolesc Med*. (2006) 160(7):686–90. doi: 10.1001/archpedi.160.7.686

9. Friedman KG, Gauvreau K, Hamaoka-Okamoto A, Tang A, Berry E, Tremoulet AH, et al. Coronary artery aneurysms in kawasaki disease: risk factors for progressive disease and adverse cardiac events in the US population. *J Am Heart Assoc*. (2016) 5 (9):e003289. doi: 10.1161/JAHA.116.003289

10. Santimahakullert K, Vijarnsorn C, Wongswadiwat Y, Chanthong P, Khrongsrattha S, Panamonta M, et al. A retrospective cohort study of major adverse cardiac events in children affected by kawasaki disease with coronary artery aneurysms in Thailand. *PLoS One*. (2022) 17(1):e0263060. doi: 10.1371/journal.pone.0263060

11. Fukazawa R, Kobayashi T, Mikami M, Saji T, Hamaoka K, Kato H, et al. Nationwide survey of patients with giant coronary aneurysm secondary to kawasaki disease 1999-2010 in Japan. *Circ J*. (2018) 82(1):239–46. doi: 10.1253/circj.CJ-17-0433

12. de Ferranti SD, Gauvreau K, Friedman KG, Tang A, Baker AL, Fulton DR, et al. Association of initially normal coronary arteries with normal findings on follow-up echocardiography in patients with kawasaki disease. *JAMA Pediatr*. (2018) 172(12): e183310. doi: 10.1001/jamapediatrics.2018.3310

13. Wang Q, Morikawa Y, Akahoshi S, Miyata K, Sakakibara H, Matsushima T, et al. Follow-up duration of echocardiography in patients with kawasaki disease with no initial coronary aneurysms. *J Pediatr*. (2022) 244:133–8.e1. doi: 10.1016/j.jpeds.2021.11.022

14. Newburger JW, Burns JC. Kawasaki disease. *Vasc Med*. (1999) 4(3):187–202. doi: 10.1177/1358836X9900400310

15. Scott JS, Ettedgui JA, Neches WH. Cost-effective use of echocardiography in children with kawasaki disease. *Pediatrics*. (1999) 104(5):e57. doi: 10.1542/peds.104.5.e57

16. Brogan P, Burns JC, Cornish J, Diwakar V, Eleftheriou D, Gordon JB, et al. Lifetime cardiovascular management of patients with previous kawasaki disease. *Heart*. (2020) 106(6):411–20. doi: 10.1136/heartjnl-2019-315925

17. Kahn AM, Budoff MJ, Daniels LB, Oyamada J, Gordon JB, Burns JC. Usefulness of calcium scoring as a screening examination in patients with a history of kawasaki disease. *Am J Cardiol*. (2017) 119(7):967–71. doi: 10.1016/j.amjcard.2016.11.055

frontiers | Frontiers in Pediatrics

TYPE Original Research
PUBLISHED 20 March 2023
DOI 10.3389/fped.2023.1137841

OPEN ACCESS

EDITED BY
Shikai Yu,
Tongji University, China

REVIEWED BY
Kai-Sheng Hsieh,
China Medical University, Taiwan
Xiaohui Li,
Children's Hospital of Capital Institute of Pediatrics, China

*CORRESPONDENCE
N. Sekarski
✉ Nicole.sekarski@chuv.ch

SPECIALTY SECTION
This article was submitted to Children and Health, a section of the journal Frontiers in Pediatrics

RECEIVED 04 January 2023
ACCEPTED 20 February 2023
PUBLISHED 20 March 2023

CITATION
Bressieux-Degueldre S, Gradoux E, Di Bernardo S and Sekarski N (2023) Complete and incomplete Kawasaki disease: Clinical differences and coronary artery outcome from a national prospective surveillance study in Switzerland.
Front. Pediatr. 11:1137841.
doi: 10.3389/fped.2023.1137841

Complete and incomplete Kawasaki disease: Clinical differences and coronary artery outcome from a national prospective surveillance study in Switzerland

S. Bressieux-Degueldre[1], E. Gradoux[2], S. Di Bernardo[1] and N. Sekarski[1]* on behalf of the Swiss Paediatric Surveillance Unit (SPSU)

[1]Pediatric Cardiology Unit, Department of Women-Mother-Child, Lausanne University Hospital, Lausanne, Switzerland, [2]Department of Women-Mother-Child, Lausanne University Hospital, Lausanne, Switzerland

Introduction: The aim of this national prospective surveillance study was to compare the clinical presentation, laboratory findings, treatment, and coronary artery outcome in patients with incomplete and complete Kawasaki disease (KD).
Methods: Between March 2013 and February 2019, children with a diagnosis of complete and incomplete KD were reported by the Swiss Paediatric Surveillance Unit and prospectively enrolled. Clinical data, laboratory values, treatment, and echocardiographic features were collected at diagnosis and 1 year of follow-up. Data were compared between children with complete or incomplete KD.
Results: A total of 351 questionnaires were registered from children with a diagnosis of KD. Of them, 219 (62.4%) children had complete KD, and 132 (37.6%) children had incomplete KD. Children with incomplete KD were younger and had a longer-lasting fever; however, there were no differences in the level of C-reactive protein. All but four children received intravenous immunoglobulin treatment, whereas 14% of children were treated with corticosteroids. Children with incomplete KD were more often treated with corticosteroids than children with incomplete KD ($p = 0.01$). At diagnosis, 39 (11.1%) patients had only coronary artery dilation and 57 (16.2%) had at least one coronary artery aneurysm. There were no differences in coronary artery involvement between the two groups. At follow-up, 273 of 294 (92.8%) patients had no coronary artery involvement, with no difference between the two groups ($p = 0.609$). The overall incidence of coronary artery aneurysms at diagnosis was 16.2%. At follow-up, most coronary artery aneurysms had regressed, and coronary artery aneurysms were present in only 5.8% of the patients. Coronary artery aneurysms were slightly more frequent in patients with incomplete KD at follow-up ($p = 0.039$) but not at diagnosis ($p = 0.208$).
Conclusion: Although the clinical presentation in children with incomplete and complete KD differs, the absence of coronary artery involvement does not. The use of corticosteroids appears to be preventive against the development of coronary artery aneurysms in these patients. However, the results of this study suggest a lower rate of coronary artery aneurysm regression in patients with incomplete KD. Further studies on a larger scale are needed to assess the risk of non-regression of coronary artery aneurysms in this particular group of patients.

KEYWORDS
Kawasaki disease, outcome, complete form, incomplete form, coronary artery aneurysm

Introduction

A diagnosis of Kawasaki disease (KD) is based on clinical and laboratory criteria, and no definitive diagnostic test exists. The diagnosis of incomplete KD remains challenging, and diagnostic delays often occur, especially in infants. A more severe coronary outcome in children with incomplete KD has been suggested but remains controversial (1, 2). A previous study on the epidemiology of KD in Switzerland showed that children aged under one year of age or older than eight had more echocardiographic abnormalities at diagnosis (3).

A prompt diagnosis and rapid treatment with intravenous immunoglobulin (IVIG) remain the mainstays, as they have been shown to be effective in reducing coronary artery aneurysms (CAAs) (4).

The aim of the present study was to compare the clinical presentation, laboratory findings, treatment, and mid-term coronary artery outcome in patients with complete or incomplete KD in Switzerland. We hypothesized a more severe coronary outcome for patients with incomplete KD.

Methods

Children aged under 18 years with a diagnosis of complete or incomplete KD who were admitted between March 2013 and February 2019 in one of the 33 pediatric clinics in Switzerland and reported by the Swiss Paediatric Surveillance Unit (SPSU) were prospectively enrolled.

As for our previous study on the epidemiology of KD in Switzerland (3), an announcement was made by the physician in charge of the patient through the SPSU (www.spsu.ch), which is a surveillance system for rare pediatric diseases in hospitalized children in each of the 33 Swiss pediatric hospitals set up by the Swiss Pediatric Association and the Federal Office of Public Health. After receiving the initial anonymous announcement from the SPSU, a questionnaire was sent to the physician in charge of the patient during the hospital stay.

Demographic and clinical data were collected, including diagnostic clinical features for KD (bilateral non-purulent conjunctivitis, oral mucosal changes, cervical lymphadenopathy, skin rash, and changes in the extremities) and the duration of the fever. The results from laboratory investigations were recorded, including the most abnormal values during hospitalization for C-reactive protein (CRP), albumin, hemoglobin (HBG), white blood cell count (WBC), and platelet count.

Patients with a diagnosis of KD were matched either to the "incomplete KD" or the "complete KD" group according to the American Heart Association (AHA) guidelines (5, 6).

A follow-up questionnaire was sent 1 year after diagnosis to the pediatric cardiologist listed on the initial questionnaire. Clinical symptoms were recorded during the follow-up. This included symptoms of heart failure, chest pain, and/or shortness of breath at rest or during exercise.

The data from the echocardiography indicating a presence or absence of coronary artery dilation and/or aneurysms were recorded at the time of diagnosis and during the follow-up. In the case of coronary artery involvement and data availability, coronary artery dimensions for the right coronary and the left coronary artery (expressed in mm) were recorded and z-scores were calculated (7). Coronary artery dilation and the degree of the coronary aneurysm were defined according to the AHA guidelines (6).

Initial treatments with IVIG and doses of acetylsalicylic acid (ASA), together with any additional immunomodulatory therapy (e.g., corticosteroids, anakinra), were recorded. Medical treatments during the follow-up were collected.

Demographic data, clinical symptoms and signs, laboratory values, treatments, and coronary artery outcomes at presentation were compared between the incomplete and complete KD groups.

The coronary artery outcome between the two groups was compared during the follow-up.

Data have been reported as the mean with SD or the median with interquartile range, as appropriate. The statistical significance of differences between patients with complete and incomplete KD was assessed using the Student's *t*-test for continuous variables and Pearson's chi-square test for categorical variables. A p-value <0.05 was considered significant.

The research protocol was approved by the Institutional Ethics Board (CER-VD). Because of the anonymous data collection, the Ethics Committee waived informed consent. The study was performed in compliance with the 1964 Helsinki Declaration and its later amendments.

Results

Between March 2013 and February 2019, 351 questionnaires were collected from children with a diagnosis of KD. Of them, 219 (62.4%) children had complete KD, and 132 (37.6%) children had incomplete KD. In children aged under one year of age, the proportion of incomplete KD was even higher, at 54.5%. The demographic, clinical, and laboratory features of children with complete or incomplete KD at the time of diagnosis are illustrated in **Table 1**.

The mean age at diagnosis was 3.4 ± 1.2 years. Children with an incomplete KD were younger and had a longer-lasting fever. The typical clinical symptoms were significantly less frequent in children with incomplete KD, with rash being the most common symptom in both groups. There were no differences in inflammatory markers, such as CRP levels, but all other recorded laboratory parameters (hemoglobin, thrombocytes, white blood cells, and albumin) did differ (**Table 1**). For the latter laboratory parameters, the children with incomplete KD had more abnormal levels compared to the children with complete KD.

The medical therapies at the time of diagnosis and 1 year of follow-up are illustrated in **Table 2**. All but four (98.6%) children received IVIG and aspirin treatment at the time of diagnosis, with no differences between the two groups. Of them, one child was diagnosed retrospectively with incomplete KD due to axillary artery aneurysms more than 1 year after the acute disease, two children had a late diagnosis of KD and were already afebrile at the time of diagnosis, and in one child, no details were given regarding the reason for no treatment. Interestingly, these last three children did present with a complete form of KD. All

TABLE 1 Clinical and laboratory data at diagnosis.

	Incomplete KD	Complete KD	*p*-value
Age [mean (SD) in months]	34.8 (32.3)	45.0 (35.3)	0.004
Sex (male *N*, %)	81 (61%)	128 (58%)	0.787
Clinical symptoms			
Rash	88/128	212/218	0.005
ADP	35/121	135/214	<0.001
Extremities	48/127	181/215	<0.001
Mucosa	78/127	210/219	<0.001
Conjunctivitis	72/122	204/219	<0.001
Duration of fever [mean (SD) in days]	9.1 (4.0), $n = 105$	7.2 (3.3), $n = 167$	<0.001
Laboratory			
CRP level, g/L (mean/SD)	117.8 (77.0)	115.2 (87.5)	0.389
HBG level, g/L (mean/SD)	97.3 (18.3)	104.8 (16.3)	<0.001
Thrombocytes G/L (mean/SD)	407.9 (220.75)	344.0 (148.8)	<0.001
WBC	20.7 (22.7)	17.3 (11.3)	<0.001
Albumin	30.0 (6.2)	32.2 (9.4)	0.030

KD, Kawasaki disease; ADP, adenopathy; CRP, C-reactive protein; HBG, hemoglobin; WBC, white blood cell count.
Continuous variables are expressed in mean (SD). Categorical variables are expressed in *N* (%).

children received an IVIG dose of 2 g/kg, whereas the initial aspirin dose varied between 50 and 80 mg/kg in patients with incomplete KD. Approximately one-fifth of the patients received a second dose of IVIG; however, there were no differences between the children with complete and incomplete KD. Of all the children, 14% were treated with corticosteroids. Children with incomplete KD were more often treated with corticosteroids compared to children with incomplete KD ($p = 0.01$).

Additional anticoagulation therapy with vitamin K antagonists or antiplatelet therapy with clopidogrel was added in 12 patients.

The follow-up questionnaires of 294 patients were reviewed. The remaining 56 patients were either lost to follow-up or the questionnaire was not returned. One child died during the acute phase of KD.

The mean time from diagnosis to follow-up was 10.1 ± 5.5 months. This is explained by the fact that, although the questionnaire was sent out 1 year after the acute illness, some cardiologists in charge of the patients did see them earlier for follow-up and discharged them earlier. At follow-up, aspirin was continued in 36 (12.2%) patients. Six patients received therapy with vitamin K antagonists. Two patients had additional therapy (one patient had clopidogrel, and one had beta-blockers).

At the time of follow-up, all patients were free of cardiovascular symptoms.

In total, 255 (72.6%) children had no coronary artery involvement at the time of diagnosis. Of the 96 (27.3%) children with coronary artery involvement, 39 (11.1%) patients had only coronary artery dilation, and 57 (16.2%) had at least one CAA on echocardiography. There were no differences in coronary artery involvement between both groups (**Table 3**). For those patients with coronary aneurysms, right coronary artery (RCA) aneurysms were more frequent in patients with incomplete KD compared with patients with complete KD ($p = 0.038$).

TABLE 2 Medical therapy at diagnosis and at follow-up.

	Incomplete KD	Complete KD	*p*-value
Treatment at baseline			
Dose of IVIG in g/kg	2	2	
IVIG (initial treatment), *N* (%)	131 (99.2)	216 (98.6)	0.95
2nd dose of IVIG, nb of patients (%)	29/125 (23.2) 29/132 (22)	43/207 (20.7) 43/219 (19.6)	0.60 0.64
Corticosteroids, nb of patients (%)	23/132 (17.4)	28/219 (12.8)	0.01
Aspirin treatment at diagnosis, *N* (%)	131 (99.2)	216 (98.6)	0.95
Dose of Aspirin at diagnosis in mg/kg (Median/IQR)	80 (50-80)	80	
- VKA (*n*/%) - Clopidogrel (*n*/%) - Other (*n*/%)	7 (5.3) 2 (1.5) 0 (0)	1 (0.4) 2 (0.9) 1 (0.4)*	
Treatment at FU			
- Aspirin (*n*/%) - VKA (*n*/%) - Clopidogrel (*n*/%) - Betablocker (*n*/%)	20 (15) 4 (3.0) 0 0	16 (7.3) 2 (0.9) 1 (0.5) 1 (0.5)	

IVIG, intravenous immunoglobulins; IQR, interquartile range; VKA, Vitamin K antagonist; FU, follow up.
*Enalapril.

10.3389/fped.2023.1137841

Of the 57 patients with at least one CAA, 30 (52.6%) patients had small CAAs, 18 (31.6%) patients had medium-sized CAAs, and 8 (14.0%) patients had giant CAAs. Of those patients with giant CAAs, five had incomplete KD, and three had complete KD. **Figure 1** shows the distribution of the severity of CAAs between the two groups. In one patient with CAA, no data were given on the exact size; therefore, the severity of the CAA could not be assessed. Small, medium-sized, and giant CAAs were equally present in both groups (**Figure 1**).

At the follow-up, 273 of 294 (92.8%) patients had no coronary artery involvement, with no difference between the two groups ($p = 0.609$). Coronary artery dilation was seen in 5 (1.7%) patients and 16 (5.8%) patients had at least one coronary aneurysm. The presence of at least one CAA was slightly more prevalent in incomplete KD ($p = 0.039$). In total, five patients had small CAAs, eight had medium-sized CAAs, and two had giant CAAs at the time of follow-up. In one patient, the dimension of the CAA was not specified. **Figure 2** shows coronary artery involvement at follow-up in children with complete or incomplete KD. When comparing the severity of CAAs in patients with complete or incomplete KD, no significant difference was found between the two groups (**Figure 2**).

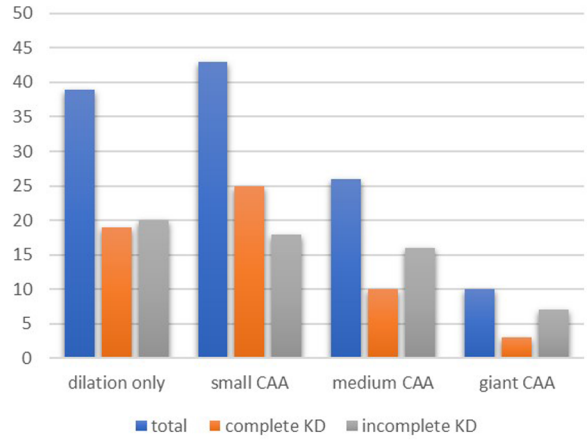


FIGURE 1
Coronary artery involvement at diagnosis. Pearson's chi-square test showed no differences between the groups for complete and incomplete KD in patients with dilation only ($p = 0.08$), small CAA ($p = 0.91$), medium CAA ($p = 0.11$), and giant CAA ($p = 0.14$). KD, Kawasaki disease; CAA, coronary artery aneurysm.

Discussion

This is the first prospective study comparing cardiac outcomes in complete or incomplete KD during acute illness and mid-term follow-up in Switzerland.

The proportion of patients with incomplete KD versus complete KD in this national prospective surveillance study is in line with recent studies (3, 8, 9), and slightly higher than in a previous retrospective single-center study in Switzerland between 1981 and 2014, where incomplete KD represented 29.5% of all patients with KD (10).

TABLE 3 Coronary artery involvement.

At diagnosis	Incomplete KD ($n = 132$)	Complete KD ($n = 219$)	*p*-value
No CA involvement	86 (65.1%)	169 (77.2%)	0.201
CA dilation only	20 (15.1%)	19 (8.7%)	0.080
At least one aneurysm	26 (19.7%)	31 (14.2%)	0.208
RCA dilation	17 (12.9%)	23 (10.5%)	0.514
RCA aneurysm	12 (9.1%)	8 (3.7%)	0.038
LCA dilation	37 (28.0%)	43 (19.6%)	0.111
LCA aneurysm	12 (9.1%)	9 (4.1%)	0.065
At follow-up	**Incomplete KD ($n = 111$)**	**Complete KD ($n = 183$)**	***p*-value**
No CA involvement	99 (89.2%)	174 (95.1%)	0.609
CA dilation only	2 (1.8%)	3 (1.6%)	0.873
At least one aneurysm	10 (9.0%)	6 (3.3%)	0.039
RCA dilation	2 (1.8%)	0 (0%)	
RCA aneurysm	6 (5.4%)	4 (2.2%)	
LCA dilation	2 (4.5%)	4 (2.2%)	
LCA aneurysm	8 (7.2%)	3 (1.6%)	

KD, Kawasaki disease; CA, coronary artery; RCA, right coronary artery; LCA, left coronary artery.

Indeed, several epidemiological studies have shown a rise in the incidence of incomplete KD over the last several years, with some reports showing that more than 40% of KD patients have incomplete KD (2, 11–12). This is thought to be due to the impact of the guidelines published in 2004, including the laboratory criteria (13); it may also reflect the lower threshold for the diagnosis and treatment of patients with suspected KD in order to avoid cardiac sequels (12).

In the present study, the age of onset was lower in patients with incomplete KD than in those with complete KD, and in patients aged under one year of age, more than half fulfilled the criteria for incomplete KD. Indeed, the proportion of patients with incomplete KD has been shown to be particularly high in patients aged younger than one (14) and even higher, up to 78.1%, in patients aged under six months (15, 16). This might be due to their immature immune systems, leading to a weaker response to vasculitis in the younger patient population (17).

Not surprisingly, classic clinical symptoms were less prevalent in children with incomplete KD in our study. This is in line with the American Heart Association algorithm (6), which defines incomplete KD in children as a fever of 5 days or more and two or three compatible criteria, or in infants as a fever lasting 7 days or more without any other explanation. Other studies also found significant differences in the clinical characteristics between complete or incomplete KD (1, 12), with children with incomplete KD having less conjunctival congestion, lymphadenopathy, and hand and foot redness (18).

One clinical difference between the two groups is the duration of fever, which was longer in the group with incomplete KD. This can be due to the delay in diagnosis in the last group, which was not evaluated in our study, and because of the definition of incomplete KD in infants (6), but also due to the higher rate of IVIG resistance. Other studies also reported a longer fever duration in incomplete KD patients (18).

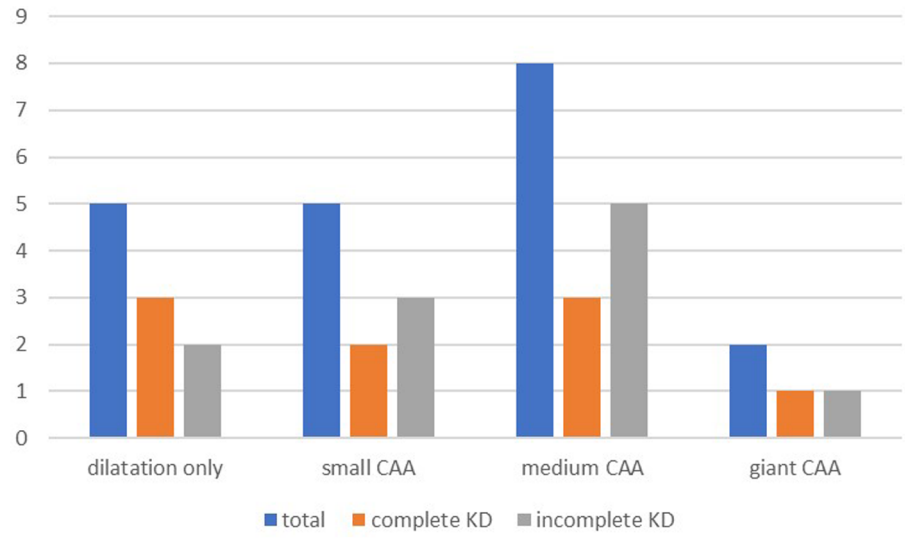


FIGURE 2
Coronary artery involvement at follow-up. Pearson's chi-square test showed no differences between the groups for complete and incomplete KD in patients with dilation only ($p = 0.873$), small CAA ($p = 0.307$), medium CAA ($p = 0.149$), and giant CAA ($p = 0.741$). KD, Kawasaki disease; CAA, coronary artery aneurysm.

Despite the longer duration of fever in incomplete KD patients, there were no differences in inflammatory markers, such as CRP levels, between the two groups. This has also been observed in another study comparing children with complete and incomplete KD (1, 18). In the present study, this might be explained by the greater use of corticosteroids in children with incomplete KD.

Incomplete KD is characterized by some but not all of the diagnostic criteria for KD (6). As a result, one can expect that the laboratory values in incomplete KD may not be as pronounced as those seen in complete KD. However, in this study, all laboratory values, except for CRP levels, were more abnormal in patients with incomplete KD. This might be explained by the fact that the most abnormal laboratory value during the hospital stay was recorded and not the baseline value at diagnosis. In a large retrospective study by Manlhiot et al. (1), most laboratory values differed between incomplete and complete KD, with incomplete KD having the most abnormal values.

In this study, patients with incomplete KD did not receive a second dose of IVIG more often; however, they were more often treated with corticosteroids. This might be due to the fact that patients with incomplete KD have a higher rate of IVIG resistance, needing, in addition to a second dose of IVIG, second-line treatments such as corticosteroids. Furthermore, patients in this group are younger, some aged under one year, making them a high-risk group for treatment with corticosteroids in addition to IVIG.

In this national prospective surveillance study, the overall incidence of CAA at diagnosis was 16.2%. Tulloh et al. (19) reported, in a prospective population survey in the UK and Ireland between 2013 and 2015, a rate of CAA of 19% and an incidence of 1.6% for giant CAAs during the acute phase, which is similar to this study.

At follow-up, most CAAs had regressed, and CAAs were present in only 5.8% of the patients.

Overall, 72.6% and 92.8% of the patients had no coronary artery involvement at diagnosis and follow-up, respectively, with no differences between patients with incomplete and complete KD, despite a longer duration of fever in the first group. CAAs were slightly more frequent in patients with incomplete KD at follow-up but not at diagnosis. This suggests that the CAA regression rate is lower in incomplete KD than in complete KD. Friedman et al. (20) found an association between a higher CAA *z*-score at diagnosis and a lack of regression. This cannot explain a lower regression rate in incomplete KD in our study, as there were no differences in the size of CAAs at diagnosis between the two groups. However, because of the small number of patients, further studies are warranted to identify any potential association between the regression rate of CAAs in incomplete and complete KD.

In Asian countries, especially in Japan, numerous risk scores, including Kobayashi et al. (21), Egami et al. (22), and Sano et al. (23), have been developed to estimate IVIG resistance and the increased risk of cardiac complications. However, no score has been validated in North American and European populations (24, 25).

Previous studies in non-Asian countries have been contradictory regarding the risk of coronary artery involvement in incomplete versus complete KD. A retrospective study by Manlhiot et al. (1) found no differences between children with incomplete and complete KD. Davidson et al. (26) identified from a retrospective study in South Australia that children with incomplete KD were more likely to develop CAAs. However, both were retrospective studies, and the mid-term outcome was not analyzed. In a population-based study between 2004 and 2014 in Sweden, Mossberg et al. (27) described a much higher rate of CAA (31%) during the acute phase and an association between CAA and incomplete KD, with an incidence of CAA of 46.7% in this group. However, about one-quarter of patients with incomplete KD were not treated within 10 days with IVIG. In the present study, the time from the first day of fever to treatment

with IVIG was not recorded; however, the mean duration of fever was 9 days in patients with incomplete KD. The distribution of the size of the CAAs was similar to the present study, with more than half of the patients having small CAAs.

In this study, the use of corticosteroids was higher in patients with incomplete KD. This could explain the lack of difference in inflammatory markers and coronary artery involvement between the two groups despite the longer duration of fever in children with incomplete KD. Indeed, steroids have been shown to reduce the risk of coronary artery development in addition to IVIG in KD, especially when given as an initial treatment (28). Some authors recommend the use of corticosteroids as initial therapy in patients with a high risk for IVIG resistance, for example, in children aged under 1 year (29, 30).

A high index of suspicion and prompt treatment with IVIG and, when indicated, corticosteroids are crucial to reducing the risk of coronary artery involvement.

Limitations

The present study has some limitations. First, several clinical and paraclinical data items were not completed in the questionnaire. The echocardiographic data from the left coronary artery were recorded, but the questionnaire did not specify the branches. If not specified by the treating cardiologist, we used the *z*-scores for the left main coronary artery. This might underestimate some results in terms of the severity of the CAAs of the left coronary artery. Furthermore, a number of patients were lost to follow-up. Second, during the study period, the international guidelines for the diagnosis and management of KD changed in 2017. This might have led to changes in clinical practice in the different hospitals involved in the study.

Conclusion

Although the clinical presentation in children with incomplete and complete KD is different, especially in the duration of fever, freedom from coronary artery involvement did not differ in this nationwide prospective surveillance study in Switzerland. The use of corticosteroids appears to be protective against the development of CAAs in this patient population. However, the results of this study suggest a lower rate of CAA regression in patients with incomplete KD. Further studies on a larger scale are needed to assess the risk of non-regression of CAA in this particular group of patients.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors upon reasonable request.

Ethics statement

The studies involving human participants were reviewed and approved by the Commission cantonal d'éthique de la recherche sur l'être humain (Canton de Vaud). Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and institutional requirements.

Author contributions

NS and EG designed the study. SB and EG collected the data. SB conducted the data analysis and wrote the first draft. All authors contributed to the article and approved the submitted version.

Funding

Open access funding by University of Lausanne.

Acknowledgments

We thank the representatives of the Swiss Paediatric Surveillance Unit (SPSU): M. Albisetti, W. Bär, V. Bernet, M. Bianchetti, L. Buetti, H. U. Bucher, M. Büttcher, F. Cachat, A. Castiglione, V. Colombo, C. Däster, P. Diebold, Z. Dovhunovà, S. Ferroni, S. Fluri, M. Gebauer, M. Gehri, E. Giannoni, P. Götschel, S. Grupe, L. Hegi, K. Held-Egli, M. Horn, P. Imahorn, T. Karen, C. Kind, L. Kottanattu, B. Laubscher, R. Lauener, U. Lips, H. Madlon, V. Maghaouri-Slim, A. Malzacher, J. McDougall, J.-C. Minet, M. Mönkhoff, A. Moser, V. Muehlethaler, A. Niederer, V. Pezzoli, N. Piol, K. Posfay Barbe, G. Ramos y Munoz, L. Reinhard, T. Riedel, H. Roten, C. Rudin, K. P. Rühs, M. Russo, V. Schlumbom, N. Schöbi, G. Simonetti, S. Stirnemann, C. Stüssi, E. Süess, R. Tabin, M. Tomaske, A. Ughetto, R. Villiger, S. Wellmann, J. Wildhaber, K. Woll, M. Wopmann, A. Wörner, G. Zeilinger, A. Zemmouri, U. Zimmermann, and S.-A. Zoubir; the SPSU board: A. Wörner, I. Bolt, C. Hagmann, B. Laubscher, G. Simonetti, F. Stollar, M. Mäusezahl, D. Beeli, and all the dedicated physicians for taking care of the patients and helping to complete the questionnaires. We thank all pediatric cardiologists who followed up with the patients and completed the questionnaires: Y. Aggoun, C. Balmer, M. Beghetti, Z. Beric, M. Bouhabib, T. Boulos Ksontini, B. Burkhardt, A. Cavigelli, M. Christmann, M. Dechant, B. Donner, D. Ehrlinspiel, M. Fasnacht, M. Frenzel, R. Ghisla, M. Glöckler, M. Gittermann, J. Günthard, M. Hämmerli, R. Hoop, S. Hormann, D. Hutter, D. Jakob, W. Knirsch, O. Kretschmar, P. Kuen, C. Leoni-Foglia, C. Mann, K. Mayer, Y. Mivelaz, A. Oxenius, M. Pavlovic, J.-P. Pfammatter, M. Prsa, D. Quandt, T. Seiler, R. Soyka, D. Stambach, A. Stefani-Glücksberg, H. Steinmann, B. Stiansy, C. Tissot, M. Tomaske, E. Valsangiacomo, R. Weber, and D. Wütz.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Manlhiot C, Christie E, McCrindle BW, Rosenberg H, Chahal N, Yeung RSM. Complete and incomplete Kawasaki disease: two sides of the same coin. *Eur J Pediatr*. (2012) 171:657–62. doi: 10.1007/s00431-011-1631-2

2. Shivalingam G, Prashanth GP, Hebbal K, Aguiar R. Clinical presentation and cardiovascular outcome in complete versus incomplete Kawasaki disease. *Indian Pediatr*. (2017) 54(10):844–7. doi: 10.1007/s13312-017-1147-6

3. Gradoux E, Di Bernardo S, Bressieux-Degueldre S, Mivelaz Y, Boulos Ksontini T, Prsa M, et al. Epidemiology of Kawasaki disease in children in Switzerland: a national prospective cohort study. *Swiss Med Wkly*. (2022) 152:w30171. doi: 10.4414/SMW.2022.w30171

4. Oates-Whitehead RM, Baumer JH, Haines L, Love S, Maconochie IK, Gupta A, et al. Intravenous immunoglobulin for the treatment of Kawasaki disease in children. *Cochrane Database Syst Rev*. (2003) 2003(4):CD004000. doi: 10.1002/14651858.CD004000

5. Newburger JW, Takahashi M, Gerber MA, Gewitz MH, Tani LY, Burns JC, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a statement for health professionals from the committee on rheumatic fever, endocarditis and Kawasaki disease, council on cardiovascular disease in the young, American Heart Association. *Circulation*. (2004) 110:2747–71. doi: 10.1161/01.CIR.0000145143.19711.78

6. McCrindle BW, Rowley AH, Newburger JW, Burns JC, Bolger AF, Gewitz M, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a scientific statement for health professionals from the American Heart Association. *Circulation*. (2017) 135(17):e927–99. doi: 0.1161/CIR.0000000000000484

7. McCrindle BW, Li JS, Minich LL, Colan SD, Atz AM, Takahashi M, et al. Coronary artery involvement in children with Kawasaki disease: risk factors from analysis of serial normalized measurements. Pediatric Heart Network Investigators. *Circulation*. (2007) 116(2):174–9. doi: 10.1161/CIRCULATIONAHA.107.690875

8. Xie LP, Yan WL, Huang M, Huang M-r, Chen S, Huang G-y, et al. Epidemiologic features of Kawasaki disease in Shanghai from 2013 through 2017. *J Epidemiol*. (2020) 30:429–35. doi: 10.2188/jea.JE20190065

9. Ae R, Makino N, Kosami K, Kuwabara M, Matsubara Y, Nakamura Y. Epidemiology, treatments, and cardiac complications in patients with Kawasaki disease: the nationwide survey in Japan, 2017–2018. *J Pediatr*. (2020) 225:23–29.e2. doi: 10.1016/j.jpeds.2020.05.034

10. De La Harpe M, di Bernardo S, Hofer M, Sekarski N. Thirty years of Kawasaki disease: a single-center study at the university hospital of lausanne. *Front Pediatr*. (2019) 7:11. doi: 10.3389/fped.2019.00011

11. Li T, Feng J, Li N, Liu T. Correct identification of incomplete Kawasaki disease. *J Int Med Res*. (2021) 49(3):3000605211001712. doi: 10.1177/03000605211001712

12. Robinson C, Chanchlani R, Gayowsky A, Brar S, Darling E, Demers C, et al. Incidence and short-term outcomes of Kawasaki disease. *Pediatr Res*. (2021) 90(3):670–7. doi: 10.1038/s41390-021-01496-5

13. Ghelani SJ, Sable C, Wiedermann BL, Spurney CF. Increased incidence of incomplete Kawasaki disease at a pediatric hospital after publication of the 2004 American Heart Association guidelines. *Pediatr Cardiol*. (2012) 33(7):1097–103. doi: 10.1007/s00246-012-0232-9

14. Mastrangelo G, Cimaz R, Calabri GB, Simonini G, Lasagni D, Resti M, et al. Kawasaki disease in infants less than one year of age: an Italian cohort from a single center. *BMC Pediatr*. (2019) 19(1):321. doi: 10.1186/s12887-019-1695-0

15. Moreno E, Garcia SD, Bainto E, Salgado AP, Parish A, Rosellini BD, et al. Presentation and outcomes of Kawasaki disease in Latin American infants younger than 6 months of age: a multinational multicenter study of the REKAMLATINA network. *Front Pediatr*. (2020) 8:384. doi: 10.3389/fped.2020.00384

16. Grasa CD, Fernández-Cooke E, Sánchez-Manubens J, Carazo-Gallego B, Aracil-Santos J, Anton J, et al. Kawasaki disease in children younger than 6 months of age: characteristics of a Spanish cohort. *Eur J Pediatr*. (2022) 181(2):589–98. doi: 10.1007/s00431-021-04215-8

17. Chang FY, Hwang B, Chen SJ, Lee PC, Meng CC, Lu JH. Characteristics of Kawasaki disease in infants younger than six months of age. *Pediatr Infect Dis J*. (2006) 25(3):241–4. doi: 10.1097/01.inf.0000202067.50975.90

18. Cai WJ, Ding SG. Retrospective analysis of clinical characteristics and related influencing factors of Kawasaki disease. *Medicine (Baltimore)*. (2022) 101(52):e32430. doi: 10.1097/md.0000000000032430

19. Tulloh RMR, Mayon-White R, Harnden A, Ramanan AV, Tizard EJ, Shingadia D, et al. Kawasaki disease: a prospective population survey in the UK and Ireland from 2013 to 2015. *Arch Dis Child*. (2019) 104(7):640–6. doi: 10.1136/archdischild-2018-315087

20. Friedman KG, Gauvreau K, Hamaoka-Okamoto A, Tang A, Berry E, Tremoulet AH, et al. Coronary artery aneurysms in Kawasaki disease: risk factors for progressive disease and adverse cardiac events in the US population. *J Am Heart Assoc*. (2016) 5(9):e003289. doi: 10.1161/JAHA.116.003289

21. Kobayashi T, Inoue Y, Takeuchi K, Okada Y, Tamura K, Tomomasa T, et al. Prediction of intravenous immunoglobulin unresponsiveness in patients with Kawasaki disease. *Circulation*. (2006) 113:2606–12. doi: 10.1161/CIRCULATIONAHA.105.592865

22. Egami K, Muta H, Ishii M, Suda K, Sugahara Y, Iemura M, et al. Prediction of resistance to intravenous immunoglobulin treatment in patients with Kawasaki disease. *J Pediatr*. (2006) 149:237–40. doi: 10.1016/j.jpeds.2006.03.050

23. Sano T, Kurotobi S, Matsuzaki K, Yamamoto T, Maki I, Miki K, et al. Prediction of nonresponsiveness to standard high-dose gamma-globulin therapy in patients with acute Kawasaki disease before starting initial treatment. *Eur J Pediatr*. (2007) 166:131–7. doi: 10.1007/s00431-006-0223-z

24. Sleeper LA, Minich LL, McCrindle BM, Li JS, Mason W, Colan SD, et al. Evaluation of Kawasaki disease risk-scoring systems for intravenous immunoglobulin resistance. *J Pediatr*. (2011) 158:831–5.e3. doi: 10.1016/j.jpeds.2010.10.031

25. Tremoulet AH, Best BM, Song S, Wang S, Corinaldesi E, Eichenfield JR, et al. Resistance to intravenous immunoglobulin in children with Kawasaki disease. *J Pediatr*. (2008) 153:117–21. doi: 10.1016/j.jpeds.2007.12.021

26. Davidson H, Kelly A, Agrawal R. Retrospective review of Kawasaki disease at the women's and children's hospital, South Australia. *J Paediatr Child Health*. (2021) 57:1893–8. doi: 10.1111/jpc.15603

27. Mossberg M, Mohammad AJ, Kahn F, Segelmark M, Kahn R. High risk of coronary artery aneurysm in Kawasaki disease. *Rheumatology (Oxford)*. (2021) 60(4):1910–4. doi: 10.1093/rheumatology/keaa512

28. Kobayashi T, Saji T, Otani T, Otani T, Takeuchi K, Nakamura T, Arakawa H, et al. Efficacy of immunoglobulin plus prednisolone for prevention of coronary artery abnormalities in severe Kawasaki disease (RAISE study): a randomised, open-label, blinded-endpoints trial. *Lancet*. (2012) 379(9826):1613–20. doi: 10.1016/S0140-6736(11)61930-2

29. Eleftheriou D, Levin M, Shingadia D, Tulloh R, Klein NJ, Brogan PA. Management of Kawasaki disease. *Arch Dis Child*. (2014) 99(1):74–83. doi: 10.1136/archdischild-2012-302841

30. Chen S, Dong Y, Kiuchi MG, Wang J, Li R, Ling Z, et al. Coronary artery complication in Kawasaki disease and the importance of early intervention: a systematic review and meta-analysis. *JAMA Pediatr*. (2016) 170(12):1156. doi: 10.1001/jamapediatrics.2016.2055

frontiers | Frontiers in Pediatrics

TYPE Case Report
PUBLISHED 06 April 2023
DOI 10.3389/fped.2023.1103094

OPEN ACCESS

EDITED BY
Shikai Yu,
Tongji University, China

REVIEWED BY
Mahdi Hosseinzadeh,
Sports Sciences Research Institute of Iran (SSRII), Iran
Wen-Hui Wu,
Tongji University, China

*CORRESPONDENCE
Elisabet Børsheim
✉ EBorsheim@uams.edu

SPECIALTY SECTION
This article was submitted to Pediatric Cardiology, a section of the journal Frontiers in Pediatrics

RECEIVED 19 November 2022
ACCEPTED 23 March 2023
PUBLISHED 06 April 2023

CITATION
Edwards T, Tas E, Leclerc K and Børsheim E (2023) Case report: A proposed role for cardiopulmonary exercise testing in detecting cardiac dysfunction in asymptomatic at-risk adolescents.
Front. Pediatr. 11:1103094.
doi: 10.3389/fped.2023.1103094

Case report: A proposed role for cardiopulmonary exercise testing in detecting cardiac dysfunction in asymptomatic at-risk adolescents

Timothy Edwards[1,2], Emir Tas[2,3], Kenneth Leclerc[4] and Elisabet Børsheim[1,2,3,5]*

[1]Arkansas Children's Nutrition Center, Little Rock, AR, United States, [2]Arkansas Children's Research Institute, Little Rock, AR, United States, [3]Department of Pediatrics, University of Arkansas for Medical Sciences, Little Rock, AR, United States, [4]Department of Cardiology, Legacy Medical Group, Tualatin, OR, United States, [5]Department of Geriatrics, University of Arkansas for Medical Sciences, Little Rock, AR, United States

Noninvasive cardiopulmonary exercise testing (CPET) provides the valuable capacity to analyze pulmonary gas exchange and cardiovascular responses that can be used to differentiate normal cardiopulmonary responses from abnormal. This case report highlights a proposed role for CPET in identifying potential cardiac pathologies in at-risk adolescents. An abnormal CPET response in an asymptomatic adolescent revealed a family history of early-age CAD. The significance of the abnormal CPET response was further supported by the presence of an elevated concentration of circulating high sensitivity C-reactive protein (hs-CRP). These findings emphasize the importance of a thorough clinical evaluation in at-risk adolescents, as CPET can aid in the early detection and management of cardiac pathologies, especially when combined with other relevant biomarkers such as plasma hs-CRP concentration, which can further suggest underlying pathology. Management considerations using serial CPET evaluations are recommended. Thus, CPET abnormalities combined with elevated hs-CRP should be taken seriously and provide justification for further evaluation and monitoring in adolescents at risk for cardiovascular disease.

KEYWORDS

case report, cardiac dysfunction, cardiopulmonary exercise testing (CPET), adolescents, family history

Introduction

Cardiopulmonary exercise testing (CPET) is a well-recognized, but underutilized diagnostic and prognostic test for clinical evaluation in the symptomatic pediatric and adult populations. However, an effective preventive healthcare clinical workflow for apparently healthy asymptomatic individuals at-risk for future cardiovascular disease (e.g., family history, overweight/obesity, elevated hs-CRP) is not well established, especially in adolescents. As a non-invasive and radiation-free test, CPET provides a simultaneous evaluation of cardiovascular, pulmonary, and skeletal muscle responses that may detect early-stage disease states. Therefore, a clinical workflow utilizing CPET has the potential to improve the current preventive healthcare strategy.

Abbreviations
AT, anaerobic threshold; CPET, cardiopulmonary exercise testing; HR, heart rate; hs-CRP, high sensitivity C-reactive protein; O_2 pulse, ratio of oxygen consumption and heart rate; $\dot{V}O_2$, oxygen consumption; WR, work rate.

The value of CPET is based on its ability to accurately measure oxygen consumption ($\dot{V}O_2$), which is the product of cardiac output and arterial-venous O_2 difference. Cardiac output is measured indirectly by tracking HR and O_2 pulse (surrogate of stroke volume) throughout incremental exercise. In healthy individuals, $\dot{V}O_2$ and HR increase linearly along with a linear or curvilinear O_2 pulse when a linear ramping work rate (WR) protocol is used on a cycle ergometer. Key CPET parameters ($\Delta\dot{V}O_2/\Delta WR$, $\Delta HR/\Delta WR$, ΔO_2 pulse/ΔWR) reflect how $\dot{V}O_2$, HR, and O_2 pulse respond to increasing workloads and provide important insight into cardiovascular function (1, 2). Deviation of these parameters from their expected trajectories signals that a closer analysis may be warranted to assess any underlying pathology. Some disease states may not be detected using resting studies, as in the example of this case. Therefore, CPET may reveal abnormalities in asymptomatic adolescents that suggest possible underlying cardiopulmonary disease states. This case report describes the abnormal CPET response in an asymptomatic adolescent male that later revealed a significant family history risk factor of early-age CAD. The abnormal CPET response was further supported by the presence of an elevated concentration of circulating high sensitivity C-reactive protein (hs-CRP) which adds to the probability of an underlying cardiac pathology and emphasizes the importance of the need for a more thorough clinical evaluation.

Case report

This paper reports on a 14-year-old Caucasian male participant with an overweight BMI percentile for age and sex who underwent a cardiopulmonary fitness test during a research study visit for apparently healthy adolescents. This Case Report comes from a follow-up study. The original study was approved by the Institutional Review Board at the University of Arkansas for Medical Sciences (IRB #206291), and the usage of data for this Case Report was approved by the same IRB (#263026).

The participant was enrolled in the original cohort study and was later recalled for a study visit when he was 14 years old, at which point the visit also included a CPET test. The case participant had no known previous or current medical history, was not taking any prescription medications, and was reportedly asymptomatic at the time of testing. **Table 1** shows the demographics of both the case participant and a healthy control from the same study matched on age, sex and race, but with no significant family health history.

Per the study protocol, the participant underwent fasting blood sampling to determine circulating levels of cardiometabolic and inflammatory markers. Vitals and blood sampling were followed by cardiopulmonary fitness testing *via* a maximum effort CPET using a metabolic cart (MGC Diagnostics Ultima PFX, St. Paul, Minnesota, USA) and cycle ergometer (Lode Corival, Gronigen, The Netherlands) with a linear ramp protocol of 20 watts per minute. The participant stopped the test due to leg fatigue and reached a respiratory exchange ratio of 1.16 (significant metabolic acidosis representing good effort), a peak HR of 93% of his age-predicted value (220-age), an anaerobic threshold (AT) of <40% of the predicted peak $\dot{V}O_2$, an O_2 pulse at peak exercise (surrogate of peak stroke volume) of 58% of predicted, a $\Delta\dot{V}O_2/\Delta WR$ of 6.4 $ml \cdot min^{-1} \cdot Watt^{-1}$ (64% of predicted) (3), and a peak $\dot{V}O_2$ of 21.3 $ml \cdot kg^{-1} \cdot min^{-1}$ (55% of predicted) (4). Blood pressure and electrocardiogram (EKG) were not measured during the exercise as peak $\dot{V}O_2$ was the study test's primary outcome. Graphically, his HR response as a function of $\dot{V}O_2$, and O_2 pulse as a function of WR, became abnormal in the period following the AT. Steepening of the HR response as a function of $\dot{V}O_2$ with a simultaneous flattening of the O_2 pulse response and a slowing of the $\dot{V}O_2$ response as functions of WR were noted at a WR of 78 watts. **Figure 1** illustrates normal HR vs. $\dot{V}O_2$ and O_2 pulse vs. WR responses of the control participant (mentioned in **Table 1**) compared to the abnormal case participant.

CPET slopes ($\Delta\dot{V}O_2/\Delta WR$, $\Delta HR/\Delta WR$, ΔO_2 pulse/ΔWR) percent change were calculated by comparing the slope corresponding to the 2 min of exercise prior to test termination (slope 2) to the slope corresponding to the 2 min preceding AT (slope 1, baseline slope). This quantitative analysis showed a 286% steepening in $\Delta HR/\Delta WR$ in slope 2 compared to slope 1 and a 105% decrease in O_2 pulse using the same slope comparison process, suggesting an underlying cardiac dysfunction. **Table 2** displays these abnormal slope changes compared to the control and other published healthy cohort slope data (1, 2). **Figure 2** illustrates the normal HR response of the control compared to the abnormal case participant's HR response.

Following the study visit, the abnormal CPET pattern indicative of cardiac dysfunction was identified. The center physician soon informed the parent of the finding and advised them to follow-up with a cardiology appointment. It was then that the parent revealed the case adolescent had a family history

TABLE 1 Case participant and healthy control characteristics.

Demographic	Case participant	Control
Age (years)	14	14
Race	Caucasian	Caucasian
Sex	Male	Male
BMI percentile	87th	49th
Significant family history risk factors	Paternal early-age CAD	None
Vitals		
Resting heart rate (beats/min)	67	68
Resting blood pressure (mmHg)	115/63	125/80
Blood measures		
Hs-CRP (mg/L) (5%–95% interval in children: 0.1–2.8 mg/L) (5)	5.3	0.1
Glucose (mg/dl)	89	92
Total cholesterol (mg/dl)	109	133
HDL (mg/dl)	45	56
LDL (mg/dl)	52	76
Triglycerides (mg/dl)	74	41

BMI, body mass index; CAD, coronary artery disease; HDL, high density lipoprotein; LDL, low density lipoprotein. To convert total cholesterol, HDL cholesterol, and LDL cholesterol values to mmol/L, multiply by 0.0259; to convert triglyceride values to mmol/L, multiply by 0.0113.

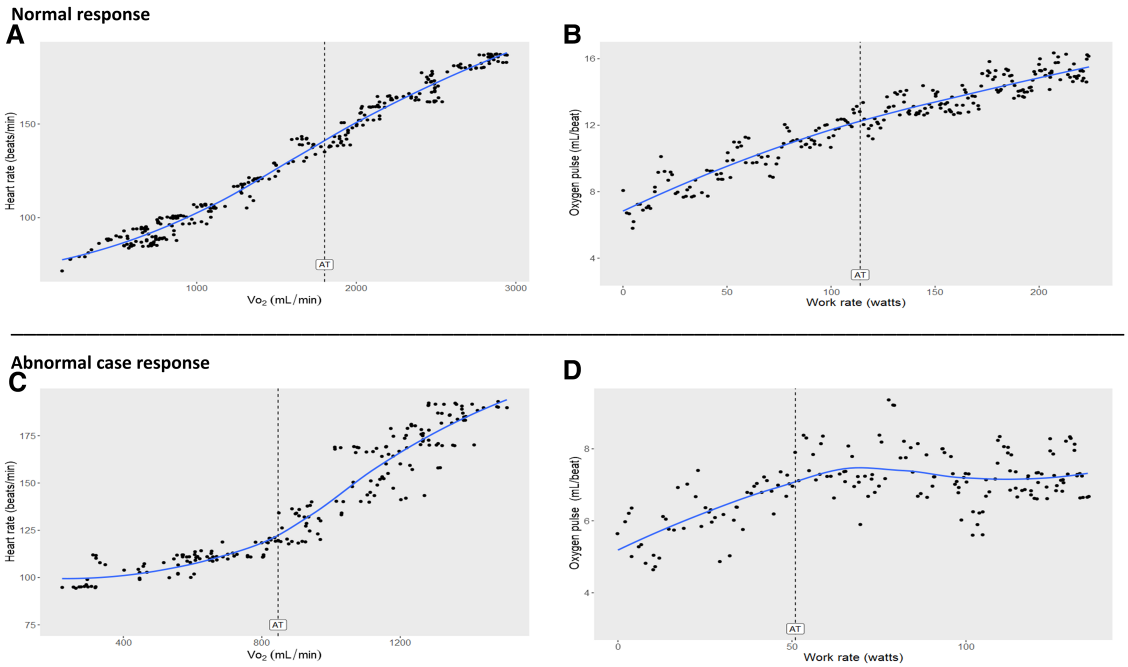


FIGURE 1
(A,B): Normal cardiopulmonary exercise test (CPET) responses (normal cardiac function) in a healthy 14-year old male control. Note there is little change in trajectories after AT compared to before AT. (C,D): Abnormal CPET responses (cardiac dysfunction) from the case participant 14-year old male with elevated hs-CRP and a family history risk factor for early-age coronary artery disease. Note the significant steepening of heart rate trajectory with abrupt flattening of oxygen pulse after AT compared to before AT. AT, anaerobic threshold; Oxygen pulse, $\dot{V}O_2$/HR (index of stroke volume x arteriovenous oxygen difference); $\dot{V}O_2$, oxygen uptake. SI conversion factors: To convert $\dot{V}O_2$ and AT values to L/min, multiply by.001; to convert $\dot{V}O_2$/HR (oxygen pulse, ml/beat) to L/beat, multiply by.001.

TABLE 2 CPET slope changes: case participant vs. healthy control and published cohorts.

CPET slopes % change (slope 2 vs. slope 1)	Case participant (adolescent)	Control (healthy adolescent)	Chaudhry et al. (1) (healthy adult cohort)	Van De Sande et al. (2) (healthy adult cohort)
ΔHR/ΔWR	286%	−5%	−6%	−24%
ΔO_2 pulse/ΔWR	−105%	32%	NA	4%

The case participant has a significant acceleration of HR response and decrease in O_2 pulse response in late exercise (ΔHR/ΔWR and ΔO_2 pulse/ΔWR slopes) compared to healthy individuals. CPET, cardiopulmonary exercise testing; ΔHR/ΔWR, change in heart rate relative to the change in work rate slope in the 2 min prior to exercise test termination compared to baseline; ΔO_2 pulse/ΔWR, change in oxygen pulse relative to the change in work rate slope in the 2 min prior to exercise test termination compared to baseline; NA, not available.

that was significant for early-onset coronary artery disease (CAD), with his father having a myocardial infarction before 50 years of age. The participant was seen by a pediatric primary care provider for further evaluation. A resting EKG was performed which showed normal sinus rhythm and no further testing was recommended by the provider. Thus, there was no intervention for the case. Unfortunately, we were not in a position to influence this decision, as it is our opinion that the case adolescent did not get sufficient thorough follow-up testing which should go beyond resting EKG measurements, as further discussed below.

Because of the irregular findings reported here, early serum sample analyses were done for the case and a control participant. It was found that the case participant's serum hs-CRP was elevated at 5.3 mg/L vs. 0.1 mg/L in the control participant (5%–95% interval in children: 0.1–2.8 mg/L) (5) (**Table 1**).

Discussion

Previous CPET research has mostly focused on symptomatic individuals and few investigative studies have been published utilizing CPET to assess the cardiovascular and pulmonary function in asymptomatic at-risk individuals (6). However, evidence of the utility of CPET as a unique diagnostic tool is emerging. This case highlights the contrast between a healthy adolescent control at low risk for cardiovascular disease and an adolescent at a significantly increased risk due to family history of paternal early-age CAD and being in the overweight BMI percentile. The abnormal CPET responses indicative of cardiac dysfunction combined with elevated hs-CRP levels add further importance to the need for a more thorough clinical evaluation. Therefore, the evidence highlighted in this case raises awareness to the potential value of using CPET in this at-risk population

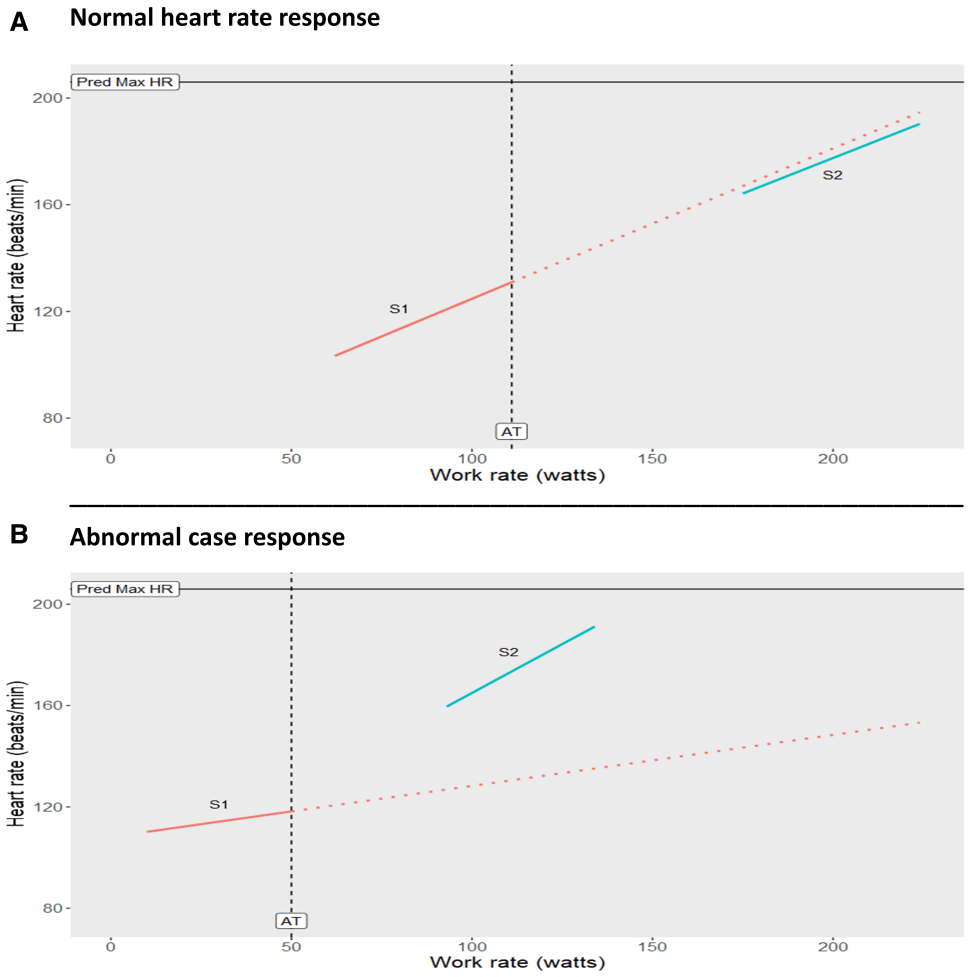


FIGURE 2
(**A**): Normal heart rate response seen in a healthy 14-year old male control showing normal cardiac function. Note there is only a slight change in slope (−5%) between the 2 min prior to exercise test termination (S2) and the 2 min prior to AT (S1). (**B**): Abnormal heart rate response from the case participant 14-year old male showing cardiac dysfunction. Note the significant steepening of slope S2 (286%) in late exercise compared to the baseline S1. S1 = slope of line of best fit for heart rate response in the 2 min prior to the exercise test termination. Dashed lines represent trajectory of S1 (baseline slope). AT, anaerobic threshold; Pred Max HR, predicted maximum heart rate.

and the need for further testing and monitoring beyond a resting EKG and other common resting measures (e.g., blood pressure, cholesterol, etc). As such, CPET may contribute to early detection of cardiopulmonary abnormalities, which again would enable early interventions.

During CPET in healthy individuals, there is little change in the trajectory of key parameters in late exercise compared to early exercise when using a continuous linear WR protocol on a cycle ergometer (**Figure 1**, panels A and B). A normal AT, $\Delta\dot{V}O_2/\Delta WR$, and peak $\dot{V}O_2$ (relative to the percent predicted 3, 4) in response to exercise is required for an individual to have appropriate oxygen transport and physiological function. Substantial steepening in the HR slope and significant decrease in the O_2 pulse slope after the AT in the case participant, reflect a compensatory HR response caused by the inability to augment stroke volume (7) (arteriovenous O_2 difference normally increases relatively linearly from rest to peak $\dot{V}O_2$ (8)) — all while WR and minute ventilation increased linearly. These findings, combined with reduced AT, $\Delta\dot{V}O_2/\Delta WR$, and peak $\dot{V}O_2$ are typical physiological markers of inadequate oxygen transport. Since a slowing of $\Delta\dot{V}O_2/\Delta WR$ was observed in late exercise, rather than a plateau, it may suggest the presence of a modifiable early-stage disease state. In adults, the significant early plateauing of $\Delta\dot{V}O_2/\Delta WR$ and ΔO_2 pulse/ΔWR is often indicative of exercise-induced myocardial ischemia, a late-stage manifestation of obstructive coronary artery disease (9, 10). Interestingly, a case report by Chaudhry et al. (11) detailed CPET's ability to detect and track the progression and regression of cardiac dysfunction in an asymptomatic young adult with a strong family history of early-age CAD. Therefore, our case findings suggest cardiac dysfunction may be detected by CPET at an even earlier age.

Obesity is characterized with a low-grade systemic inflammation. However, as an adjunct screening tool to lipid screening, the predictive role of hs-CRP in the future occurrence of cardiovascular diseases in at-risk adults has been recognized (12). This is particularly important given that a significant

percentage of adults with CAD have normal LDL cholesterol at hospital admission (13). In fact, a recent publication detailing hs-CRP levels in a large multi-cohort of adolescents with varying metabolic phenotypes provides strong evidence that the abnormal case participant CPET responses are grossly different from adolescents who are metabolically unhealthy and obese (14). This suggests that findings in the case adolescent may not simply be attributed to an unhealthy metabolic phenotype or excess weight.

Comparing slope changes of key CPET parameters of the case participant to the slope changes of the control and other published adult slope data (1, 2) make these abnormalities evident (**Table 2**). Although abnormal, there is no evidence suggesting to terminate a CPET prematurely when the individual is asymptomatic throughout testing. Recently, a study assessing early flattening of O_2 pulse in asymptomatic middle-aged adults found it was associated with cardiovascular risk factors (15). This data strengthens our findings, which are novel due to the young adolescent age of the case participant. Significant differences in cardiorespiratory fitness have been found in children and adolescents when comparing those with normal weight to those with obesity (16). Usually, these studies focus on peak $\dot{V}O_2$ as the primary outcome and do not assess for abnormal patterns that may reveal disease states, as we did in ours. This highlights the role of CPET in early detection of abnormal patterns, which would enable early intervention as long as the importance of the findings are recognized and proper follow-up is given. Further, a plan that incorporates CPET for prognosis of future cardiovascular diseases in at-risk asymptomatic adolescents is again novel, but presents challenges as described below. The current findings highlight the need for more research into abnormal CPET responses and their causes in this population, and identify best management practices.

One of the barriers to identifying a pathology following an abnormal CPET in young persons may be the assumption that subtle abnormalities are not too concerning since adolescents are viewed as being "naturally healthy" despite growing reports of negative health effects of poor diet and physical inactivity at young ages. This age bias may result in little to no follow-up testing after an abnormal CPET, especially in asymptomatic individuals, as in the example of this case. Since CPET research in this population is in its infancy and this testing is largely reserved for clinical populations, there are no evidence-based guidelines available for clinicians.

Likewise, it is known that some abnormalities are only first revealed during exercise, as in the example of this case. For instance, diastolic dysfunction, microvascular disease and endothelial dysfunction can cause abnormal CPET responses similar to this case, but the likelihood of identifying those disease states using the standard follow-up resting tests in an asymptomatic adolescent is low. In adults with suspected CAD, compared to ECG-only cardiac stress testing, CPET had superior sensitivity (88% vs. 48%) and specificity (98% vs. 55%) in detecting and excluding exercise-induced myocardial ischemia when nuclear SPECT imaging and coronary angiography were used to determine true CAD (10). Doppler echocardiogram provides valuable information on left ventricular function at rest, however, in asymptomatic apparently healthy adolescents, heart size and ejection fraction are usually normal. Without the evidence provided by CPET, objective signs of evolving pathologies may be absent. Thus, CPET is probably the most sensitive and comprehensive test available when screening for development of disease in high-risk individuals. An effective diagnostic work flow following an abnormal CPET must be driven by the CPET pathophysiological pattern that points toward the organ of cause. Therefore, work-up beyond the classic resting tests are likely needed. As the use of CPET increases in the clinical setting, providers should receive appropriate training to understand the role of CPET in disease detection and management.

Management considerations

In adolescents with strong family histories of CAD, initial screening for cardiac dysfunction using CPET with simultaneous measures of hs-CRP has potential to provide valuable information on the cardiovascular status and prognosis for early-age CAD risk. At-risk adolescents with abnormal CPET responses and elevated hs-CRP should receive a structured management process, as it may indicate early asymptomatic cardiac dysfunction in the presence of a proinflammatory state. Inflammation has a well-established connection with atherosclerosis development in adults, further underscoring the importance of addressing these findings in a timely and appropriate manner. When abnormal CPET responses are revealed, peak $\dot{V}O_2$ and O_2 pulse (stroke volume) as percent of predicted values may be used to assess to what extent the dysfunction is affecting health status. In general, peak $\dot{V}O_2$ and O_2 pulse in the range of 70%–84% of predicted is classified as a mild cardiopulmonary impairment. However, if peak $\dot{V}O_2$ and O_2 pulse are moderately to severely affected (<70% of predicted), a referral to a pediatric cardiologist could be considered for further assessment and treatment as needed. Serial CPET testing can be utilized to assess the effectiveness of the intervention with the goal of improving peak $\dot{V}O_2$ and O_2 pulse compared to the initial CPET result. Even if a definitive diagnosis cannot be reached after a thorough clinical evaluation, an abnormal CPET result should not be ignored as it may be an early sign of an evolving disease process. Lifestyle interventions utilizing structured diet and individualized exercise prescriptions to target modifiable cardiovascular risk factors may prove to reduce the inflammatory environment and has the potential to normalize the cardiac dysfunction if the driver of the dysfunction is in a modifiable state. Serial CPET testing may help clinicians determine the optimum interval for further workup. Information gained from CPET may be a valuable tool for preventive medicine and should be made more accessible for asymptomatic adolescents who have an increased risk for cardiovascular disease. Collaborating with clinical exercise physiologists with experience in CPET testing and interpretation can optimize clinical workflow, and also underscores the important role of

exercise physiology in healthcare. Currently these results, since from a unique test, cannot be effectively applied in a universal way due to barriers previously mentioned. However, we urge clinicians and policy makers not to underestimate the risk and consequences of early-age CAD. We call for studies aiming for a better understanding of early-age CAD with a particular focus on investigation of effective early detection testing and diagnoses in at-risk adolescents to inform treatment and reduce major adverse cardiac event risk.

Conclusion

Current resting tests and measures are often ineffective at detecting subtle cardiopulmonary abnormalities and cannot detect exercise-induced abnormalities. A detailed assessment of key CPET slopes may enhance sensitivity in detecting abnormalities in asymptomatic at-risk individuals such as the adolescent highlighted in this case report. Serial CPET measures might be important to perform in adolescents with strong family histories of CAD, especially early-age CAD. Research in this at-risk population should strive to better define the clinical role of CPET in the evaluation of cardiac dysfunction for the purpose of improving preventive healthcare. As the use of CPET grows, so will the need to improve healthcare practices and education to incorporate the pathophysiology that CPET may reveal in asymptomatic adolescents at-risk for cardiovascular events.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Institutional Review Board at the University of Arkansas for Medical Sciences. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

TE: conceived and wrote the manuscript. ET, KL, and EB: reviewed and revised the manuscript. All authors contributed to the article and approved the submitted version.

Acknowledgments

The authors thank the Physical Activity and Clinical Research cores at the Arkansas Children's Nutrition Center. Special thanks to Colton Morrison, BS, for support with slopes template and Clark Sims, PhD, for support with graphs. The original study (parent study) was supported by the USDAARS Project 6026-51000-012-06S.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Chaudhry S, Kumar N, Behbahani H, Bagai A, Singh BK, Menasco N, et al. Abnormal heart-rate response during cardiopulmonary exercise testing identifies cardiac dysfunction in symptomatic patients with non-obstructive coronary artery disease. *Int J Cardiol.* (2017) 228:114–21. doi: 10.1016/j.ijcard.2016.11.235

2. Van De Sande DAJP, Schoots T, Hoogsteen J, Doevendans PA, Kemps HMC. O_2 pulse patterns in male master athletes with normal and abnormal exercise tests. *Med Sci Sports Exerc.* (2019) 51(1):12–8. doi: 10.1249/mss.0000000000001772

3. Wasserman K, Hansen JE, Sue DY, Stringer WW, Sietsema KE, Sun XG. *Priniciples of exercise testing and interpretation*. 5th ed Philadelphia, PA: Lippincott Williams and Wilkins (2012).

4. James FW, Kaplan S, Glueck CJ, Tsay JY, Knight MJ, Sarwar CJ. Responses of normal children and young adults to controlled bicycle exercise. *Circulation.* (1980) 61(5):902–12. doi: 10.1161/01.cir.61.5.902

5. Schlebusch H, Liappis N, Kalina E, Klein C. High sensitive CRP and creatinine: reference intervals from infancy to childhood. *Laboratoriums Medizin.* (2002) 26(5–6):341–6. doi: 10.1046/j.1439-0477.2002.02071.x

6. Smith DL, Graham EL, Douglas JA, Jack K, Conner MJ, Arena R, et al. Subclinical cardiac dysfunction is associated with reduced cardiorespiratory fitness and cardiometabolic risk factors in firefighters. *Am J Med.* (2022) 135(6):752–760.e3. doi: 10.1016/j.amjmed.2021.12.025

7. Yoshida S, Adachi H, Murata M, Tomono J, Oshima S, Kurabayashi M. Importance of compensatory heart rate increase during myocardial ischemia to preserve appropriate oxygen kinetics. *J Cardiol.* (2017) 70(3):250–4. doi: 10.1016/j.jjcc.2016.11.010

8. Agostoni P, Wasserman K, Perego GB. Oxygen transport to muscle during exercise in chronic congestive heart failure secondary to idiopathic dilated cardiomyopathy. *Am J Cardiol.* (1997) 79(8):1120–4. doi: 10.1016/s0002-9149(97)00061-1

9. Belardinelli R, Lacalaprice F, Carle F. Exercise-induced myocardial ischaemia detected by cardiopulmonary exercise testing. *Eur Heart J.* (2003) 24(14):1304–13. doi: 10.1016/s0195-668x(03)00210-0

10. Belardinelli R, Lacalaprice F, Tiano L, Muçai A, Perna GP. Cardiopulmonary exercise testing is more accurate than ECG-stress testing in diagnosing myocardial ischemia in subjects with chest pain. *Int J Cardiol.* (2014) 174(2):337–42. doi: 10.1016/j.ijcard.2014.04.102

11. Chaudhry S, Arena RA, Hansen JE, Lewis GD, Myers JN, Sperling LS, et al. The utility of cardiopulmonary exercise testing to detect and track early-stage ischemic heart disease. *Mayo Clin Proc*. (2010) 85(10):928–32. doi: 10.4065/mcp.2010.0183

12. Yeh ETH. High-sensitivity C-reactive protein as a risk assessment tool for cardiovascular disease. *Clin Cardiol*. (2005) 28(9):408–12. doi: 10.1002/clc.4960280905

13. Sachdeva A, Cannon CP, Deedwania PC, Labresh KA, Smith SC Jr, Dai D, et al. Lipid levels in patients hospitalized with coronary artery disease: an analysis of 136,905 hospitalizations in get with the guidelines. *Am Heart J*. (2009) 157 (1):111–117.e2. doi: 10.1016/j.ahj.2008.08.010

14. Agostinis-Sobrinho C, Rosário R, Santos R, Norkiene S, Mota J, Rauckienė-Michaelsson A, et al. Higher cardiorespiratory fitness levels may attenuate the detrimental association between weight Status, metabolic phenotype and C-reactive protein in adolescents—a multi-cohort study. *Nutrients*. (2020) 12(5):1461. doi: 10.3390/nu12051461

15. Almeida VR, Ostolin TLVDP, Gonze BB, de Almeida FR, Romiti M, Arantes RL, et al. Early flattening of the oxygen pulse during the cardiopulmonary exercise test in asymptomatic adults and its association with cardiovascular risk factors. *Int J Cardiol*. (2022) 367:65–73. doi: 10.1016/j.ijcard.2022.08.011

16. Grzyb A, Domagalska-Szopa M, Siwiec A, Kwiecień-Czerwieniec I, Szopa A. Cardiopulmonary capacity in overweight and obese children and adolescents: a cross-sectional study. *Front Physiol*. (2021) 12:671827. doi: 10.3389/fphys.2021.671827

frontiers | Frontiers in Public Health

TYPE Original Research
PUBLISHED 12 April 2023
DOI 10.3389/fpubh.2023.1142414

OPEN ACCESS

EDITED BY
Shikai Yu,
Tongji University, China

REVIEWED BY
Xiaohui Li,
Children's Hospital of Capital Institute of Pediatrics, China
Iman H. Kamel,
National Research Center, Egypt

*CORRESPONDENCE
Chien-Ning Hsu
✉ chien_ning_hsu@hotmail.com

SPECIALTY SECTION
This article was submitted to Children and Health, a section of the journal Frontiers in Public Health

RECEIVED 11 January 2023
ACCEPTED 28 March 2023
PUBLISHED 12 April 2023

CITATION
Li L-C, Tain Y-L, Kuo H-C and Hsu C-N (2023) Cardiovascular diseases morbidity and mortality among children, adolescents and young adults with dialysis therapy.
Front. Public Health 11:1142414.
doi: 10.3389/fpubh.2023.1142414

Cardiovascular diseases morbidity and mortality among children, adolescents and young adults with dialysis therapy

Lung-Chih Li[1,2], You-Lin Tain[3], Hsiao-Ching Kuo[4] and Chien-Ning Hsu[4,5]*

[1]Division of Nephrology, Department of Internal Medicine, Kaohsiung Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Kaohsiung, Taiwan, [2]Institute for Translational Research in Biomedicine, Kaohsiung Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Kaohsiung, Taiwan, [3]Division of Pediatric Nephrology, Kaohsiung Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Kaohsiung, Taiwan, [4]Department of Pharmacy, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan, [5]School of Pharmacy, Kaohsiung Medical University, Kaohsiung, Taiwan

Background: The age-specific burden of cardiovascular disease (CVD) and mortality in pediatric and young adult patients with end-stage kidney disease (ESKD) remains unclear. We aimed to examine the prevalence and incidence of CVD and all-cause mortality in children and adolescents compared with adults with dialysis in Taiwan.

Methods: This retrospective observational cohort study comprised 3,910 patients with more than 2 time point receipts of dialysis therapy in a year, including 156 aged <12 years (children), 250 aged 13–20 years (adolescents), 1,036 aged 21–30 years (young adults) and 2,468 aged 31–40 years (adults) in a large healthcare delivery system in Taiwan (2003–2017). Age groups were classified by the date of first receipt of dialysis therapy. The outcomes include the composite of CVD events and any cause of death. Death-censored Cox proportional hazard models were used to evaluate the composite outcome risk of CVD in the four age groups.

Results: Among patients receiving dialysis treatment, the risk of composite CVD events [HR, 1.63 (1.22–2.19)] and mortality [HR, 1.76 (1.38–2.25)] was greater in children than the dialysis initiated in older patients. Non-atherosclerotic CVD was more prevalent, especially in younger patients, within the first 6 months after the initiation of dialysis. After 6 months of initial dialysis, the risk of atherosclerotic CVD was higher in adults than those for adolescents and children. The magnitude of CVD risk in adolescents who initiated dialysis therapy was higher in females [HR, 2.08 (1.50–2.88)] than in males [HR, 0.75 (0.52–1.10)].

Conclusion: Younger patients undergoing chronic dialysis with a higher risk of CVD events than older patients are associated with a faster onset of non-atherosclerotic CVD and a higher risk of both CVD- and non-CVD-related mortality.

KEYWORDS

cardiovascular disease, end-stage kidney disease, dialysis, children, adolescents, young adults

Introduction

The increasing size of the population of patients with chronic kidney disease (CKD) and CKD-related morbidity and mortality is a great burden to health systems worldwide. Cardiovascular disease (CVD) is a leading cause of death among patients with end-stage kidney disease (ESKD) (1); however, the risk is compounded by additional factors. In adults aged ≥45 years, 87% have CVD reported at the time of ESKD onset, and approximately 50% of deaths are attributed to CVD in the 2016 United States Renal Data System (USRDS). In pediatric patients with ESKD, mortality is attributed to CVD in 23% of children in the United States and up to 50% in other countries (2, 3). However, the spectrum of CVD in children and young adults (aged <40 years) with ESKD remains unclear in Taiwan and worldwide.

Many CVD risk factors, including traditional risk factors (age, lifestyle, left ventricular hypertrophy, dyslipidemia, hypertension, and diabetes mellitus) and novel risk factors for CVD such as inflammation, endothelial dysfunction, sympathetic overactivation, oxidative stress, vascular calcification, and volume overload, are prevalent in patients with CKD (4, 5). In fact, these cardiovascular risks can increase very early in the progression of CKD at an estimated glomerular filtration rate of approximately 75 ml/min and increase continuously with declining kidney function (6). Patients undergoing chronic hemodialysis have multiple comorbidities and many metabolic disorders, causing cardiovascular comorbidity, mortality, including early mortality.

Studies have provided global estimates of the effects of multiple modifiable risk factors of CVD and mortality. Although data linking risk factors with CVD and mortality have mostly been derived from adult patients older than 40 years in the Annual Report on Kidney Disease in Taiwan (7), the impact of modifiable and non-modifiable risk factors on CVD and mortality may vary by age group. The current study aimed to examine and compare the prevalence and incidence of CVD and all-cause mortality among patients starting dialysis for ESKD of different age groups, including children, adolescents, young adults, and adults. Additionally, the risk profile differences in these groups for all-cause mortality and CVD incidence were compared.

Methods

Study design

The cohort study was identified based on all patients aged 0–40 years who received dialysis for ESKD between January 1, 2003, and December 31, 2017. Based on the age at the first receipt of dialysis for ESKD, the study cohort was categorized into children (aged <12 years), adolescents (13–20 years), young adults (21–30 years), and adults (31–40 years). Ascertainment of dialysis for ESKD was based on the billing codes for dialysis (Supplementary Table 1). Only patients who had received at least two dialysis modules in a year were included in the study cohort. The index date was defined as the earliest date of receiving dialysis. To identify the incidence of CVD, patients diagnosed with congenital heart disease were excluded (Supplementary Figure 1).

Data sources

Electronic health record data for this dialysis cohort were obtained from the largest healthcare delivery system in Taiwan, the Chang Gung Memorial Hospital network. This network, with a total of 9,584 beds, delivered approximately 11% of the health services reimbursed by Taiwan's National Health Insurance program in 2018, including over 9.1 million emergency and outpatient department visits and 300,000 hospital admissions (7, 8). These contain data regarding patient diagnoses, demographic characteristics, healthcare procedures, laboratory results, prescriptions and dispensing (9). This study was approved by the institutional review board of the Chang Gung Medical Foundation in Taipei, Taiwan (permit number, 202001176B0).

Outcomes

CVD was defined using the International Classification of Diseases, Ninth or Tenth Revision (ICD 9/10) for hospitalization discharge codes as defined in the USRDS (Supplementary Table 1) (10). Baseline and incident CVD were defined as at least one of the following conditions: atherosclerotic CVD (myocardial infarction, atherosclerosis, coronary artery bypass graft, percutaneous transluminal coronary angioplasty), non-atherosclerotic CVD (cardiovascular/circulatory disease, heart failure, atrial fibrillation, cerebrovascular accident/transient ischemic attack, stroke, artery disease), or other CVD (other heart disease and valve disease) in inpatient or outpatient settings. Information on hospitalization death was based on discharge diagnosis (11).

Variables

The algorithm of one inpatient or outpatient specified diagnosis code before the index date was used to determine the presence of CKD etiology, including congenital anomalies of the kidney and urinary tract (CAKUT), non-CAKUT CKD (glomerular disease, and other CKD), and baseline conditions commonly associated with CKD as risk factors (hypertension, hyperlipidemia), co-occurrence, or consequences of the CVD conditions (Supplementary Table S1). Congenital anomalies (without CAKUT and congenital heart disease) were assessed in all the patients. Pediatric Medical Complexity Algorithm with three categories: no chronic disease, non-complex chronic disease, and complex chronic disease was employed to examine the baseline medical complexity of pediatric patients with kidney replacement therapy (12), and Charlson Comorbid Index was employed for adult patients (13).

Statistical analysis

The time from the index date to the first occurrence of the composite outcome of CVD, censored at the date of last follow-up

10.3389/fpubh.2023.1142414

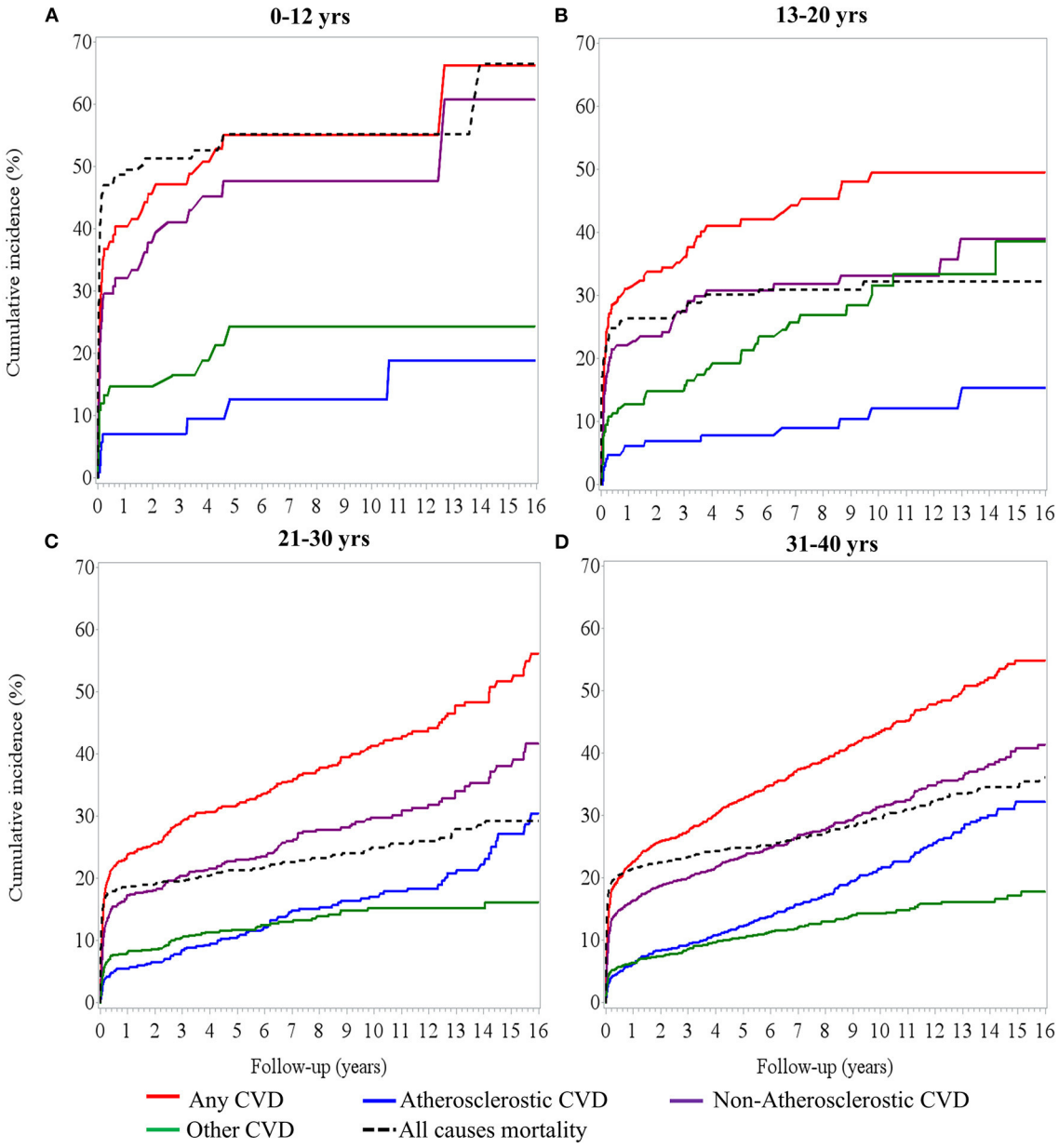


FIGURE 1
Cumulative incidence of cardiovascular event and mortality over time in **(A)** 0–12 years of age, **(B)** 13–20 years of age, **(C)** 21–30 years, and **(D)** 31–40 years of age with dialysis treatment.

or the latest date in the dataset (December 31st, 2017), was described using the cumulative incidence function method with hospitalization death treated as a censored event.

Sensitivity analyses were performed to determine the timing of cardiovascular event onset. First, the rates of the composite event of CVD were calculated separately for times at risk after the index date (first receipt of dialysis) and after the index date plus 6 months for any CVD event of interest in the follow-up period. Second, stratified analyses were performed by sex, congenital anomaly, and CKD type in different age groups.

Results

Characteristics of the study cohort

The analytic cohort comprised 3,910 patients with dialysis aged 0–40 years, including 156 aged ≤12 years, 250 aged 13–20 years, 1,036 aged 21–30 years and 2,468 aged 31–40 years (Supplementary Figure 1). A total of 825,259 patient-dialysis receipts were analyzed for the study cohort, including 1,134 (29%) who ever had at least two modalities of dialysis and 2,776 who received single dialysis modality: 2,652 patients with hemodialysis,

TABLE 1 Study cohort characteristics by age group.

	Overall (n = 3,910)		Age group								*P*-value*
			0–12 years (n = 156)		13–20 years (n = 250)		21–30 years (n = 1,036)		31–40 years (n = 2,468)		
Sex, *n* (%)											0.0016
Female	1,601	(40.95)	72	(46.15)	114	(45.60)	462	(44.59)	953	(38.61)	
Male	2,309	(59.05)	84	(53.85)	136	(54.40)	574	(55.41)	1515	(61.39)	
CKD, *n* (%)											<0.0001
CAKUT	89	(2.28)	5	(3.21)	14	(5.60)	26	(2.51)	44	(1.78)	
Non-CAKUT	2,339	(59.82)	22	(14.10)	122	(48.80)	638	(61.58)	1557	(63.09)	
Glomerular disease	1,678	(42.92)	22	(14.10)	104	(41.60)	474	(45.75)	1078	(43.68)	
Non-CKD	1,482	(37.90)	129	(82.69)	114	(45.60)	372	(35.91)	867	(35.13)	
AKI diagnosis, *n* (%)	516	(13.20)	17	(10.90)	47	(18.80)	145	(14.00)	307	(12.44)	0.0246
Baseline CVD, *n* (%)	294	(7.52)	13	(8.33)	29	(11.60)	65	(6.27)	187	(7.58)	0.0375
Atherosclerotic CVD	93	(2.38)	2	(1.28)	9	(3.60)	18	(1.74)	64	(2.59)	0.1920
Non-atherosclerotic CVD	176	(4.50)	10	(6.41)	15	(6.00)	38	(3.67)	113	(4.58)	0.2273
Cardiovascular/circulatory disease	10	(0.26)	0	(0.00)	2	(0.80)	2	(0.19)	6	(0.24)	0.3236
Heart failure	95	(2.43)	1	(0.64)	4	(1.60)	24	(2.32)	66	(2.67)	0.3195
Atrial fibrillation/flutter	31	(0.79)	1	(0.64)	4	(1.60)	7	(0.68)	19	(0.77)	0.5099
Cerebrovascular/artery disease	65	(1.66)	8	(5.13)	6	(2.40)	11	(1.06)	40	(1.62)	0.0022
Other CVD	111	(2.84)	1	(0.64)	17	(6.80)	28	(2.70)	65	(2.63)	0.0006
Hypertension, *n* (%)	1,443	(36.91)	10	(6.41)	69	(27.60)	367	(35.42)	997	(40.40)	<.0001
Hyperlipidemia, *n* (%)	545	(13.94)	5	(3.21)	17	(6.80)	135	(13.03)	388	(15.72)	<.0001
In-hospital mortality event, *n* (%)	1,081	(27.65)	85	(54.49)	80	(32)	242	(23.36)	674	(27.31)	<.0001

Data are presented as counts and count (percentages). Atherosclerotic CVD: coronary artery disease (CAD) and infarction; non-atherosclerotic CVD: cardiovascular/circulatory, (congestive) heart failure, atrial fibrillation, cerebrovascular disease, artery disease; other CVD: other heart disease, valve disease.

*P-values are based on the chi-square test for categorical variables among age groups.

CKD, chronic kidney disease; CAKUT, congenital anomalies of the kidney and urinary tract; CVD, cardiovascular disease.

26 patients with peritoneal dialysis and 98 patients received continuous renal replacement therapy.

The patient characteristics are shown in Table 1. Glomerular disease (42.92%) was the most common cause of CKD and the proportion was higher in patients aged >12 years than in younger children (14.1%). Patients with hydronephrosis and those who did not meet with a definition of CKD before the index date (37.9%) were classified into the non-CKD group. Hypertension (36.91%) and hyperlipidemia (13.94%) were commonly present at baseline, and the proportion was higher in older patients. Other common comorbid conditions, such as diabetes (27.27%) and liver disease (20.62%) were common in the 31–40 years group, whereas neurological disorders (19.87%) were prevalent in the 0–12 years group, and immunological (20.8%), gastrointestinal, and metabolic (19.6%) disorders were common in the 13–20 years group (Supplementary Table 2).

Onset and cardiovascular disease risk

Overall, 7.52% of the patients had a form of specific CVD at baseline, and non-atherosclerotic CVD was more prevalent (4.5%) than other forms of CVD (Table 1). The rate of composite CVD events was 31.83% in the incident cohort (n = 3,616) after the initiation date of dialysis during the study period. A high rate of CVD was found in the first 6 months of follow-up (18.47%), and younger patients had a higher risk than older patients (Table 2).

Figure 1 illustrates the patterns of cumulative incidence of composite and individual types of CVD over 16 years of follow-up. The children group (0–12 years) had the highest rate of composite CVD events, especially within 6 months of dialysis (up to 40%). Non-atherosclerotic CVD, including cerebrovascular disease, heart failure, cerebrovascular disease, and arrhythmia,

TABLE 2 Incidence rate of cardiovascular disease and mortality rate by age group.

Outcome event	Overall (n = 3,616)		Age group								P-value*
			0–12 years (n = 143)		13–20 years (n = 221)		21–30 years (n = 971)		31–40 years (n = 2,281)		
Within the first 6 months follow-up											
Any CVD, n (%)	668	(18.47)	43	(30.07)	52	(23.53)	183	(18.85)	390	(17.1)	0.0002
Atherosclerotic CVD	146	(4.04)	6	(4.2)	8	(3.62)	39	(4.02)	93	(4.08)	0.9895
Non-atherosclerotic CVD	487	(13.47)	33	(23.08)	39	(17.65)	128	(13.18)	287	(12.58)	0.001
Cardiovascular/ circulatory disease	27	(0.75)	2	(1.4)	0		8	(0.82)	17	(0.75)	0.4644
Heart failure	255	(7.05)	10	(6.99)	15	(6.79)	72	(7.42)	158	(6.93)	0.9648
Atrial fibrillation/ flutter	99	(2.74)	8	(5.59)	6	(2.71)	27	(2.78)	58	(2.54)	0.1939
Cerebrovascular/ artery disease	158	(4.37)	17	(11.89)	24	(10.86)	33	(3.4)	84	(3.68)	<.0001
Other CVD	206	(5.70)	15	(10.49)	20	(9.05)	62	(6.39)	109	(4.78)	0.0017
From the first 6 months to end-of-follow up											
Any CVD, n (%)	483	(13.36)	12	(8.39)	24	(10.86)	126	(12.98)	321	(14.07)	0.1467
Atherosclerotic CVD	286	(7.91)	3	(2.10)	8	(3.62)	73	(7.52)	202	(8.86)	0.0016
Non-atherosclerotic CVD	339	(9.38)	12	(8.39)	16	(7.24)	90	(9.27)	221	(9.69)	0.6536
Cardiovascular/ circulatory disease	40	(1.11)	3	(2.10)	2	(0.90)	7	(0.72)	28	(1.23)	0.3929
Heart failure	188	(5.20)	5	(3.50)	15	(6.79)	51	(5.25)	117	(5.13)	0.5724
Atrial fibrillation/flutter	92	(2.54)	1	(0.70)	5	(2.26)	23	(2.37)	63	(2.76)	0.4592
Cerebrovascular/artery disease	138	(3.82)	6	(4.20)	5	(2.26)	35	(3.60)	92	(4.03)	0.5890
Other CVD	166	(4.59)	4	(2.80)	22	(9.95)	37	(3.81)	103	(4.52)	0.0007
Over the follow-up period											
Any CVD, n (%)	1,151	(31.83)	55	(38.46)	76	(34.39)	309	(31.82)	711	(31.17)	0.2591

Patients who were diagnosed with CVD before or on the date of dialysis were excluded from the incidence of composite CVD events (n = 294).
Data are presented as counts and count (percentages). Atherosclerotic CVD: coronary artery disease (CAD) and infarction; non-atherosclerotic CVD: cardiovascular/circulatory disease, (congestive) heart failure, atrial fibrillation, cerebrovascular disease, artery disease; other CVD: other heart disease and valve disease. *P-values are based on the chi-square test for categorical variables among age groups.

are the leading causes of CVD in children and remained for 16 years of follow-up (Figure 1A). The adolescent group (13–20 years) had the second highest rate of CVD (up to 30%). Despite that non-atherosclerotic CVD was still the most prevalent CVD, the incidence of other CVD, including valvular heart disease, increased progressively and became similar to the incidence of non-atherosclerotic CVD after 10 years of dialysis (Figure 1B). In young adult and adult group, non-atherosclerotic CVD remained the dominant cause of CVD; however, atherosclerotic CVD, such as coronary artery disease or myocardial infarction, increased progressively to up to 30% in these groups (Figures 1C, D).

Compared to the 31–40 years group, patients aged 0–12 years had a highest risk of developing CVD [aHR, 1.63 (1.22–2.19)], an additional 77% risk for non-atherosclerotic CVD [aHR, 1.77 (1.28–2.45)], and a 2.43-fold risk for other forms of CVD [aHR, 2.43 (1.47–4.01)] (Supplementary Figure S2). Considering the onset of CVD after 6 months of dialysis therapy in the sensitivity analysis, the rate of composite events of CVD was 16.38% (n = 483) in the remaining 2,948 patients at risk. The risk of composite events of CVD changed across age groups, but statistical power was insufficient to support the increased risk in those aged 0–12 years [aHR, 1.63 (0.89–2.98)] and 13–20 years [aHR, 1.47 (0.95–2.28)], compared with the 31–40 years adult group. However, young adults (21–30 years) had a significantly lower risk [aHR, 0.79 (0.64–0.98)] than the 31–40 years patient group (Supplementary Figure S2, secondary cohort analysis). These results suggest that a high rate of composited CVD events, particularly for non-atherosclerotic CVD (i.e., artery disease and other types of CVD), had faster deterioration in pediatric patients undergoing dialysis therapy in the first 6 months of follow-up.

10.3389/fpubh.2023.1142414

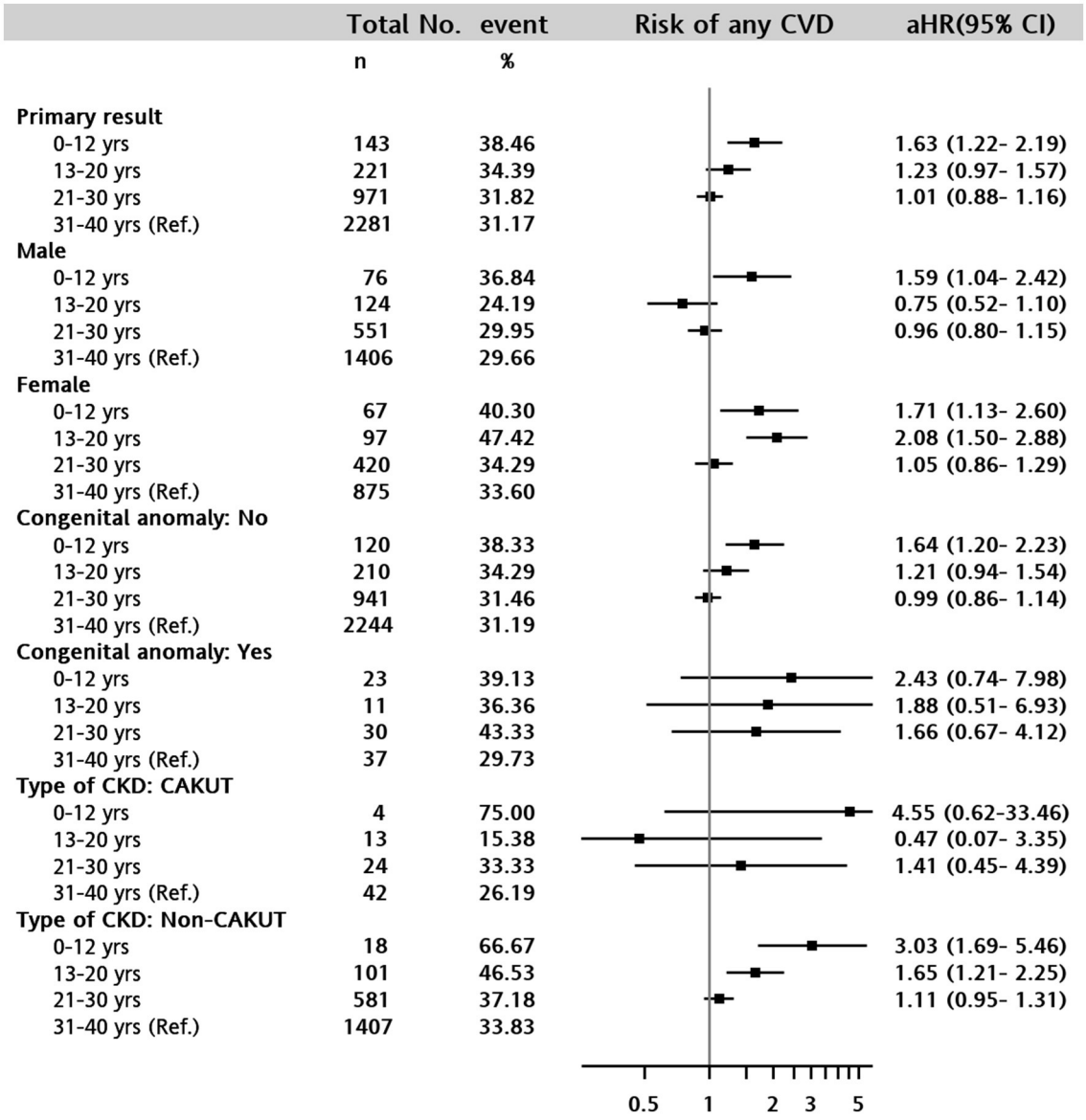


FIGURE 2
Forest plot of adjusted hazard ratio for the composite cardiovascular disease event in 0–12 years, 13–20 years, 21–30 years, and 31–40 years (reference) of age groups. The following covariates were adjusted for in the death-censored Cox proportional hazards model: Sex, type of CKD (CAKUT, non-CAKUT, and non- CKD), any congenital anomalies, baseline comorbid conditions of liver disease, severe liver disease, diabetes with and without complications, cancer, metastatic cancer, hypertension, hyperlipidemia, and AKI diagnosis.

Risk of CVD modifiers: Sex, congenital anomaly, type of CKD

Stratified analyses were performed to examine the individual impact of sex, congenital anomalies, and etiology of CKD on the association between ESKD and CVD. Girls showed a higher risk than boys in the age <20 years groups, particularly adolescents [aHR, 2.08 (1.5–2.88)] (Figure 2).

In the stratum without any congenital anomaly, patients in the 0–12 years group had a 1.64-fold risk of composited CVD [aHR, 1.64 (1.2–2.23)] and a 1.21-fold in the 13–20 years group [aHR, 1.21 (0.94–1.54)], compared to patients in the 31–40 years group. The statistical power was insufficient to support the impact of any congenital anomaly on age-associated CVD risks (Figure 2). In addition, non-CAKUT CKD enhanced the association between children (0–12 years) and adolescents (13–20 years) and the risk of CVD [aHR, 3.03 (1.69–5.46) and 1.65 (1.21–2.25), respectively] compared with adults in the 31–40 years group (Figure 2).

All-cause mortality

The overall in-hospital mortality rate was 27.65% ($n = 1,081$) in the entire study cohort. The association between all-cause mortality and age was significantly higher in the 0–12 years of age group

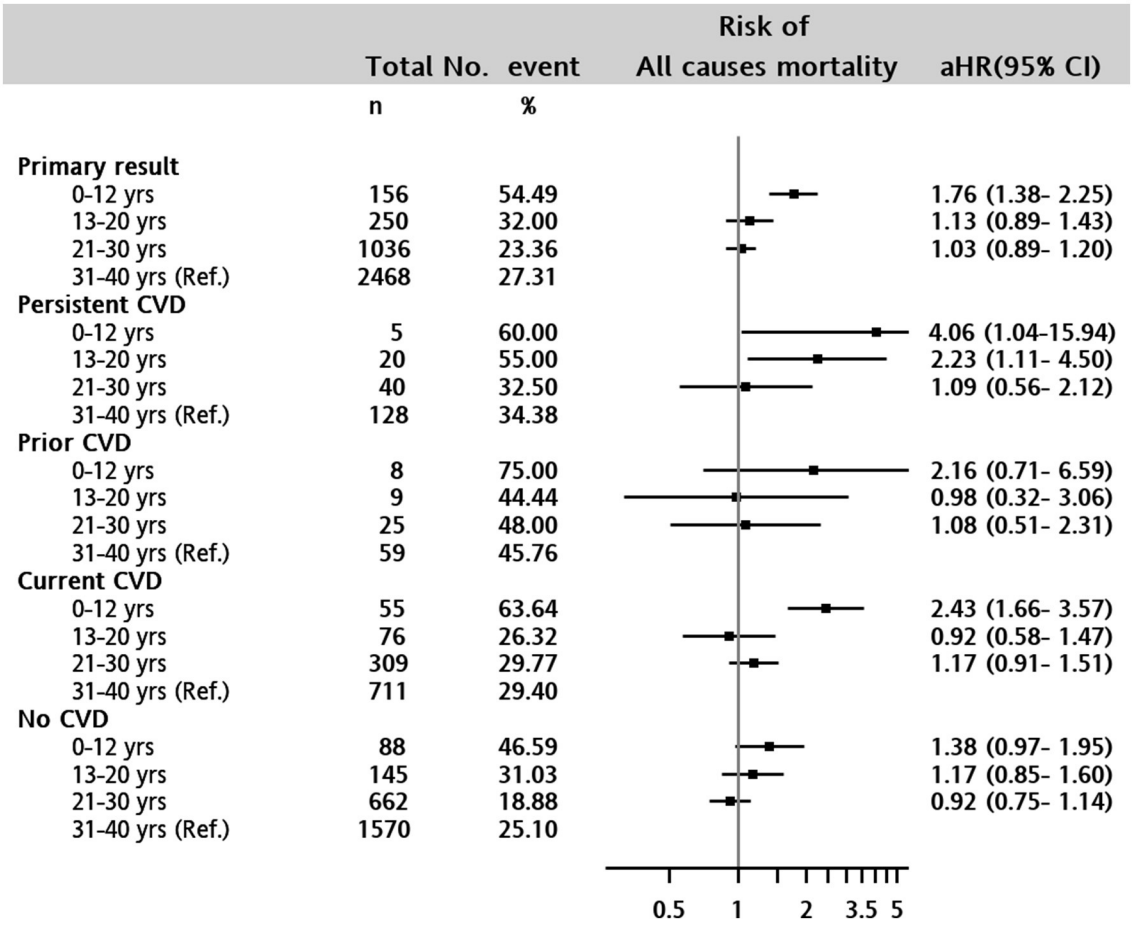


FIGURE 3
Forest plot of adjusted hazard ratio for in-hospital mortality in 0–12 years, 13–20 years, 21–30 years, and 31–40 years (reference) of age groups. Persistent CVD: patients with any CVD both baseline and during the following covariates were adjusted for in the Cox proportional hazards model: Sex, type of CKD (CAKUT, non-CAKUT, and non-CKD), any congenital anomalies, baseline comorbid conditions of liver disease, severe liver disease, diabetes with and without complications, cancer, metastatic cancer, hypertension, hyperlipidemia, AKI diagnosis, and CVD at baseline and any time before death event.

[aHR, 1.76 (1.38–2.25)] and 13–20 years of age group [aHR, 1.13 (0.89–1.43)] than in the adult group (Figure 3) after controlling for baseline characteristics and presence of CVD.

Of the 1,081 patients with a hospital death event, 34.69% ($n = 375$) had a CVD diagnosis at discharge (7.03% with atherosclerotic and 28.31% with non-atherosclerotic CVD). The rate of any CVD diagnosis was higher in children aged <12 years ($n = 39$, 45.88%), followed by 13–20 years ($n = 27$, 33.75%), 21–30 years ($n = 94$, 38.84%) and 31–40 years ($n = 215$, 31.9%). Visually, the all-cause mortality risk was close to that of non-atherosclerotic CVD in the 13–20 years and 21–30 years age groups over time (Figure 1). Figure 4 shows that (congestive) heart failure was the most common diagnosis, accompanied by in-hospital mortality, and was independently associated with age. However, arterial disease and other CVD were more prevalent in children and adolescents than in adults, details of CVD at discharge are listed in Supplementary Table 3. Other common disease conditions were liver failure and related diseases, acute kidney injury, sepsis, pneumonia, kidney failure, gastrointestinal bleeding, fluid overload, and electrolyte imbalance, which were prevalent at hospital discharge among patients with in-hospital death events.

Discussion

In the current study, we compared the morbidity of CVD onset in four age groups when dialysis therapy was initiated. Dialysis treatment initiated in pediatric patients carries a greater risk of mortality and CVD than that in adults. In general, non-atherosclerotic CVD was more prevalent, especially in younger patients, within the first 6 months after the initiation of dialysis. After 6 months of initial dialysis, the risk of atherosclerotic CVD was higher in adults than that in adolescents and children. Girls showed a higher risk of CVD than boys in the 13–20 years age group.

Previous reports have shown that CVD-related mortality can be up to 500 times and even one thousand times higher than in age-matched young adults (10) and children (14), respectively. Our

10.3389/fpubh.2023.1142414

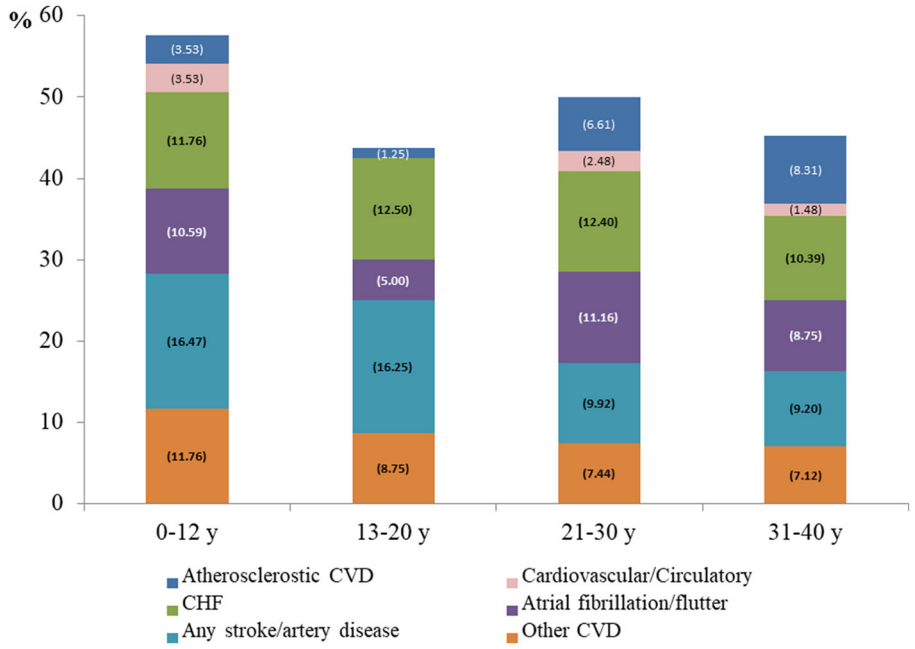


FIGURE 4
Discharge diagnosis of cardiovascular disease among patients with in-hospital mortality Atherosclerotic CVD, coronary artery disease and infarction; Non-atherosclerotic CVD, cardiovascular/circulatory, (congestive) heart failure, atrial fibrillation/flutter, any stroke, artery disease; other CVD, other heart disease and valve disease.

results supported that pediatric patients had a higher mortality rate than older patients. Furthermore, it is critical to delineate the etiologies of CVD in different age groups at the time of dialysis initiation. In the current study, children had the highest rate of all-cause mortality and composite CVD events especially at the initiation (within 6 month) of dialysis. Non-atherosclerotic CVD, such as heart failure or arrhythmia (atrial fibrillation/flutter), are the leading causes of CVD and the most prevalent diagnosis accompanying death events in children. After 6 months, the incidence of CVD has become less common in children than that in adolescents and adults, which is consistent with a previous publication from USRDS (10). In another study from USRDS 2006–2008, the causes of cardiac death in children 0–19 years of age with CKD were cardiac arrest/arrhythmia, followed by cerebrovascular diseases and heart failure (15). Unlike older adults, children generally have neither diabetes nor symptomatic atherosclerosis at the time of CKD diagnosis. Previous studies have shown that left ventricular (LV) hypertrophy and LV dysfunction occur early in CKD, and heart failure and atrial fibrillation may appear early after dialysis initiation (16, 17). CV abnormalities develop early and progress during the course of CKD, eventually leading to high mortality and CV events at the beginning of ESKD in children.

In addition to CVD, underlying diseases may also contribute to the high mortality in children. Of note, all-cause mortality rate was higher than composite CVD in the first 3 years and then became close to all CVD afterwards (Figure 1A). In contrast, a recent study using data from the USRDS (10) demonstrated a lower CVD incidence in children than in young adults. This discrepancy may be explained because our data originated from medical centers, where patients tended to have more comorbidities, such as liver diseases and cancer, which may also be responsible for the high mortality observed in the children. Moreover, although CAKUT CKD is prevalent in childhood ESKD (18), the role of CAKUT in CVD remains unclear. Our study showed that CAKUT played a minor role compared to other CKDs in the progression of CVD. Other non-CAKUT related CKDs contribute more to CVD development in children.

In the group aged 13–20 years, the incidence of CVD was approximately 23.5% at the beginning of dialysis therapy, which is lower than that in children but higher than that in adults. Non-atherosclerotic CVD is the most prevalent CVD. However, the incidence of other CVD, including other heart and valve diseases, increased progressively and catch up non-atherosclerotic CVD after 10 years of dialysis. Notably, girls showed a higher risk of CVD than boys, particularly in this age group. The etiology of CKD in this group is more glomerular disease (19), associated with the highest connective tissue disease, immunological, neurological, and pulmonary diseases. Autoimmune or connective tissue disease-related glomerulonephropathy, such as IgA nephropathy (8) or systemic lupus erythematosus (20), contributes to CKD in adolescents, especially in girls. Inflammation plays an important role in autoimmune and systemic-related CKD and CVD. The treatment of underlying diseases and screening for underlying CVD may help control mortality in adolescents.

In young adults and adults undergoing dialysis, non-atherosclerotic CVD remains the dominant cause of CVD. However, atherosclerotic CVD, such as coronary artery disease or myocardial infarction, increased progressively to up to 30% in these groups. The most common diseases associated with atherosclerotic CVD are diabetes, hypertension, and hyperlipidemia, which

represent the traditional risks of CVD in the general population (21). Moreover, other CKD-related factors such as uremic toxins, vascular calcification, protein-energy waste, systemic inflammation, and oxidative stress are also important risk factors for CVD, and the influence of these factors may outweigh the traditional factors in advanced CKD or even post-dialysis (21–24). Unlike children, the incidence rates of CVD and mortality in the group aged 20–40 years were the lowest (<20%) at the beginning of ESKD but increased progressively to 50% and 30%, respectively, after more than 10 years of dialysis (Figures 1C, D). The control of traditional and non-traditional CKD-related risk factors for atherosclerotic CVD may help reduce the long-term CVD burden in young adults and adults.

The strength of the current study is the accurate quantification of the prevalence and incidence of cardiovascular events for different age groups at the time of dialysis therapy, to compare cardiovascular risk in a large dialysis cohort aged <40 years, and to explore atherosclerotic and non-atherosclerotic CVD-specific risk factors. Our findings have important implications for the assessment of cardiovascular risk in CKD patients. First, high CV events and mortality rates occur in the early stages of dialysis in children, and non-atherosclerotic CV events, such as heart failure, arrhythmia, and cerebrovascular diseases, are the main contributors to mortality. Second, as dialysis therapy proceeds, the role of atherosclerosis in CVD becomes increasingly important in young and older adults. Both traditional and CKD-related non-traditional risk factors for atherosclerotic CVD contribute to the etiology of CVD in these groups.

This study had certain limitations. First, CVD ascertainment relies on routinely collected electronic health record data in a healthcare delivery system, which may underestimate the prevalence and incidence of CVD. Second, based on the demographics of the study cohort and national health insurance program-supported healthcare system in Taiwan, our findings may not be generalizable to other countries.

Conclusion

The rates of cardiovascular morbidity and mortality were high and varied in different age groups, which remind clinicians to apply different strategies for CVD and mortality prevention in patients of different ages requiring chronic dialysis.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by the Institutional Review Board of the Chang Gung Medical Foundation in Taipei, Taiwan. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Author contributions

Research idea, study design, data analysis, and interpretation: L-CL, C-NH, and Y-LT. Data acquisition: C-NH. Statistical analysis: H-CK. Supervision or mentorship: C-NH and Y-LT. Each author contributed important intellectual content during manuscript drafting or revision and agrees to be personally accountable for the individual's own contributions and to ensure that questions pertaining to the accuracy or integrity of any portion of the work, even one in which the author was not directly involved, are appropriately investigated and resolved, including with documentation in the literature if appropriate. All authors contributed to the article and approved the submitted version.

Funding

This study was funded by Kaohsiung Chang Gung Memorial Hospital (CFRPG8K0041 to L-CL). The funder had no role in the design of the study, the interpretation of the study findings, the drafting of the manuscript, or the decision to submit the manuscript for publication.

Acknowledgments

The authors thank Mrs. Chun-Hua Liao and Ying-Jen Hsu from the Department of Management of Information Systems, Chang Gung Memorial Foundation, for their technical assistance with electronic health records acquisition and data retrieval.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2023.1142414/full#supplementary-material

References

1. Foley RN, Parfrey PS, Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic renal disease. *Am J Kidney Dis.* (1998) 32:S112–9. doi: 10.1053/ajkd.1998.v32.pm9820470

2. Groothoff JW. Long-term outcomes of children with end-stage renal disease. *Pediatr Nephrol.* (2005) 20:849–53. doi: 10.1007/s00467-005-1878-9

3. McDonald SP, Craig JC, Australian and New Zealand Paediatric Nephrology. Long-term survival of children with end-stage renal disease. *N Engl J Med.* (2004) 350:2654–62. doi: 10.1056/NEJMoa031643

4. Stenvinkel P, Carrero JJ, Axelsson J, Lindholm B, Heimburger O, Massy Z, et al. Emerging biomarkers for evaluating cardiovascular risk in the chronic kidney disease patient: how do new pieces fit into the uremic puzzle? *Clin J Am Soc Nephrol.* (2008) 3:505–21. doi: 10.2215/CJN.03670807

5. Chavers B, Schnaper HW. Risk factors for cardiovascular disease in children on maintenance dialysis. *Adv Ren Replace Ther.* (2001) 8:180–90. doi: 10.1053/jarr.2001.26355

6. Vanholder R, Massy Z, Argiles A, Spasovski G, Verbeke F, Lameire N, et al. Work, chronic kidney disease as cause of cardiovascular morbidity and mortality. *Nephrol Dial Transplant.* (2005) 20:1048–56. doi: 10.1093/ndt/gfh813

7. Hwang S-J. Annual report on kidney disease in Taiwan. *J Formosan Med Assoc.* (2022) 121:E1–E12, S1–S82.

8. Coppo R. Pediatric IgA nephropathy: clinical and therapeutic perspectives. *Semin Nephrol.* (2008) 28:18–26. doi: 10.1016/j.semnephrol.2007.10.003

9. Shao SC, Chan YY, Kao Yang YH, Lin SJ, Hung MJ, Chien RN, et al. The Chang Gung Research Database—a multi-institutional electronic medical records database for real-world epidemiological studies in Taiwan. *Pharmacoepidemiol Drug Saf.* (2019) 28:593–600. doi: 10.1002/pds.4713

10. Modi ZJ, Lu Y, Ji N, Kapke A, Selewski DT, Dietrich X, et al. Risk of cardiovascular disease and mortality in young adults with end-stage renal disease: an analysis of the US Renal Data System. *JAMA Cardiol.* (2019) 4:353–62. doi: 10.1001/jamacardio.2019.0375

11. Huang YT, Chen YJ, Chang SH, Kuo CF, Chen MH. Discharge status validation of the Chang Gung Research database in Taiwan. *Biomed J.* 45:907–13. doi: 10.1016/j.bj.2021.12.006

12. Simon TD, Cawthon ML, Stanford S, Popalisky J, Lyons D, Woodcox P, et al. Excellence on quality of care measures for children with complex needs medical complexity working, pediatric medical complexity algorithm: a new method to stratify children by medical complexity. *Pediatrics.* (2014) 133:e1647–54. doi: 10.1542/peds.2013-3875

13. Rattanasompattikul M, Feroze U, Molnar MZ, Dukkipati R, Kovesdy CP, Nissenson AR, et al. Charlson comorbidity score is a strong predictor of mortality in hemodialysis patients. *Int Urol Nephrol.* (2012) 44:1813–23. doi: 10.1007/s11255-011-0085-9

14. Parekh RS, Carroll CE, Wolfe RA, Port FK. Cardiovascular mortality in children and young adults with end-stage kidney disease. *J Pediatr.* (2002) 141:191–7. doi: 10.1067/mpd.2002.125910

15. Mitsnefes MM. Cardiovascular disease in children with chronic kidney disease. *J Am Soc Nephrol.* (2012) 23:578–85. doi: 10.1681/ASN.2011111115

16. Mitsnefes MM, Kimball TR, Witt SA, Glascock BJ, Khoury PR, Daniels SR, et al. Left ventricular mass and systolic performance in pediatric patients with chronic renal failure. *Circulation.* (2003) 107:864–8. doi: 10.1161/01.CIR.0000049744.23613.69

17. Mitsnefes MM. Cardiovascular complications of pediatric chronic kidney disease. *Pediatr Nephrol.* (2008) 23:27–39. doi: 10.1007/s00467-006-0359-0

18. Renkema KY, Winyard PJ, Skovorodkin IN, Levtchenko E, Hindryckx A, Jeanpierre C, et al. Novel perspectives for investigating congenital anomalies of the kidney and urinary tract (CAKUT). *Nephrol Dial Transplant.* (2011) 26:3843–51. doi: 10.1093/ndt/gfr655

19. Ferris ME, Gipson DS, Kimmel PL, Eggers PW. Trends in treatment and outcomes of survival of adolescents initiating end-stage renal disease care in the United States of America. *Pediatr Nephrol.* (2006) 21:1020–6. doi: 10.1007/s00467-006-0059-9

20. Levy DM, Kamphuis S. Systemic lupus erythematosus in children and adolescents. *Pediatr Clin North Am.* (2012) 59:345–64. doi: 10.1016/j.pcl.2012.03.007

21. Muntner P, He J, Astor BC, Folsom AR, Coresh J. Traditional and nontraditional risk factors predict coronary heart disease in chronic kidney disease: results from the atherosclerosis risk in communities study. *J Am Soc Nephrol.* (2005) 16:529–38. doi: 10.1681/ASN.2004080656

22. Fouque D, Kalantar-Zadeh K, Kopple J, Cano N, Chauveau P, Cuppari L, et al. A proposed nomenclature and diagnostic criteria for protein-energy wasting in acute and chronic kidney disease. *Kidney Int.* (2008) 73:391–8. doi: 10.1038/sj.ki.5002585

23. Muntner P, Hamm LL, Kusek JW, Chen J, Whelton PK, He J, et al. The prevalence of nontraditional risk factors for coronary heart disease in patients with chronic kidney disease. *Ann Intern Med.* (2004) 140:9–17. doi: 10.7326/0003-4819-140-1-200401060-00006

24. Himmelfarb J, Stenvinkel P, Ikizler TA, Hakim RM. The elephant in uremia: oxidant stress as a unifying concept of cardiovascular disease in uremia. *Kidney Int.* (2002) 62:1524–38. doi: 10.1046/j.1523-1755.2002.00600.x

frontiers | Frontiers in Pediatrics

TYPE Original Research
PUBLISHED 13 April 2023
DOI 10.3389/fped.2023.1164304

OPEN ACCESS

EDITED BY
Shikai Yu,
Tongji University, China

REVIEWED BY
Runmei Zou,
Central South University, China
Cheng Wang,
Central South University, China

*CORRESPONDENCE
Ying Liao
liaoyingwww@163.com
Hongfang Jin
jinhongfang51@126.com

SPECIALTY SECTION
This article was submitted to Pediatric Cardiology, a section of the journal Frontiers in Pediatrics

RECEIVED 12 February 2023
ACCEPTED 27 March 2023
PUBLISHED 13 April 2023

CITATION
Du X, Tao C, Li X, Du J, Liao Y and Jin H (2023) Predicting therapeutic efficacy of oral rehydration salts in children with vasovagal syncope.
Front. Pediatr. 11:1164304.
doi: 10.3389/fped.2023.1164304

Predicting therapeutic efficacy of oral rehydration salts in children with vasovagal syncope

Xiaojuan Du[1], Chunyan Tao[1], Xueying Li[2], Junbao Du[1,3], Ying Liao[1]* and Hongfang Jin[1]*

[1]Department of Pediatrics, Peking University First Hospital, Beijing, China, [2]Department of Statistics, Peking University First Hospital, Beijing, China, [3]State Key Laboratory of Vascular Homeostasis and Remodeling, Peking University, Beijing, China

Objective: This study was designed to develop an easy-to-perform and inexpensive measure to predict efficacy of the oral rehydration salts (ORS) in children with vasovagal syncope (VVS).
Materials and methods: Children diagnosed with VVS and treated with ORS for a median of 3 months at the Peking University First Hospital, China, were enrolled and followed up. Demographic data, clinical hemodynamic parameters, and variables related to red blood cells were collected at the baseline. On the basis of changes in symptom scores after treatment, participants were divided into effective or ineffective groups at the end of the follow-up. Logistic regression analysis was used to investigate parameters related to therapeutic efficacy of ORS and a predictive model of ORS effectiveness was created. The predictive efficiency was evaluated using the receiver operating characteristic curve. The accuracy/consistency was evaluated by the Hosmer–Lemeshow test and calibration curve. Internal validation was done using the bootstrap approach.
Results: Totally 97 pediatric participants were included in the study and 4 (4.1%) were lost during the follow-up. ORS therapy was effective in 46 children and ineffective in 47 children. Children in the effective group had higher baseline red blood cell count, hemoglobin, and hematocrit than those in the ineffective group ($p < 0.01$). Through logistic regression analysis, the baseline hematocrit and body mass index (BMI) were included in predictive model for the response to ORS treatment. The predictive efficacy of the model showed an area under the curve of 0.77 ($p < 0.01$). The predicted probability cut-off value of 0.5 was found to be optimal, with a resulting sensitivity of 67.4% and specificity of 80.9%. In the Hosmer–Lemeshow test, p-value was 0.75, and the calibration plot showed a good model fitness. Internal validation was performed using the bootstrap approach ($n = 1{,}000$), showing 95% confidence interval of 0.67–0.86.
Conclusion: Hemoglobin combined with BMI was useful for predicting the therapeutic efficacy of ORS in children with VVS.

KEYWORDS

oral rehydration salts, nomogram, vasovagal syncope, predictive model, body mass index, hematocrit

Abbreviations
AUC, area under receiver operating characteristic curve; BMI, body mass index; CI, confidence interval; DCA, decision curve analysis; HUT, head-up tilt test; ORS, oral rehydration salts; ROC, receiver operating characteristic curve; VVS, vasovagal syncope.

1. Introduction

Syncope is defined as a temporary loss of consciousness caused by reversible cerebral hypoperfusion with heterogeneous etiology. The most prevalent underlying cause of syncope is vasovagal syncope (VVS), which accounts for approximately 60% of all the syncopal causes in children (1). The pathogenesis of VVS is complex and includes, but is not limited to, hypovolemia (2–4), enhanced sympathetic nerve activity (5, 6) and catecholamine levels (7), and excessive peripheral vasodilation (8). It was found that during an attack of VVS, the orthostatic stress, which was the major trigger, may initially stagnate blood in the veins of lower extremities due to gravitational forces (9) and thereby reduced the circulating blood volume, which activated an aberrant autonomic regulation (10), resulting in bradycardia (11, 12) and/or hypotension, and ultimately decreasing the cerebral blood flow (13–15) and oxygen saturation (15, 16). The relative central hypovolemia can be the initial factor that promotes the whole process.

In clinical practice, the efficacy of oral rehydration salts (ORS) therapy is not satisfactory for VVS (17, 18), although it is the treatment targeting hypovolemia. Considering the complex pathogenesis of VVS as mentioned above, we hypothesized that ORS would be an ideal therapeutic option for children suffering from VVS with hypovolemia as the main pathogenesis, other than VVS with the abnormal sympathetic nerve activity (5, 6) and excessive vascular dilation.

Therefore, to increase the effectiveness of ORS on VVS patients, it is extremely necessary to find out some stable and easy-to-perform predictors or develop practical predictive models to indicate those VVS children with hypovolemia as the main pathogenesis to select ORS as the clinical therapeutic options. Previously, body mass index (BMI) (19) or 24-hour urinary sodium excretion (20) were utilized to predict the effectiveness of ORS in patients with VVS. Although both can indirectly reflect blood volume, the predictive value of a single indicator is always limited and has its own limitations. BMI can be easily influenced by congenital factors such as genetic background (21) and acquired factors such as nutrition and economic conditions (22, 23). Twenty-four-hour urine is not convenient to collect for outpatients. Some previous studies have suggested that hematocrit and red blood cell-associated parameters, which are relatively stable and easy to obtain, can indicate blood volume (14, 24). In order to predict the effectiveness of ORS in children with VVS, we sought to develop an easy-to-perform prediction model in this study.

2. Materials and methods

2.1. Subjects

Inclusion criteria for the participants were (1) children hospitalized due to VVS between July 2012 and December 2022, as determined by the existing criteria (25); (2) age of the patients ranged from 5 to 17 years old; and (3) patients treated by health education (avoidance of triggers and physical counterpressure maneuvers) and ORS.

Exclusion criteria were (1) children with uncertain illness or other causes of transient loss of consciousness such as cardiogenic syncope, orthostatic hypotension, or psychogenic pseudosyncope; (2) patients with anemia or other hematological disorders; (3) irregular use of ORS; (4) children treated with other medicines, such as beta-blockers and hydrochloride midodrine; and (5) patients with incomplete medical data.

2.2. Therapy and follow-up

ORS was administered daily to all participants (Anjian Pharma Company, Xi'an, China). Each bag included 3,375 mg of waterless glucose, 725 mg of sodium citrate, 650 mg of sodium chloride, and 375 mg of potassium chloride (25, 26). The treatment with ORS was initiated from the diagnosis of VVS made after hospitalization, and the median duration of treatment was 3 months.

Three months after starting therapy, follow-up was conducted by a professional investigator by telephone or outpatient visits. Demographic information, symptoms and signs, and baseline hemodynamic and hemocytometric variables were collected before the therapy. As indicated before (19), symptom score was calculated before and at the end of the follow-up depending on the occurrence and frequency of syncope: 0 point indicated no syncopal event; 1 point, 1 event per month; 2 points, 2–4 events per month; 3 points, 2–7 events per week; 4 points, >once per day. When the symptom score decreased by at least 1 point, the treatment was considered to be effective (19).

2.3. Collection of demographic data, symptoms, and baseline hemodynamic and hemocytometric variables

Demographic information and symptoms were recorded. Using a Dash 2000 multichannel physiological monitor (General Electric Company, New York, United States), baseline hemodynamics was obtained.

Before collection of the blood samples, participants were requested to fast for 4 h, and then venous blood (2–3 ml) was collected in the morning. All the patients did not have symptoms like vomiting and/or diarrhea that might cause dehydration 3 days before the blood sample collection. Sysmex XE-5,000 (Sysmex Corporation, Kobe, Japan) was used to measure hemocytometric variables.

2.4. Head-up tilt test

The head-up tilt test (HUT) was conducted in a darkly lit, warm, quiet environment. Before HUT, patients must fast for 4 h and quit autonomic nerve-affecting medicines for 5 half-lives. Children were monitored for 20 min while supine on a tilt table (SHUT-100A, Standard, Jiangsu, and ST-711, Juchi, Beijing,

China). The tilt table was slanted at 60° and the test was terminated when a positive reaction appeared, or 45 min-process was completed.

2.5. Statistical analysis

SPSS 26.0 (IBM Corp, Armonk, NY, United States) was used in the present study. The Kolmogorov–Smirnov test for normal distributivity was performed, continuous data were analyzed with the *t*-test and nonparametric Mann–Whitney *U* test, and categorical data were analyzed with the χ^2 test. Variables with *p* less than 0.05 and demographic variables were included into model built by logistic regression (stepwise regression method). Multicollinearity between the variables was checked using their corresponding variance inflation factor (VIF). Evaluation of the model was done by the receiver operating characteristic (ROC) curve, calibration plot (calibrate, MASS package), Hosmer–Lemeshow test, and decision curve analysis (DCA) (R, version 4.2.0, rmda package). A bootstrap self-sampling method (n = 1,000) was used to internally validate the model. A nomogram was used to illustrate the model results. $p < 0.05$ indicated a significant difference.

3. Results

3.1. The baseline items

Totally 97 patients treated with ORS for a median of 3 months were enrolled; however, 4 were subsequently lost during follow-up (Figure 1). According to changes in symptom scores, the ORS therapy was effective in 46 cases (effective group) and ineffective in the other 47 cases (ineffective group). There was no significant

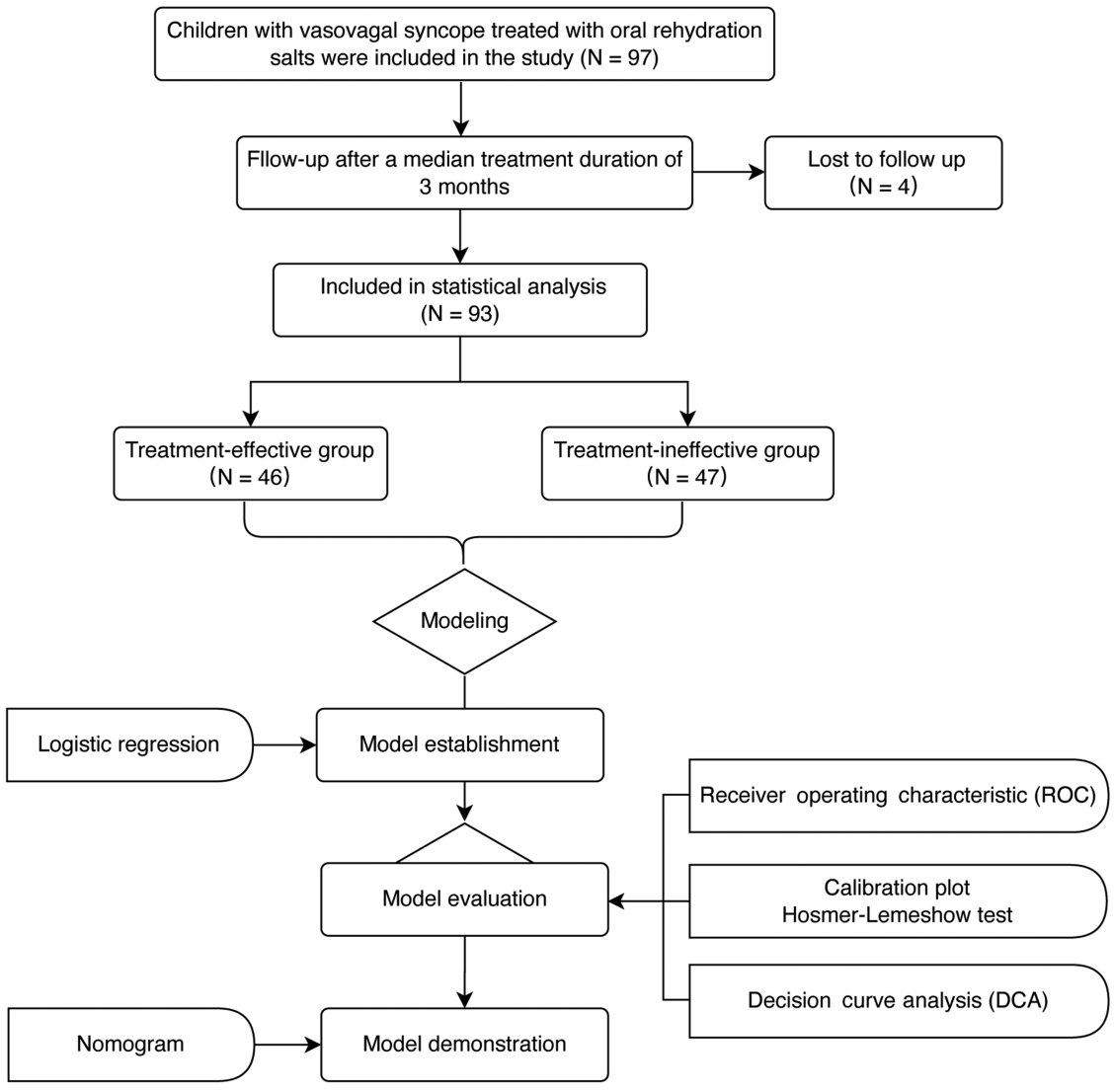


FIGURE 1
The flowchart of the research.

difference in pretherapy symptom score, age, BMI, duration of therapy, and hemodynamic parameters between the two groups ($p > 0.05$). There was statistical difference in red blood cell count, hemoglobin, and hematocrit between the two groups ($p < 0.05$). The levels of red blood cell count, hemoglobin, and hematocrit were higher in the effective group than those in the ineffective group ($p < 0.01$, Table 1).

3.2. Construction of predictive models

The items with p-values below 0.05 (red blood cell count, hematocrit, and hemoglobin) and demographic variables (gender, age, and BMI) were tested for multicollinearity. According to multicollinearity analysis (Table 2, VIF < 10), the six items mentioned were included in multivariate regression analysis. As per the results of regression analysis, hematocrit and BMI were two independent factors associated with the efficacy (Table 3), and the regression equation is shown as

$$\text{logit}(p) = -12.438 - 0.189 \times \text{BMI} + 0.389 \times \text{hematocrit}$$

TABLE 1 Baseline demographic and clinical data between effective and ineffective groups.

Items	Ineffective, $N = 47$	Effective, $N = 46$	p-value
Age (years)[a]	10.00 (8.00–12.50)	12.00 (8.25–13.00)	0.195
Gender[b]			0.114
Male	14 (30%)	21 (46%)	
Female	33 (70%)	25 (54%)	
Pretherapy symptom score (points)[a]	1.00 (1.00–1.00)	1.00 (1.00–1.25)	0.285
Symptom score at the end of follow-up (points)[a]	1.00 (1.00–1.00)	0.00 (0.00–0.00)	<0.001
Duration of therapy (months)[a]	3.00 (2.00–3.00)	3.00 (2.00–3.00)	0.847
Body mass index (kg/m^2)[a]	17.44 (15.69–19.38)	16.41 (15.50–19.15)	0.341
Pretherapy heart rate (bpm)[a]	76 (71–87)	75 (71–85)	0.744
Pretherapy systolic blood pressure (mmHg)[a]	105 (98–112)	104 (97–115)	0.881
Pretherapy diastolic blood pressure (mmHg)[c]	62 (8)	62 (8)	>0.9
Pretherapy red blood cell count (10^{12}/L)[c]	4.66 (0.35)	4.90 (0.36)	0.002
Pretherapy hemoglobin (g/L)[c]	135 (9)	142 (10)	0.001
Pretherapy hematocrit (%)[c]	39.40 (2.66)	41.56 (2.49)	<0.001
Pretherapy mean corpuscular volume (fl)[a]	84.8 (82.4–86.7)	84.2 (82.2–88.3)	0.620
Pretherapy mean corpuscular hemoglobin (pg)[c]	28.86 (1.19)	28.97 (1.26)	0.666
Pretherapy mean corpuscular hemoglobin concentration (g/L)[a]	342 (336–348)	342 (334–347)	0.797
Pretherapy red blood cell distribution width (%)[c]	12.59 (0.58)	12.81 (0.67)	0.099

[a]Median (interquartile range): U test.
[b]N (%): χ^2 test.
[c]Mean (SD): t-test.

TABLE 2 The multicollinearity analysis.

Items	Tolerance	VIF
Red blood cell count (10^{12}/L)	0.155	6.465
Hematocrit (%)	0.108	9.266
Hemoglobin (g/L)	0.139	7.173
Age (years)	0.561	1.783
Body mass index (kg/m^2)	0.795	1.257
Gender	0.727	1.376

VIF, variance inflation factor.

TABLE 3 Multivariate logistic regression of the construction of predictive models.

Items	B	SE	Wald	OR	95% CI	p-value
Body mass index (kg/m^2)	−0.189	0.094	4.046	0.827	0.688–0.995	0.044
Hematocrit (%)	0.389	0.104	13.933	1.475	1.203–1.809	<0.001
Constant	−12.438	3.987	9.734	—	—	0.002

CI, confidence interval; SE, standard error; OR, odds ratio.

3.3. Evaluation of predictive model

3.3.1. Degree of differentiation

ROC analysis showed that the area under curve (AUC) was 0.77 ($p < 0.01$). To predict the effectiveness, the ideal cut-off value was 0.5, producing a sensitivity of 67.4% and a specificity of 80.9% (Figure 2A).

3.3.2. Calibration

The Hosmer–Lemeshow test indicated that the predicted and observed values were not substantially different ($p = 0.75$), indicating a good model suitability. The calibration curve is shown in Figure 2B.

3.3.3. Clinical utility

Clinical utility was analyzed using DCA, and the results are shown in Figure 2C. Our study showed that within 0.1–0.8 of the threshold probability, the net benefit of the prediction model ranged between 0.01 and 0.5. We found that treatment decisions based on model predictions will provide higher net benefit than that without using the model. For instance, at a threshold of 0.4, the calculated net benefit based on intervention for model is about 0.22, while the calculated net benefit based on intervention for all is about 0.16.

3.3.4. Internal validation

Internal validation of the data performed using the bootstrap approach ($n = 1{,}000$) showed a good predictive accuracy: an AUC of 0.77 and 95% confidence interval (CI) of 0.67–0.86 (Figure 2D).

3.4. Nomogram of the predictive model

A nomogram of predictive model consisting of the two factors (hematocrit and BMI) were created to visually predict ORS

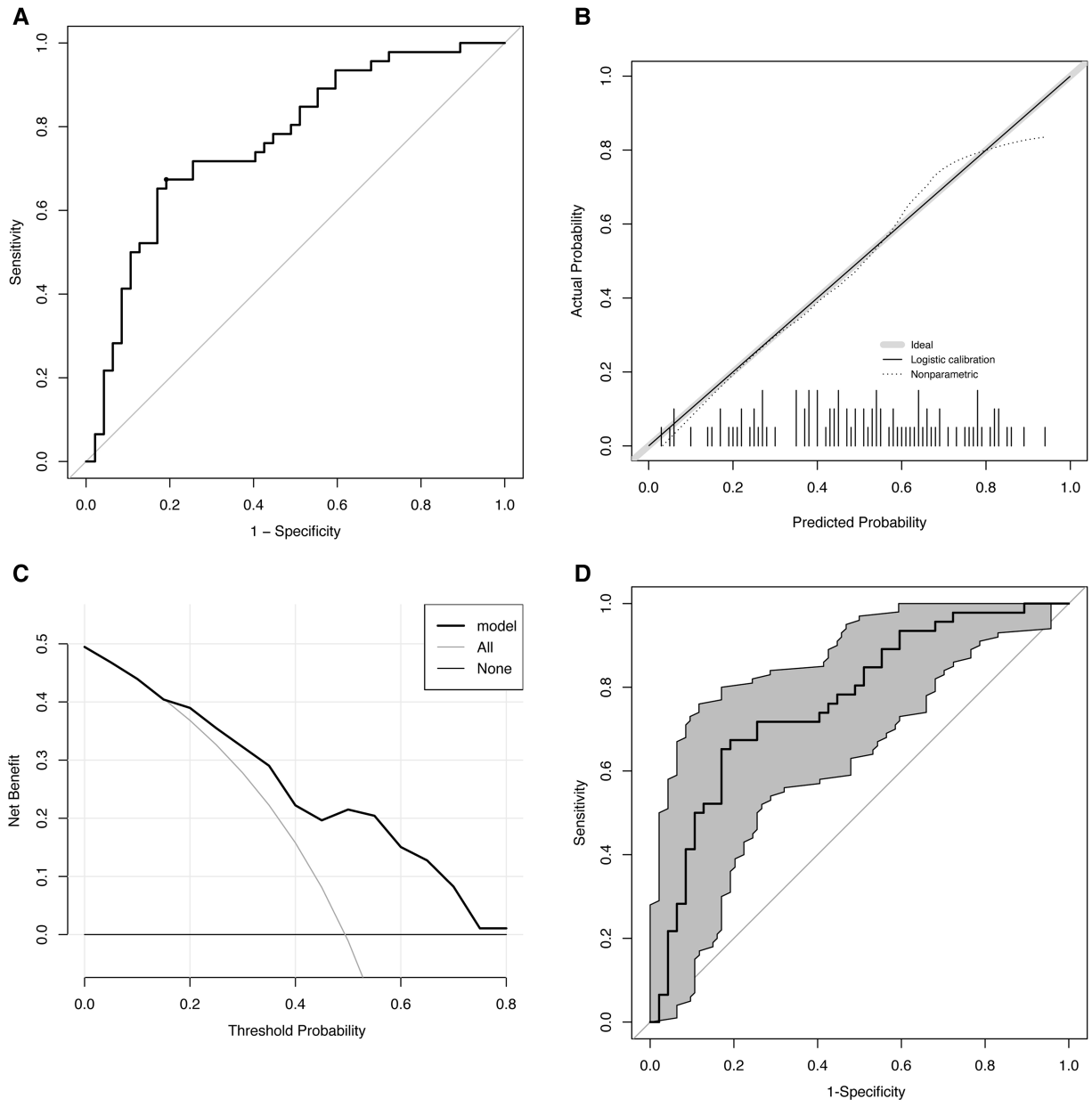


FIGURE 2
Evaluation of the predictive model. (**A**) ROC. AUC: 0.77 ($p < 0.01$), cut-off value: 0.5, sensitivity: 67.4%, and specificity: 80.9%. (**B**) Calibration curve. The gray line indicates the ideal reference line where predicted (x-axis) and observed probability (y-axis) coincide. The black line represents the performance of the model. The closer the black line is to the gray line, the more accurately the model predicts. (**C**) DCA. ORS treatment is regarded as an intervention, and the purpose of the ORS is naturally to obtain a "good result" (positive outcome). DCA includes results for "ORS for all," "ORS for none," and "ORS for model." The x-axis displays the probability threshold. The y-axis indicates the degree of benefit to which the patient benefited from the intervention (ORS). (**D**) Bootstrap-corrected receiver operating characteristic curve ($n = 1{,}000$). The gray part is the 95% confidence interval (0.67–0.86). ROC, receiver operating characteristic curve; AUC, area under receiver operating characteristic curve; DCA, decision curve analysis; ORS, oral rehydration salts.

treatment efficacy based on different scores (Figure 3). A nomogram is a graphical representation of the solution to an equation that approximates the risk with reasonable accuracy. For instance, when the BMI is 27 kg/m^2, the score is approximately 20%. When hematocrit is 39%, the score is approximately 40%. The total score is approximately 60, resulting in a predicted effective rate of approximately 0.1. Therefore, ORS treatment is not recommended.

4. Discussion

We followed up 97 children with VVS treated with ORS, and after a median duration of 3 months of treatment, 46 patients responded well to the treatment, with an effective rate of less than 50%. There were statistical differences in gender, red blood cell count, hemoglobin, and hematocrit between effective and ineffective groups. Subsequently, logistic regression was carried

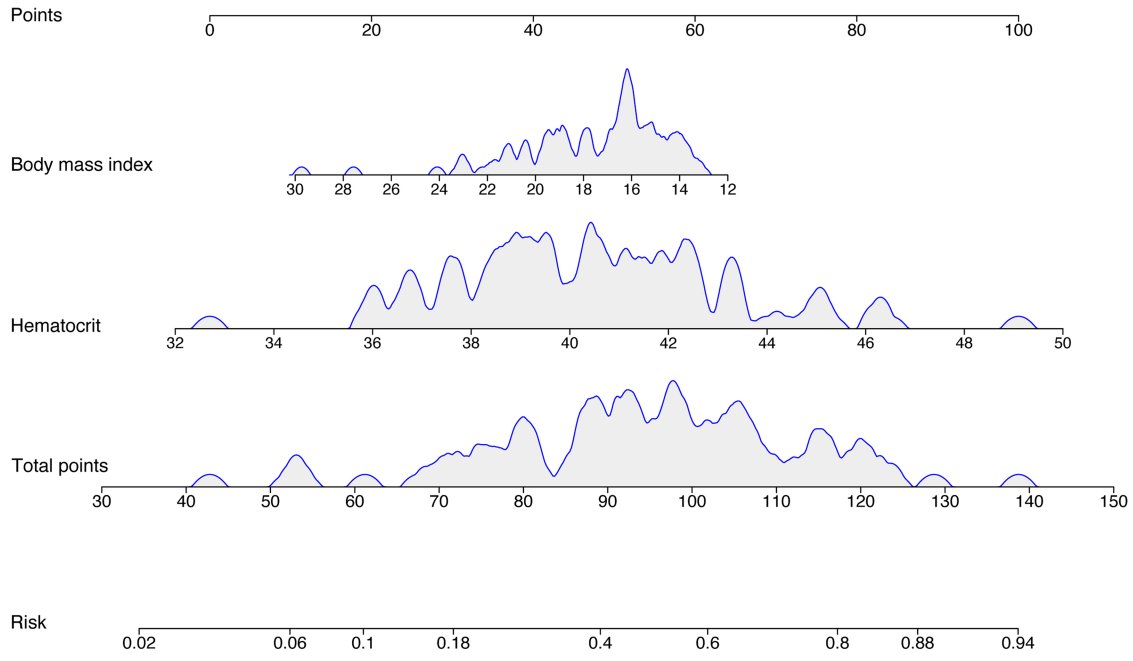


FIGURE 3
Nomogram of the prediction model. The nomogram is applied by placing each patient's items on a variable axis and then drawing a vertical line to determine the points for each item. The total points were then placed on the number axis of the total points line, and a vertical line is drawn to the final axis.

out to generate a new model in which hematocrit and BMI were related to the effectiveness of ORS therapy. The model was evaluated, and the ROC curve demonstrated that the sensitivity and specificity were 67.4% and 80.9%, respectively, and the DCA suggested that using the model to predict the effectiveness of ORS in children with VVS would improve clinical outcomes. We also presented the results in a nomogram to facilitate the decision-making by clinicians and to enhance the practicability of the model.

To increase the water and salt intake is an acknowledged measure in the management of VVS. However, a confusing fact is that the empirically unselected use of oral rehydration salts as a first-line therapy for children with VVS showed limited efficacy (17). Therefore, there is a strong need to find out useful markers to indicate the VVS patients with hypovolemia as the main pathogenesis to guide the ORS therapy. It has been noted that BMI and 24-hour sodium excretion collection have correlation with blood volume (27) and were used to predict the effectiveness of ORS therapy for children with VVS (19, 20). However, as an indirect correlative factor to blood volume, BMI may be influenced by the genetic factors as well as the content of body fat, which may challenge the value of BMI in predicting the effectiveness of fluid and salt supplementation. Although the predictive power is similar between our model and 24-hour urinary sodium excretion based on the AUC of ROC curve (0.77 vs. 0.84), the parameters in our study are more readily available as the latter needs a 24-hour urine collection procedure. Furthermore, our model can provide an exact estimated effective rate, which is an important advantage of a nomogram. The nomogram of this study makes it more intuitive for clinical applications. In this study, we demonstrated that hematocrit combined with BMI was useful in the prediction of the efficacy of ORS treatment in children with VVS. Moreover, a clinical utility analysis was performed, and a graphic tool was created to assist the clinical decision-making, which may improve the current individualized treatment.

However, there are several limitations of our research. Due to the single-center design, selection bias was inevitable. In the future, multicenter-based studies are expected. The follow-up duration was not long enough, and the sample size was not large enough. We will continue to confirm the conclusions in future studies to achieve sufficient quantity. Second, the therapeutic efficacy was only evaluated by patients' symptoms, while other indicators involving investigations such as negative rate of HUT need to be considered in future studies. Despite the limitations, our results suggest that hematocrit combined with BMI constitutes a clinically valuable model for predicting the efficacy of ORS therapy in pediatric patients with VVS, providing a useful strategy for the personalized treatment of VVS.

5. Conclusions

This study confirmed the hematocrit and BMI as useful, easy-to-obtain, and inexpensive indicators to forecast the therapeutic response to ORS in children with VVS, and we constructed a nomogram for an individualized prediction of the usefulness to

ORS in pediatric VVS patients, which would greatly help in making treatment strategies.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Institutional Ethics Committees at Peking University First Hospital (2022-496). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

JD, HJ, and YL designed the project and the hypothesis. CT performed the systematic search and reviewed the literature. XD extracted and evaluated the data and composed the first article draft. XL, HJ, and YL participated in the design of the research and article revision. All authors contributed to the article and approved the submitted version.

Funding

This research was supported by National High Level Hospital Clinical Research Funding (grant no. 2022CR59) and the Clinical Medicine Plus X-Young Scholars Project of Peking University, the Fundamental Research Funds for the Central Universities (grant no. PKU2022LCXQ028).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Romme JJ, van Dijk N, Boer KR, Dekker LR, Stam J, Reitsma JB, et al. Influence of age and gender on the occurrence and presentation of reflex syncope. *Clin Auton Res*. (2008) 18(3):127–33. doi: 10.1007/s10286-008-0465-0

2. Brignole M, Rivasi G, Sutton R, Kenny RA, Morillo CA, Sheldon R, et al. Low-blood pressure phenotype underpins the tendency to reflex syncope. *J Hypertens*. (2021) 39(7):1319–25. doi: 10.1097/hjh.0000000000002800

3. Jacob G, Barbic F, Glago M, Dipaola F, Porta A, Furlan R. Cardiovascular autonomic profile in women with constitutional hypotension. *J Hypertens*. (2018) 36(10):2068–76. doi: 10.1097/hjh.0000000000001790

4. Jaeger FJ, Maloney JD, Castle LW, Fouad-Tarazi FM. Is absolute hypovolemia a risk factor for vasovagal response to head-up tilt? *Pacing Clin Electrophysiol*. (1993) 16 (4 Pt 1):743–50. doi: 10.1111/j.1540-8159.1993.tb01654.x

5. Iwase S, Nishimura N, Mano T. Role of sympathetic nerve activity in the process of fainting. *Front Physiol*. (2014) 5:343. doi: 10.3389/fphys.2014.00343

6. Morillo CA, Eckberg DL, Ellenbogen KA, Beightol LA, Hoag JB, Tahvanainen KU, et al. Vagal and sympathetic mechanisms in patients with orthostatic vasovagal syncope. *Circulation*. (1997) 96(8):2509–13. doi: 10.1161/01.cir.96.8.2509

7. Smith GD, Watson LP, Mathias CJ. Cardiovascular and catecholamine changes induced by supine exercise and upright posture in vasovagal syncope. Comparisons with normal subjects and subjects with sympathetic denervation. *Eur Heart J*. (1996) 17(12):1882–90. doi: 10.1093/oxfordjournals.eurheartj.a014807

8. Galetta F, Franzoni F, Plantinga Y, Ghiadoni L, Merico G, Tocchini L, et al. Endothelial function in young subjects with vasovagal syncope. *Biomed Pharmacother*. (2006) 60(8):448–52. doi: 10.1016/j.biopha.2006.07.014

9. Blaber AP, Hinghofer-Szalkay H, Goswami N. Blood volume redistribution during hypovolemia. *Aviat Space Environ Med*. (2013) 84(1):59–64. doi: 10.3357/asem.3424.2013

10. Yadav K, Singh A, Jaryal AK, Coshic P, Chatterjee K, Deepak KK. Modulation of cardiac autonomic tone in non-hypotensive hypovolemia during blood donation. *J Clin Monit Comput*. (2017) 31(4):739–46. doi: 10.1007/s10877-016-9912-y

11. Posch AM, Luippold AJ, Mitchell KM, Bradbury KE, Kenefick RW, Cheuvront SN, et al. Sympathetic neural and hemodynamic responses to head-up tilt during isoosmotic and hyperosmotic hypovolemia. *J Neurophysiol*. (2017) 118(4):2232–7. doi: 10.1152/jn.00403.2017

12. Yadav K, Jaryal AK, Coshic P, Chatterjee K, Deepak KK. Effect of hypovolemia on efficacy of reflex maintenance of blood pressure on orthostatic challenge. *High Blood Press Cardiovasc Prev*. (2016) 23(1):25–30. doi: 10.1007/s40292-016-0130-y

13. Romero SA, Moralez G, Rickards CA, Ryan KL, Convertino VA, Fogt DL, et al. Control of cerebral blood velocity with furosemide-induced hypovolemia and upright tilt. *J Appl Physiol (1985)*. (2011) 110(2):492–8. doi: 10.1152/japplphysiol.01060.2010

14. Moralez G, Romero SA, Rickards CA, Ryan KL, Convertino VA, Cooke WH. Effects of dehydration on cerebrovascular control during standing after heavy resistance exercise. *J Appl Physiol (1985)*. (2012) 112(11):1875–83. doi: 10.1152/japplphysiol.01217.2011

15. Skytioti M, Søvik S, Elstad M. Internal carotid artery blood flow in healthy awake subjects is reduced by simulated hypovolemia and noninvasive mechanical ventilation. *Physiol Rep*. (2016) 4(19):e12969. doi: 10.14814/phy2.12969

16. Hisdal J, Landsverk SA, Hoff IE, Hagen OA, Kirkebøen KA, Høiseth L. Associations between changes in precerebral blood flow and cerebral oximetry in the lower body negative pressure model of hypovolemia in healthy volunteers. *PLoS One*. (2019) 14(6):e0219154. doi: 10.1371/journal.pone.0219154

17. Tao C, Cui Y, Zhang C, Liu X, Zhang Q, Liu P, et al. Clinical efficacy of empirical therapy in children with vasovagal syncope. *Children (Basel)*. (2022) 9(7):1065. doi: 10.3390/children9071065

18. Chu W, Wang C, Wu L, Lin P, Li F, Zou R. Oral rehydration salts: an effective choice for the treatment of children with vasovagal syncope. *Pediatr Cardiol*. (2015) 36 (4):867–72. doi: 10.1007/s00246-015-1097-5

19. Tao CY, Chen S, Li XY, Tang CS, Du JB, Jin HF. Body mass index is a promising predictor of response to oral rehydration saline in children with vasovagal syncope. *Chin Med J (Engl)*. (2020) 134(4):463–8. doi: 10.1097/cm9.0000000000001168

20. Du X, Tao C, Wang Y, Sun Y, Zhang Q, Zhang C, et al. Twenty-four-hour urinary sodium excretion predicts therapeutic effectiveness of oral rehydration

saline in pediatric vasovagal syncope. *Children (Basel)*. (2022) 9(7):992. doi: 10.3390/children9070992

21. Silventoinen K, Li W, Jelenkovic A, Sund R, Yokoyama Y, Aaltonen S, et al. Changing genetic architecture of body mass index from infancy to early adulthood: an individual based pooled analysis of 25 twin cohorts. *Int J Obes (Lond)*. (2022) 46 (10):1901–9. doi: 10.1038/s41366-022-01202-3

22. Garcia-Montero H. Height, nutritional and economic inequality in central Spain, 1837–1936. *Int J Environ Res Public Health*. (2022) 19(6):3397. doi: 10.3390/ijerph19063397

23. Medina M, Barreto P, Natero V, Moratorio X, Severi C. Prevalence of malnutrition among children and women of reproductive age in Uruguay by socio-economic status and educational level. *Public Health Nutr*. (2020) 23(S1):s101–7. doi: 10.1017/s1368980020000804

24. Lagi A, Rossi A, Sorelli P, Cartei A, Cencetti S. Plasma volume and hematocrit changes in recurrent fainters. *Clin Auton Res*. (2003) 13(6):439–42. doi: 10.1007/s10286-003-0126-2

25. Wang C, Li YQ, Liao Y, Tian H, Huang M, Dong XY, et al. Chinese Pediatric Cardiology Society (CPCS) guideline for diagnosis and treatment of syncope in children and adolescents. *Sci Bull*. (2018) 63(23):1558–64. doi: 10.1016/j.scib.2018.09.019

26. Wen C, Wang S, Zou R, Wang Y, Tan C, Xu Y, et al. Duration of treatment with oral rehydration salts for vasovagal syncope in children and adolescents. *Turk J Pediatr*. (2020) 62(5):820–5. doi: 10.24953/turkjped.2020.05.014

27. Stewart JM, Taneja I, Medow MS. Reduced body mass index is associated with increased angiotensin II in young women with postural tachycardia syndrome. *Clin Sci*. (2007) 113(11):449–57. doi: 10.1042/cs20070104

frontiers | Frontiers in Public Health

TYPE Original Research
PUBLISHED 18 April 2023
DOI 10.3389/fpubh.2023.1157351

OPEN ACCESS

EDITED BY
Zhen-Yu Zhang,
KU Leuven, Belgium

REVIEWED BY
Jovan Gardasevic,
University of Montenegro, Montenegro
Dongmei Wei,
KU Leuven, Belgium

*CORRESPONDENCE
Rong-Ho Lin
✉ rhlin@mail.ntut.edu.tw

SPECIALTY SECTION
This article was submitted to Children and Health, a section of the journal Frontiers in Public Health

RECEIVED 02 February 2023
ACCEPTED 16 March 2023
PUBLISHED 18 April 2023

CITATION
Chuang H-H, Cherng W-J, Lin C-H, Lee L-A, Hsu K-H and Lin R-H (2023) Physical fitness mediates and predicts for high blood pressure among children in relation to weight status. *Front. Public Health* 11:1157351. doi: 10.3389/fpubh.2023.1157351

Physical fitness mediates and predicts for high blood pressure among children in relation to weight status

Hai-Hua Chuang[1,2,3,4,5], Wen-Jin Cherng[4,6], Chih-Hung Lin[2,4,7], Li-Ang Lee[2,4,5,8], Kuang-Hung Hsu[9,10,11] and Rong-Ho Lin[3]*

[1]Department of Family Medicine, Taipei and Linkou Main Branches, Chang Gung Memorial Hospital, Taoyuan, Taiwan, [2]Metabolism and Obesity Institute, Taipei and Linkou Main Branches, Chang Gung Memorial Hospital, Taoyuan, Taiwan, [3]Department of Industrial Engineering and Management, National Taipei University of Technology, Taipei, Taiwan, [4]College of Medicine, Chang Gung University, Taoyuan, Taiwan, [5]School of Medicine, National Tsing Hua University, Hsinchu, Taiwan, [6]Division of Cardiology, Department of Internal Medicine, Chang-Gung Memorial Hospital, Linkou Main Branch, Taoyuan, Taiwan, [7]Department of Plastic and Reconstructive Surgery, Linkou Main Branch, Chang-Gung Memorial Hospital, Taoyuan, Taiwan, [8]Departments of Otorhinolaryngology-Head and Neck Surgery, Linkou Main Branch, Chang-Gung Memorial Hospital, Taoyuan, Taiwan, [9]Healthy Aging Research Center, Chang Gung University, Taoyuan, Taiwan, [10]Laboratory for Epidemiology, Department of Health Care Management, Chang Gung University, Taoyuan, Taiwan, [11]Department of Emergency Medicine, Chang Gung Memorial Hospital at Linkou, Taoyuan, Taiwan

Background: Pediatric hypertension contributes to adulthood hypertension and target organ damage. Obesity is a well-known predictor for pediatric hypertension; however, the relationship between physical fitness and blood pressure (BP) is unclear among children. This study aimed to compare the differences in demographics, anthropometrics, and physical fitness across BP subgroups and investigate whether physical fitness was related to pediatric hypertension independent of weight status.

Methods: This quantitative, cross-sectional study investigated demographic, anthropometric, physical fitness, and BP measures among 360 healthy school-aged children. Continuous variables were compared across BP subgroups with the one-way analysis of variance. Mediation and moderation analyses were used to explore the mechanism. Multivariable regression models were used to assess independent associations for hypertension.

Results: There were 177 (49.2%), 37 (10.3%), and 146 (40.6%) children in the normotensive, elevated BP, and hypertensive subgroups, respectively. The hypertensive subgroup had higher body mass index (BMI) and waist/height ratio percentiles and performed worse in 800-m run, standing long jump (SLJ), and 1-min sit-ups than the normotensive subgroup. Furthermore, the 800-m run percentile (total effect: $\beta = 0.308$, standard error $= 0.044$, $p < 0.001$) and sit and reach percentile (total effect: $\beta = 0.308$, standard error $= 0.044$, $p < 0.001$) mediated the relationship between the BMI percentile and systolic BP percentile; the SLJ percentile was directly associated with the diastolic BP percentile (β,−0.197, 95% confidence interval,−0.298−0.097; $p < 0.001$). The parsimonious model of multivariable regression models revealed that the SLJ percentile (adjusted exp (β), 0.992, 95% confidence interval, 0.985–0.999; $p = 0.042$) and BMI percentile (adjusted exp (β), 1.024, 95% confidence interval, 1.016–1.032; $p <$ 0.001) were two independent predictors for pediatric hypertension.

Conclusion: Physical fitness mediates the relationship between anthropometric and BP measures. The SLJ percentile is associated with pediatric hypertension

independent of the BMI percentile. Proactive screening and health promotion for not only healthy weight status but also good physical fitness may be beneficial for BP control among school-aged students.

KEYWORDS

blood pressure, body mass index, childhood obesity, pediatric hypertension, physical fitness, standing long jump

1. Introduction

Hypertension is well-documented as a risk factor for cardiovascular diseases (1), chronic kidney disease (2), and premature mortality (3). A meta-analysis in 2019 revealed that the global prevalence of pre-hypertension and hypertension was 9.67% and 4.00% among children 19 years and younger (4). Without effective management, pediatric hypertension is likely to develop into adulthood hypertension (5) and eventually lead to target organ damage (6). However, early identification and intervention of hypertension remain to be a challenge, especially among the pediatric population (7). Compared to adulthood hypertension, pediatric hypertension is diagnosed less promptly and controlled inadequately (7, 8). Although ambulatory BP monitoring is more accurate for diagnosing hypertension than clinic-measured BP (9), in most clinical settings, it is not easy to be implemented routinely for children and adolescents (10). Therefore, identifying at-risk individuals is vital for the timely diagnosis and management of pediatric hypertension (11).

Known risk factors for primary hypertension in children include male sex, older age, overweight and obesity, high sodium intake, physical inactivity, and obstructive sleep apnea (12–14). Some evidence has indicated associations between BP and anthropometric measures. Lo et al. found that waist-to-height ratio (WHtR) had significant screening power for metabolic syndrome components in children, including hypertension (15). Wang et al. revealed that abdominal skin fold was more closely associated with hypertension than body mass index (BMI) in Chinese boys and girls (16). Moreover, previous high-quality epidemiological studies supported the reverse association of physical activity with adolescent/pediatric hypertension (17–19).

While physical activity is defined as any bodily movement produced by skeletal muscles that result in energy expenditure, physical fitness is a set of attributes that are either health- or skill-related and can be measured only with specific tests. Physical fitness represents a general health status to perform daily life functions in work and leisure activities (20). The major health-related components of physical fitness include body composition, cardiorespiratory fitness, musculoskeletal fitness, and motor fitness (21). Physical fitness is a powerful marker of health regarding abdominal adiposity, cardiovascular disease risk factors, skeletal health, quality of life, mood status, and academic performance in children and adolescents (22). In an earlier study of ours, we discovered that body composition parameters predicted pediatric hypertension better than conventional anthropometric measures (23). Some other studies have also reported a connection between physical fitness and BP in children. For example, low cardiorespiratory fitness was related to elevated systolic BP (SBP) in children (24–26). Furthermore, change in physical fitness was inversely associated with the change in BP in school-aged children (27), and persistently low muscle strength contributed to subsequently raised levels of both SBP and diastolic BP (DBP) in adolescents (28). However, the results of studies on the associations between physical fitness and pediatric hypertension have been inconclusive after adjustment for body weight status (29–31).

We hypothesized that poor physical fitness was a risk factor for high blood pressure in children. The study aimed to compare the differences in demographic, anthropometric, and physical fitness measurements across BP subgroups, to explore the mediating and moderating roles of physical fitness on the relationship between body weight status and BP status, and to investigate whether physical fitness was independently associated with pediatric hypertension after adjusting for body weight status in a sample of school-aged children in Taiwan.

2. Materials and methods

2.1. Participants

This cross-sectional study utilized a quantitative analysis to evaluate anonymous data gathered from a multidisciplinary health promotion program, administered by Chang Gung Memorial Hospital's Linkou Main Branch between 2013 and 2016. The program's target audience consisted of 1,860 students, aged between 6 and 13 years, from four elementary schools in Guishan District—a suburban city located close to Taipei in Northern Taiwan—with a population of nearly 160,000. The parents of the students in this cohort were predominantly employed in the electronics, manufacturing, and healthcare industries (32). The Institutional Review Board of the Chang Gung Medical Foundation, Taoyuan, Taiwan (No. 101-4158A3) approved the program, and written informed consent was obtained from all participants and their parents. Details regarding the program have been previously described (32). This study adhered to the principles outlined in the World Medical Association Declaration of Helsinki (33).

We enrolled seemingly healthy fourth- to sixth-grade children to investigate whether physical fitness is a risk factor for high blood pressure, while also accounting for conventional risk factors such as male sex, older age, and overweight/obesity. These grades were chosen due to the availability of normative reference data on physical fitness. The inclusion criteria were as follows: (1) age ranged from 9 to 12 years; and (2) complete demographic, anthropometric, physical fitness, and BP data. The exclusion

criteria were as follows: (1) a history of high BP or under treatment for high BP; and (2) any history of chronic illness such as diabetes mellitus, asthma, chronic pain, cystic fibrosis, congenital heart disease, attention-deficit/hyperactivity disorder, or depression (34, 35). Demographic (sex and age), anthropometric, physical fitness, and BP data were retrieved for statistical analysis.

2.2. Anthropometric measures

Body mass index (BMI) (kg/m^2) was defined as body weight (kg) divided by the body height squared (m^2). BMI percentiles were calculated based on sex and age in months according to the United States Centers for Disease Control and Prevention 2,000 growth charts (36). Waist circumference (in cm) was measured in the horizontal plane midway between the lowest ribs and the iliac crest. WHtR was calculated as waist circumference (cm) divided by the body height (cm) (37), and WHtR percentiles were obtained based on sex and age in years according to the United States National Health and Nutrition Survey, cycle III (38).

2.3. Physical fitness

In this study, the levels of physical fitness were measured by four exercise assessments, including 800-m run (800 mR), standing long jump (SLJ), 1-min sit-ups (1 mSU), and sit and reach (S&R). All physical fitness measurements were performed following the guidelines of the Ministry of Education in Taiwan (39). The detailed protocol of physical fitness measurements had been reported previously (40). Professional physical coaches conducted the assessments and recorded the results. The test results were expressed in percentiles based on sex and age in years according to the reference values for physical fitness of students aged 7–23 years in Taiwan (41).

The 800 mR (s) was defined as the time required for a participant to sprint an 800-m run (42). The 800 mR represented cardiorespiratory fitness and endurance (43).

The SLJ (cm) was defined as the maximum distance between the starting line and the heel of the closest foot after a participant took off for a forward and upward jump and landed on both feet (44). The SLJ represented lower body (leg muscles) strength (45).

The 1 mSU (times) was defined as the maximum number of correct sit-ups achieved within 1 min (46). The participant lay on a mat with knees bent, and arms crossed upon their chest. When the participant touched their knees with their elbows, it was considered a count. 1 mSU represented abdominal muscle strength and endurance (47).

The S&R (cm) was defined by the most distant point reached on the ruler with the fingertips. The participants slide their hands forward as far as possible toward their feet without bending the hamstring and maintaining the top position for at least 2 s (48). Each participant performed three times; the longest measurement out of three was used. The S&R represented the flexibility of the hamstrings (49).

2.4. Blood pressure measurements and categories

After the participant sat for at least 10 min in the classroom, SBP and DBP were measured using an automated sphygmomanometer. If a child's BP exceeded the normal range, the investigator rechecked SBP and DBP after a 5-min rest. BP was measured two times, and the lowest SBP and DBP-values were used (23).

The SBP percentile and DBP percentile were obtained based on age in years, sex, and height z-score according to the BP reference tables published in 2017 (50) as an update to the 2004 "Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents" (10). Normal BP was defined as BP of <90th percentile; elevated BP was defined as SBP and/or DBP of ≥90th to <95th percentile or 120/80 mmHg to <95th percentile (whichever is lower); pediatric hypertension was defined as SBP and/or DBP of ≥95th percentile (50).

2.5. Statistical analysis

The stratum sample size was calculated at 32 based on Pearson's correlation between cardiorespiratory fitness and systolic blood pressure ($r = 0.43$) (24) under a type-I error of 0.05 and statistical power of 0.95. Considering the heterogeneity of relationships across strata (three different grade groups, two sexes, and three blood pressure groups), a minimum of 324 children were required. Therefore, we included a representative cohort of 360 children.

Most continuous variables were normally distributed using the Kolmogorov–Smirnov test. Therefore, continuous variables were reported as means ± standard deviations (SD), and categorical variables were summarized as numbers (percentages). Furthermore, continuous variables were compared using the one-way analysis of variance with *post hoc* Tukey's honestly significant difference tests, and categorical variables were compared using the Mantel–Haenszel test for trend among three BP subgroups. The curve estimation procedure was used to identify useful functional relationships, and Pearson's correlation test was used to assess relationships between continuous variables.

All variables were included in the full models using multivariable linear or binary logistic regression models as appropriate. To identify independent variables of the parsimonious model, all variables were initially included; the variable with the highest but insignificant p-value of ≥ 0.05 was removed at one step, and the manual selection procedures were repeated until all variables with a p-value of < 0.05. To adjust the intervariable relationship within the model, the variance inflation factor of each variable was calculated and removed if its value was ≥ 5 to reduce the multicollinearity (51). Furthermore, conditional process analyses were performed to evaluate the mediation and moderation of selected variables using a PROCESS macro for SPSS (version 4.1) (52). Using 5,000 runs of bootstrapping, bias-corrected 95% confidence intervals (CIs) were estimated to verify mediation, moderated mediation, or mediated moderation. A p-value of < 0.05 was considered to be statistically significant. Statistical analysis

TABLE 1 Demographic, anthropometric, physical fitness, and blood pressure measures of the overall cohort as well as normotensive, elevated blood pressure, and hypertensive subgroups.

Variables Patients	Overall $n = 360$	Normotensive subgroup $n = 177$	Elevated blood pressure subgroup $n = 37$	Hypertensive subgroup $n = 146$	p-value[a]
Demographic measures					
Girls (*n*)	180 (50.0)	89 (50.3)	17 (45.9)	74 (50.7)	0.956
Age (years)	10.0 (0.8)	10.1 (0.8)	10.0 (0.9)	10.0 (0.9)	0.586
Anthropometric measures					
BMI (kg/m^2)	18.8 (3.9)	17.4 (3.1)[b]	18.2 (3.0)[c]	20.5 (4.4)[b,c]	< 0.001
BMI percentile (%)	60.3 (31.8)	49.5 (30.5)[b]	60.4 (32.2)[c]	73.3 (28.2)[b,c]	< 0.001
WHtR	0.46 (0.06)	0.44 (0.05)[b]	0.45 (0.05)[c]	0.49 (0.07)[b,c]	< 0.001
WHtR percentile (%)	47.0 (32.3)	37.4 (29.6)[b]	44.6 (30.0)[c]	59.3 (32.1)[b,c]	< 0.001
Physical fitness parameters					
800 mR (s)	306.9 (70.3)	298.2 (61.5)[b]	291.4 (51.2)[c]	321.8 (81.5)[b,c]	0.004
800 mR percentile (%)	51.0 (27.6)	53.9 (26.2)[b]	57.4 (23.8)	45.9 (29.4)[b]	0.012
SLJ (cm)	137.1 (25.9)	141.1 (25.8)[b]	137.6 (26.7)	132.1 (25.2)[b]	0.008
SLJ percentile (%)	57.5 (30.5)	61.2 (29.8)[b]	55.8 (33.8)	51.8 (29.6)[b]	0.006
1 mSU (times)	27.8 (8.9)	28.8 (9.0)[b]	29.3 (9.1)	26.2 (8.7)[b]	0.018
1 mSU percentile (%)	58.9 (27.6)	62.5 (27.0)[b]	62.7 (25.6)	53.7 (28.1)[b]	0.011
S&R (cm)	27.8 (8.5)	25.5 (8.1)	25.8 (11.0)	25.8 (8.5)	0.944
S&R percentile (%)	45.7 (27.2)	45.3 (26.6)	47.9 (32.7)	45.6 (26.6)	0.866
Blood pressure measures					
SBP (mmHg)	111.7 (14.5)	101.3 (7.7)[b]	110.4 (9.0)[b,c]	124.5 (11.4)[b,c]	< 0.001
SBP percentile (%)	68.3 (28.9)	53.8 (24.6)[b]	81.2 (24.1)[b,c]	94.5 (12.2)[b,c]	< 0.001
DBP (mmHg)	63.1 (12.2)	56.9 (8.4)[b]	63.3 (9.7)[b,c]	70.5 (12.6)[b,c]	< 0.001
DBP percentile (%)	53.3 (29.3)	39.1 (24.8)[b]	58.0 (27.4)[b,c]	71.5 (27.0)[b,c]	< 0.001

Data summarized as mean (standard deviation) or *n* (%) as appropriate.
[a]Data were compared using one-way analysis of variance with *post hoc* Tukey's honestly significant difference tests or Mantel–Haenszel test for trend as appropriate.
[b]p-Value < 0.05 when the variable in the normotensive subgroup was compared with the elevated blood pressure or hypertensive subgroup.
[c]p-Value < 0.05 when the variable in the elevated blood pressure subgroup was compared with the hypertensive subgroup.
BMI, body mass index; DBP, diastolic blood pressure; SBP, systolic blood pressure; S&R, sit and reach; SLJ, standing long jump; WHtR, waist/height ratio; 1 mSU, 1-min sit and ups; 800 mR, 800-m run.

was performed using SPSS software version 25.0 (International Business Machines Corp., Armonk, NY, USA).

3. Results

3.1. Participants characteristics

From a database of 1,860 elementary-school students, 1,066 were in grades 4 to 6. Among them, 533 have complete data of selected variables; 67 were excluded due to a history of high BP or under treatment for high BP, and 106 were excluded due to chronic illness. Therefore, a total of 360 children (180 [50.0%] girls and 180 [50.0%] boys) with a mean age of 10.0 ± 0.8 years (range, 9–12 years) were included in the study. There were 177 (49.2%), 37 (10.3%), and 146 (40.6%) children in the normotensive, elevated BP, and hypertensive subgroups, respectively. Furthermore, 96 (26.7%) children had isolated systolic hypertension, 22 (6.1%) children had isolated diastolic hypertension, and 28 (7.8%) had simultaneous systolic and diastolic hypertension.

3.2. Differences in participants' characteristics across various BP subgroups

Table 1 summarizes the demographic, anthropometric, physical fitness, and BP measures in the overall cohort and in the normotensive, elevated BP, and hypertensive subgroups. For anthropometrics, the hypertensive subgroup had the highest BMI percentile and WHtR percentile among all three subgroups. For physical fitness, the hypertensive subgroup had worse outcomes of the 800 mR percentile, SLJ percentile, and 1 mSU percentile compared to the normotensive subgroup. In addition, BP measures (including the SBP percentile and DBP percentile) of the hypertensive subgroup were higher than those of the normotensive

10.3389/fpubh.2023.1157351

and elevated BP subgroups, even though the distributions of age and sex were comparable across the three subgroups.

3.3. Relationship between study variables

Table 2 demonstrates the associations of BP measures with physical fitness and anthropometric variables in the overall cohort. Higher SBP percentile was related to higher DBP, BMI, and WHtR percentiles, as well as lower 800 mR and 1 mSU percentiles. After adjustment for the BMI and WHtR percentiles, the SBP percentile was significantly associated with the 800 mR percentile ($r = -0.12$; $p = 0.025$) and S&R percentile ($r = 0.14$; $p = 0.009$). A higher DBP percentile was related to higher BMI and WHtR percentiles and lower SLJ and 1 mSU percentiles. After adjustment for the BMI and WHtR percentiles, the DBP percentile was significantly associated with the SLJ percentile ($r = -0.18$; $p < 0.001$) and 1 mSU percentile ($r = -0.13$; $p = 0.017$). A higher BMI percentile was associated with a higher WHtR percentile and lower 800 mR, SLJ, 1 mSU, and S&R percentiles. A higher WHtR percentile was associated with lower 800 mR, SLJ, and 1 mSU percentiles. A higher 800 mR percentile was associated with higher SLJ and 1 mSU percentiles. A higher SLJ percentile was associated with higher 1 mSU and S&R percentiles. A higher 1 mSU percentile was associated with a higher S&R percentile.

3.4. Independent associations between physical fitness, weight status, and blood pressure

Table 3 summarizes independent associations of the BP percentile with anthropometric and physical fitness measures in the overall cohort. Multivariable linear regression modules showed BMI, WHtR, and S&R percentiles were significantly positively associated with the SBP percentile in the full model. Using manual selection approaches, BMI, WHtR, and S&R percentiles were positively related to the SBP percentile, whereas the 800 mR percentile was inversely related to the SBP percentile in the parsimonious model. The SLJ percentile was independently inversely related to the DBP percentile in the full model and the parsimonious model.

3.5. Mediation and moderation analysis

Since there were nested data structures and significant correlations among BP, anthropometric, and physical fitness measures, we performed mediation and moderation analyses to investigate the role of physical fitness measures on the relationship between anthropometric and BP measures. The main findings included the following:

1) The 800 mR percentile significantly mediated the relationship between the BMI percentile and SBP percentile (total effect = 0.308, SD = 0.835, 95% CI: 0.222–0.394, $p < 0.001$; direct effect = 0.277, SD = 0.854, 95% CI: 0.189–0.365,

TABLE 2 Pearson correlations of blood pressure measures with anthropometric and physical fitness measures in the overall cohort.

Variables	SBP percentile	DBP percentile	BMI percentile	WHtR percentile	800 mR percentile	SLJ percentile	1 mSU percentile	S&R percentile
SBP percentile	–							
DBP percentile	0.38[c]	–						
BMI percentile	0.35[c]	0.13[a]	–					
WHtR percentile	0.36[c]	0.11[a]	0.76[c]	–				
800 mR percentile	−0.22[c]	−0.08	−0.26[c]	−0.29[c]	–			
SLJ percentile	−0.08	−0.20[c]	−0.15[b]	−0.19[c]	0.27[c]	–		
1 mSU percentile	−0.15[b]	−0.14[b]	−0.16[b]	−0.25[c]	0.44[c]	0.36[c]	–	
S&R percentile	0.10	−0.02	−0.11[a]	−0.09	0.06	0.31[c]	0.12[a]	–

Data are summarized as r-value (*p*-value). The significant level is indicated as follows: [a]*p*-Value ≥ 0.01– < 0.05, [b]*p*-Value ≥ 0.001– < 0.01, [c]*p*-Value < 0.001.

TABLE 3 Independent associations of blood pressure measures with anthropometric and physical fitness measures in the overall cohort.

Variables	Full model				Parsimonious model			
	β	95% CI	p-Value[a]	VIF	β	95% CI	p-Value[b]	VIF
SBP percentile								
BMI percentile	0.167	0.037–0.296	0.012	2.363	0.162	0.033–0.291	0.014	2.347
WHtR percentile	0.161	0.032–0.291	0.015	2.445	0.171	0.044–0.299	0.009	2.385
800 mR percentile	−0.098	−0.209–0.013	0.083	1.319	−0.120	−0.222–0.019	0.020	1.098
SLJ percentile	−0.021	−0.120–0.078	0.675	1.285			Not significant	
1 mSU percentile	−0.043	−0.156–0.071	0.461	1.367			Not significant	
S&R percentile	0.146	0.043–0.250	0.006	1.113	0.136	0.037–0.231	0.007	1.013
	$R^2 = 0.173$				$R^2 = 0.171$			
DBP percentile								
BMI percentile	0.115	−0.033–0.263	0.127	2.363			Not significant	
WHtR percentile	−0.025	−0.173–0.123	0.742	2.444			Not significant	
800 mR percentile	0.031	−0.096–0.159	0.628	1.322			Not significant	
SLJ percentile	−0.177	−0.261–0.063	0.002	1.282	−0.197	−0.298–0.097	< 0.001	1.000
1 mSU percentile	−0.093	−0.223–0.036	0.158	1.364			Not significant	
S&R percentile	0.058	−0.060–0.177	0.335	1.110			Not significant	
	$R^2 = 0.058$				$R^2 = 0.040$			

[a]All anthropometric and physical fitness variables were included for multivariable linear regression models.
[b]All anthropometric and physical fitness variables were included for multivariable linear regression models with manual selections.
CI, confidence interval; VIF, variance inflation factor.

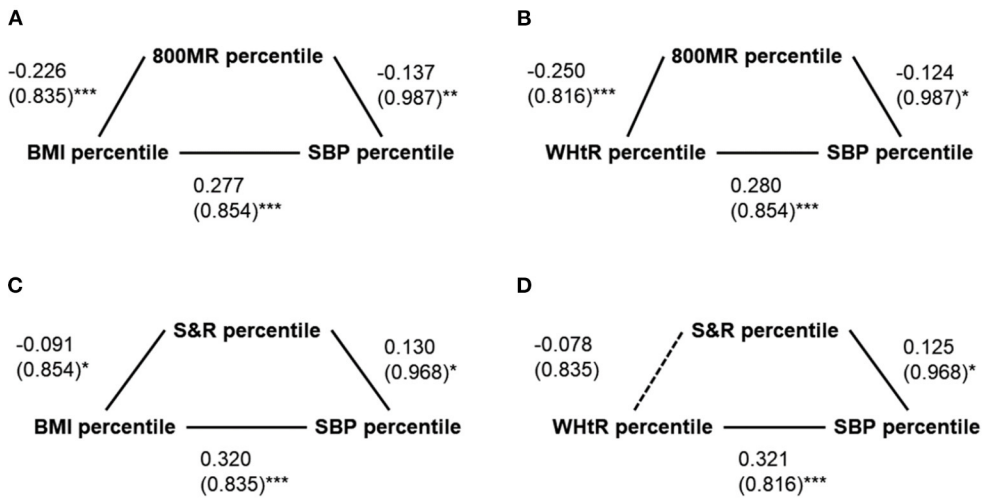


FIGURE 1
Simple mediation models of possible mediators of the relationships between anthropometric and blood pressure measures. **(A)** The 800-m run (800 mR) percentile significantly mediated the relationship between the body mass index (BMI) percentile and the systolic blood pressure (SBP) percentile. **(B)** The 800 mR percentile significantly mediated the relationship between the waist/height ratio (WHtR) percentile and the SBP percentile. **(C)** The S&R significantly mediated the relationship between the BMI percentile and the SBP percentile. **(D)** The S&R percentile did not significantly mediate the relationship between the WHtR percentile and the SBP percentile. Data are summarized as β (standard deviations). $^{*}p < 0.05$ and ≥ 0.01; $^{**}p < 0.01$ and ≥ 0.001; $^{***}p < 0.001$.

$p < 0.001$; indirect effect = 0.031, SD = 0.247, 95% CI: 0.010–0.066; mediation percentage = 10.1%) (Figure 1A) as well as the relationship between the WHtR percentile and SBP percentile (total effect = 0.311, SD = 0.816, 95% CI: 0.227–0.395, $p < 0.001$; direct effect = 0.280, SD = 0.854, 95% CI: 0.192–0.368, $p < 0.001$; indirect effect = 0.031, SD = 0.266, 95% CI: 0.006–0.059; mediation percentage = 10.0%) (Figure 1B).

TABLE 4 Independent predictors for pediatric hypertension with anthropometric and physical fitness measures in the overall cohort.

Variables	Full model				Parsimonious model			
	Exp(β)	95% CI	p-value[a]	VIF	Exp(β)	95% CI	p-value[b]	VIF
Hypertension								
BMI percentile	1.019	1.007–1.030	0.001	2.363	1.024	1.016–1.032	< 0.001	1.024
WHtR percentile	1.006	0.995–1.017	0.271	2.445			Not significant	
800 mR percentile	0.999	0.990–1.009	0.909	1.319			Not significant	
SLJ percentile	0.993	0.984–1.001	0.090	1.285	0.992	0.985–0.999	0.042	1.024
1 mSU percentile	0.995	0.985–1.004	0.266	1.367			Not significant	
S&R percentile	1.006	0.997–1.015	0.168	1.113			Not significant	
	$R^2 = 0.187$				$R^2 = 0.170$			
Systolic hypertension								
BMI percentile	1.018	1.006–1.031	0.003	2.363	1.023	1.015–1.032	< 0.001	1.072
WHtR percentile	1.007	0.996–1.018	0.229	2.445			Not significant	
800 mR percentile	0.993	0.984–1.003	0.174	1.319	0.990	0.982–0.999	0.031	1.072
SLJ percentile	0.997	0.988–1.005	0.462	1.285			Not significant	
1 mSU percentile	0.996	0.986–1.006	0.456	1.367			Not significant	
S&R percentile	1.010	1.001–1.019	0.038	1.113			Not significant	
	$R^2 = 0.192$				$R^2 = 0.169$			
Diastolic hypertension								
BMI percentile	1.015	0.998–1.031	0.077	2.363	1.012	1.001–1.023	0.029	1.023
WHtR percentile	0.996	0.981–1.011	0.626	2.445			Not significant	
800 mR percentile	1.003	0.990–1.016	0.658	1.319			Not significant	
SLJ percentile	0.984	0.972–0.995	0.006	1.285	0.982	0.972–0.992	0.001	1.023
1 mSU percentile	0.995	0.982–1.007	0.396	1.367			Not significant	
S&R percentile	0.997	0.985–1.009	0.626	1.113			Not significant	
	$R^2 = 0.104$				$R^2 = 0.098$			

[a] All anthropometric and physical fitness variables were included for multivariable binary logistic regression models.
[b] All anthropometric and physical fitness variables were included for multivariable binary logistic regression models with manual selections.

2) The S&R percentile significantly mediated the relationship between the BMI percentile and SBP percentile (total effect = 0.308, SD = 0.835, 95% CI: 0.222–0.394, $p < 0.001$; direct effect = 0.320, SD = 0.835, 95% CI: 0.234–0.406, $p < 0.001$; indirect effect = −0.012, SD = 0.133, 95% CI: −0.032–0.0002; mediation percentage = −3.9%) (Figure 1C); however, the S&R percentile did not mediate the relationship between the WHtR percentile and SBP percentile (total effect = 0.311, SD = 0.816, 95% CI: 0.227–0.395, $p < 0.001$; direct effect = 0.321, SD = 0.816, 95% CI: 0.237–0.405, $p < 0.001$; indirect effect = −0.010, SD = 0.133, 95% CI: −0.025–0.002; mediation percentage = −3.2%) (Figure 1D).

3.6. Independent predictors for pediatric hypertension

Table 4 summarizes independent predictors for pediatric hypertension in the overall cohort. Using multivariable binary logistic regression models, a higher BMI percentile was significantly correlated with pediatric hypertension in the full model. Using manual selection approaches, a higher BMI percentile and a lower SLJ percentile were associated with pediatric hypertension in the parsimonious model. A higher BMI percentile and a higher S&R percentile were significantly related to systolic hypertension in the full models; however, a higher BMI percentile and lower 800 mR were independently associated with systolic hypertension in the parsimonious model. A lower SLJ percentile was correlated with diastolic hypertension in the full model; furthermore, a higher BMI percentile and a lower SLJ percentile were independently related to diastolic hypertension in the parsimonious model.

4. Discussion

Obesity is one of the most critical risk factors for pediatric hypertension. A substantial volume of research has supported the roles of anthropometric measures (such as BMI, WHtR, and waist circumference) and body composition parameters (such as

fat mass and fat-free mass) in predicting pediatric hypertension (23, 53, 54). In line with the literature, our data showed that the hypertensive subgroup had higher BMI and WHtR percentiles; also, higher BMI and WHtR percentiles were related to the SBP percentile independent of physical fitness variables. Along with growth and development, weight status may be quite varying during childhood. The Clinical Practice Guideline developed by the European Society of Endocrinology and the Pediatric Endocrine Society has suggested regular evaluation, early identification, and prompt intervention to prevent the detrimental effects of pediatric obesity (55).

However, the connections between physical fitness and BP in children are not as conclusive as those between weight status and BP. Some research has shown that better physical fitness is associated with lower diastolic and systolic BP in children and adolescents despite mechanisms not yet fully understood (28, 30, 56, 57). Dong et al. used a complex and summative physical fitness indicator composed of forced vital capacity, SLJ, 800 mR, S&R, and 1 mSU, which could significantly predict raised systolic and diastolic hypertension in children aged 7–18 years; however, S&R was not related to high BP (26). Nevertheless, physical fitness did not well predict BP in children aged 6–11 years (58). Furthermore, a meta-analysis of randomized controlled trials conducted by García-Hermoso et al. in 2020 showed that physical exercise interventions improved BMI, waist circumference, and physical fitness, but not BP in preschoolers (59). These findings indicate that the relationships and interactions between physical fitness and pediatric hypertension need to be further delineated to yield more precise prevention and intervention strategies in terms of health promotion.

Current evidence suggests that cardiorespiratory fitness is overall inversely related to BP and multiple cardiovascular risk factors despite some discordances between studies with different epidemiological, methodological, and analytical approaches. Diaz et al. demonstrated that better cardiorespiratory fitness was associated with decreased probability of BP elevation, lower insulin resistance, and improved liver and renal functions (28, 30, 56, 57). Köchli et al. reported a less favorable micro- and macro-vascular profile in children aged 6–8 years with poor cardiorespiratory fitness (60). De Moraes et al. found that low cardiorespiratory fitness and muscular fitness accurately predicted high BP in children aged 3–17 years (61). Furthermore, Ayala-Guzmán et al. found that the relationship between low cardiorespiratory fitness and hypertension was not significant after correlation with BMI in children aged 9 to 12 years (29). The current study supported the linkage between poor cardiorespiratory fitness and high BP in children aged 9–12 years, and we further revealed that the impact was mainly on systolic BP, independent of weight status. Moreover, cardiorespiratory fitness mediated the relationships between the BMI percentile and WHtR percentile with the SBP percentile (Figures 1A, B). Future research is warranted to define clinically relevant cutoff points of cardiorespiratory fitness (62, 63) for children. Moreover, the effectiveness of cardiorespiratory fitness promotion on health outcomes needs to be examined from a public health perspective (29).

Notably, according to our data, the lower SLJ percentile was an independent and critical physical fitness indicator in predicting both hypertension and diastolic hypertension, even after adjustment for anthropometric variables. The SLJ percentile neither mediated nor moderated the associations of the DBP percentile with the BMI percentile or WHtR percentile; the effect of SLJ performance on DBP was direct. The SLJ, also known as the standing long jump, requires pushing the total body mass forward and is one of the most common physical fitness tests for children to assess lower body muscle strength. The SLJ is highly associated with isokinetic measures of lower extremity force (64). The calf muscles, including gastrocnemius and soleus, are involved in the movements of an SLJ. It is called "the second heart" by some as it pumps blood back to the trunk and improves circulation during walking and exercising (65). Calf muscle pump dysfunction can result in venous hypertension (66). Agostinis-Sobrinho found that a low level of muscular fitness was associated with a high inflammatory status in adolescents (62, 63). Delgado Floody et al. demonstrated that low maximal oxygen consumption and low body muscle strength were positively associated with high SBP (67) in children aged 11–13 years.

The solo and inverse association between the SLJ percentile and DBP percentile was a novel and particularly interesting finding of this study. In contrast to older people, in whom isolated diastolic hypertension is less prevalent and not associated with CV outcomes, emerging evidence suggests that the linkage between isolated diastolic hypertension and adverse CV effects is particularly significant in younger individuals and requires treatment (68). Cohen et al. reported a similar finding to the current study: handgrip had a protective effect against BP elevation, especially DBP (28, 30, 56, 57). Moreover, in a Korean multidisciplinary lifestyle intervention program, children and adolescents with moderate-to-severe obesity significantly improved their weight status, body composition, and DBP, but not SBP (69, 70). Future investigations on the pathogenesis of diastolic hypertension among the youth and its linkage to muscular fitness will be of interest.

Literature has suggested that the adverse effects of low physical fitness are likely to be prevented or even reversed by increasing physical activity. For example, an 8-week fitness course in indoor cycling can improve BMI, waist circumference, physical fitness (lower body muscle strength and aerobic fitness), and BP (71). Limiting sedentary behaviors, proper nutrition, increasing physical activity, and resting sufficiently may promote physical fitness and health outcomes (72, 73). Exercise can increase physical fitness and reduce BP in children and adolescents (69, 70) *via* the activation of adaptive mechanisms to improve endothelial function, induce pro-angiogenic pathways, and increase insulin sensitivity (74). Furthermore, engaging in moderate-to-vigorous physical activity, such as aerobic exercise, to achieve an improved (75) or a within-recommended level of cardiorespiratory fitness (76) reduces the incidence of hypertension. The results of the current study again highlight the importance of the assessment and promotion of physical fitness among children.

The present study has remarkable strengths derived from its comprehensive evaluation of physical fitness and BP with the exemplary sample size and the heterogeneous participants, recruited from different schools in northern Taiwan. However, this study has several limitations which merit discussion. First, all the

participants were school students in Taiwan and mainly Han. The mean intake of sodium by Taiwanese children was significantly higher than the Daily Reference Intake of Taiwan or other recommended standards (77), furthermore, children in Guishan had the highest prevalence of overweight and obesity compared to nearby areas (78), therefore the cohort of this study was at risk of high BP. This may limit the generalizability of the study. Second, the BP measurements were not standardized for medical diagnosis of hypertension as there was no confirmation through auscultation or ambulatory BP monitoring. Therefore, conditions such as white coat hypertension, masked hypertension, or isolated nocturnal hypertension could not be identified (79). Instead, automated BP measurement with the lowest SBP and DBP readings was adopted. Third, there are many exercise tests to assess the same physical fitness component [for example, 20-m aerobic cardiovascular endurance run test (25, 29), 6-min running/walking test (30), maximal ergometer cycle test (24) to cardiorespiratory fitness, or push-ups (29), and manual dynamometer (31) to measure muscular endurance], construct validity may differ across various exercise tests. Fourth, this cross-sectional study could not conclude the causality of physical fitness-mediated hypertension in children and the results should be interpreted cautiously. Longitudinal case-control and interventional studies are warranted to confirm the role of lower body muscle strength in pediatric hypertension.

In conclusion, the present study demonstrated that suboptimal weight status and physical fitness were two major risk factors for high BP among children. The BMI percentile was independently associated with the SBP percentile, systolic hypertension, and pediatric hypertension. The 800 mR was independently associated with the SBP percentile and systolic hypertension; it also mediated the relationship between weight status and BP. The SLJ was independently associated with the DBP percentile, diastolic hypertension, and pediatric hypertension. Not only weight management but also physical fitness promotion is vital for the pediatric population and the focus should be on both cardiorespiratory and muscular fitness.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by Institutional Review Board of the Chang Gung Medical Foundation, Taoyuan, Taiwan. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

H-HC, W-JC, K-HH, and R-HL conceived and planned the study. H-HC enrolled the patients. H-HC, W-JC, L-AL, and R-HL designed the study, analyzed data, made the statistics, and interpreted the results. H-HC, W-JC, L-AL, K-HH, and R-HL participated in manuscript drafting. C-HL, K-HH, and R-HL supervised the study. All authors read and approved the final manuscript.

Funding

This study was funded by the National Science and Technology Council, Taiwan (grant numbers MOST 110-2314-B-182-062 and 111-2314-B-182−019 -MY2) and Chang Gung Medical Foundation, Taiwan (grant numbers CMRPG1H0061-63, CORPG1L0011, CORPG3C0011-13, and CORPG1I0021).

Acknowledgments

The authors thank Yi-Ting Lin, Pei-Chi Yang, and Yu-Chan Liao (Department of Family Medicine, Chang Gung Memorial Hospital, Taipei and Linkou Main Branches, Taoyuan, Taiwan, ROC) for their administrative assistance. The authors also thank I-An Jen (a bio-statistician of the Department of Public Health, College of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan) for providing his assistance and consultation on data analysis.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. Fuchs FD, Whelton PK. High blood pressure and cardiovascular disease. *Hypertension.* (2020) 75:285–92. doi: 10.1161/HYPERTENSIONAHA.119.14240

2. Hamrahian SM, Falkner B. Hypertension in chronic kidney disease. *Adv Exp Med Biol.* (2017) 956:307–25. doi: 10.1007/5584_2016_84

3. Mills KT, Stefanescu A, He J. The global epidemiology of hypertension. *Nat Rev Nephrol.* (2020) 16:223–37. doi: 10.1038/s41581-019-0244-2

4. Song P, Zhang Y, Yu J, Zha M, Zhu Y, Rahimi K, et al. Global prevalence of hypertension in children: a systematic review and meta-analysis.

JAMA Pediatr. (2019) 173:1154–63. doi: 10.1001/jamapediatrics.2019.3310

5. Chen X, Wang Y. Tracking of blood pressure from childhood to adulthood: a systematic review and meta-regression analysis. *Circulation.* (2008) 117:3171–80. doi: 10.1161/CIRCULATIONAHA.107.730366

6. Tran AH, Urbina EM. Hypertension in children. *Curr Opin Cardiol.* (2020) 35:376–80. doi: 10.1097/HCO.0000000000000744

7. Hamrahian SM, Falkner B. Approach to hypertension in adolescents and young adults. *Curr Cardiol Rep.* (2022). doi: 10.1007/s11886-021-01632-x

8. Hansen ML, Gunn PW, Kaelber DC. Underdiagnosis of hypertension in children and adolescents. *JAMA.* (2007) 298:874–9. doi: 10.1001/jama.298.8.874

9. Flynn JT, Kaelber DC, Baker-Smith CM, Blowey D, Carroll AE, Daniels SR, et al. Subcommittee on screening management of high blood pressure in children. Clinical practice guideline for screening and management of high blood pressure in children and adolescents. *Pediatrics.* (2017) 140. doi: 10.1542/peds.2017-1904

10. National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. *Pediatrics.* (2004) 114:555–76. doi: 10.1542/peds.114.2.S2.555

11. Azegami T, Uchida K, Tokumura M, Mori M. Blood pressure tracking from childhood to adulthood. *Front Pediatr.* (2021) 9:785356. doi: 10.3389/fped.2021.785356

12. Rao G. Diagnosis, epidemiology, and management of hypertension in Children. *Pediatrics.* (2016) 138:e20153616. doi: 10.1542/peds.2015-3616

13. Lee LA Li HY, Lin YS, Fang TJ, Huang YS, Hsu JF, Wu CM, et al. Severity of childhood obstructive sleep apnea and hypertension improved after adenotonsillectomy. *Otolaryngol Head Neck Surg.* (2015) 152:553–60. doi: 10.1177/0194599814561203

14. Agostinis-Sobrinho CA, Vilan K. Blood pressure in children. The key role of physical activity and body fatness. *Arq Bras Cardiol.* (2021) 116:957–8. doi: 10.36660/abc.20210117

15. Lo K, Wong M, Khalechelvam P, Tam W. Waist-to-height ratio, body mass index and waist circumference for screening paediatric cardio-metabolic risk factors: a meta-analysis. *Obes Rev.* (2016) 17:1258–75. doi: 10.1111/obr.12456

16. Wang B, Yuan Y, Sun L, Zhang L, Zhang Z, Fu L, et al. Optimal cutoff of the abdominal skinfold thickness (AST) to predict hypertension among Chinese children and adolescents. *J Hum Hypertens.* (2021) 36:860–5. doi: 10.1038/s41371-021-00573-w

17. Leary SD, Ness AR, Smith GD, Mattocks C, Deere K, Blair SN, et al. Physical activity and blood pressure in childhood: findings from a population-based study. *Hypertension.* (2008) 51:92–8. doi: 10.1161/HYPERTENSIONAHA.107.099051

18. Gopinath B, Hardy LL, Teber E, Mitchell P. Association between physical activity and blood pressure in prepubertal children. *Hypertens Res.* (2011) 34:851–5. doi: 10.1038/hr.2011.46

19. Knowles G, Pallan M, Thomas GN, Ekelund U, Cheng KK, Barrett T, et al. Physical activity and blood pressure in primary school children: a longitudinal study. *Hypertension.* (2013) 61:70–5. doi: 10.1161/HYPERTENSIONAHA.112.201277

20. Tremblay MS, Colley RC, Saunders TJ, Healy GN, Owen N. Physiological and health implications of a sedentary lifestyle. *Appl Physiol Nutr Metab.* (2010) 35:725–40. doi: 10.1139/H10-079

21. Ruiz JR, Castro-Pinero J, Artero EG, Ortega FB, Sjostrom M, Suni J, et al. Predictive validity of health-related fitness in youth: a systematic review. *Br J Sports Med.* (2009) 43:909–23. doi: 10.1136/bjsm.2008.056499

22. Ortega FB, Ruiz JR, Castillo MJ, Sjostrom M. Physical fitness in childhood and adolescence: a powerful marker of health. *Int J Obes (Lond).* (2008) 32:1–11. doi: 10.1038/sj.ijo.0803774

23. Hsu CY, Lin RH, Lin YC, Chen JY Li WC, Lee LA, Liu KH, et al. Are body composition parameters better than conventional anthropometric measures in predicting pediatric hypertension? *Int J Environ Res Public Health.* (2020) 17:5771. doi: 10.3390/ijerph17165771

24. Klasson-Heggebo L, Andersen LB, Wennlof AH, Sardinha LB, Harro M, Froberg K, et al. Graded associations between cardiorespiratory fitness, fatness, and blood pressure in children and adolescents. *Br J Sports Med.* (2006) 40:25–9. doi: 10.1136/bjsm.2004.016113

25. Agostinis-Sobrinho C, Ruiz JR, Moreira C, Abreu S, Lopes L, Oliveira-Santos J. Cardiorespiratory fitness and blood pressure: a longitudinal analysis. *J Pediatr.* (2018) 192:130–5. doi: 10.1016/j.jpeds.2017.09.055

26. Dong Y, Jan C, Zou Z, Dong B, Hu P, Ma Y, et al. Comprehensive physical fitness and high blood pressure in children and adolescents: a national cross-sectional survey in China. *J Sci Med Sport.* (2020) 23:800–6. doi: 10.1016/j.jsams.2020.02.016

27. Hofman A, Walter HJ, Connelly PA, Vaughan RD. Blood pressure and physical fitness in children. *Hypertension.* (1987) 9:188–91. doi: 10.1161/01.HYP.9.2.188

28. Agostinis-Sobrinho C, Ruiz JR, Moreira C, Lopes L, Ramírez-Vélez R, García-Hermoso A, et al. Changes in muscular fitness and its association with blood pressure in adolescents. *Eur J Pediatr.* (2018) 177:1101–9. doi: 10.1007/s00431-018-3164-4

29. Ayala-Guzman CI, Cruz LGJ, Ortiz-Hernandez L. Differences in blood pressure according to physical fitness and body mass in a sample of Mexican schoolchildren. *Bol Med Hosp Infant Mex.* (2020) 77:15–22. doi: 10.24875/BMHIM.19000139

30. Pinheiro G, Mello J, Gaya A, Gaya AR. Blood pressure in children: association with anthropometric indicators, body composition, cardiorespiratory fitness and physical activity. *Arq Bras Cardiol.* (2021) 116:950–6.

31. Nunes HEG, Alves CAS, Goncalves ECA, Silva DAS. What physical fitness component is most closely associated with adolescents' blood pressure? *Percept Mot Skills.* (2017) 124:1107–20. doi: 10.1177/0031512517730414

32. Chuang HH, Lin RH, Chen JY, Yeh WC, Lin HF, Ueng SW, et al. Effectiveness of a multi-faceted intervention among elementary school children. *Medicine.* (2019) 98:e15079. doi: 10.1097/MD.0000000000015079

33. World Medical A. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA.* (2013) 310:2191–4. doi: 10.1001/jama.2013.281053

34. van der Lee JH, Mokkink LB, Grootenhuis MA, Heymans HS, Offringa M. Definitions and measurement of chronic health conditions in childhood: a systematic review. *JAMA.* (2007) 297:2741–51. doi: 10.1001/jama.297.24.2741

35. Compas BE, Jaser SS, Dunn MJ, Rodriguez EM. Coping with chronic illness in childhood and adolescence. *Annu Rev Clin Psychol.* (2012) 8:455–80. doi: 10.1146/annurev-clinpsy-032511-143108

36. Flegal KM, Cole TJ. Construction of LMS parameters for the Centers for Disease Control and Prevention 2000 growth charts. *Natl Health Stat Rep.* (2013) 1–3.

37. Ma W-Y, Yang C-Y, Shih S-R, Hsieh H-J, Hung CS, Chiu F-C, et al. Measurement of waist circumference: midabdominal or iliac crest? *Diabetes Care.* (2013) 36:1660–6. doi: 10.2337/dc12-1452

38. Sharma AK, Metzger DL, Daymont C, Hadjiyannakis S, Rodd CJ. LMS tables for waist-circumference and waist-height ratio Z-scores in children aged 5–19 y in NHANES III: association with cardio-metabolic risks. *Pediatr Res.* (2015) 78:723–9. doi: 10.1038/pr.2015.160

39. Ministry of Education in Taiwan. *Measures for the Implementation of Physical Fitness testing in Taiwan*. Taipei, Taiwan: Taiwan Ministry of Education. (2018). Available online at: https://edu.law.moe.gov.tw/LawContent.aspx?id=GL000769 (accessed March 13, 2023).

40. Hsu CY, Chen LS, Chang IJ, Fang WC, Huang SW, Lin RH, et al. Can anthropometry and body composition explain physical fitness levels in school-aged children? *Children.* (2021) 8:460. doi: 10.3390/children8060460

41. Taiwan Sports Administrain. *Normal Values of physical Fitness for Students Aged 7–23 Years*. Taipei, Taiwan: Ministry of Education in Taiwan. (2012). Available online at: https://www.fitness.org.tw/model01.php (accessed March 13, 2023).

42. Hsieh PL, Chen ML, Huang CM, Chen WC Li CH, Chang LC. Physical activity, body mass index, and cardiorespiratory fitness among school children in Taiwan: a cross-sectional study. *Int J Environ Res Public Health.* (2014) 11:7275–85. doi: 10.3390/ijerph110707275

43. Hu J, Li Z, Li S, Li H, Wang S, Wang S, et al. Skipping breakfast and physical fitness among school-aged adolescents. *Clinics.* (2020) 75:e1599. doi: 10.6061/clinics/2020/e1599

44. Wang JH, Wu MC, Chang HH. Urban-rural disparity in physical fitness of elementary schoolchildren in Taiwan. *Pediatr Int.* (2013) 55:346–54. doi: 10.1111/ped.12044

45. Reid RER, Fillon A, Thivel D, Henderson M, Barnett TA, Bigras JL, et al. Can anthropometry and physical fitness testing explain physical activity levels in children and adolescents with obesity? *J Sci Med Sport.* (2020) 23:580–5. doi: 10.1016/j.jsams.2019.12.005

46. Lovecchio N, Novak D, Sedlacek J, Hamar P, Milanovic I, Radisavljevic-Janic S, et al. Physical fitness for sedentary students: a common trend from six European countries. *J Sports Med Phys Fitness.* (2019) 59:1389–96. doi: 10.23736/S0022-4707.18.08926-0

47. Huang YC, Malina RM. Body mass index and individual physical fitness tests in Taiwanese youth aged 9-18 years. *Int J Pediatr Obes.* (2010) 5:404–11. doi: 10.3109/17477160903497902

48. Huang YC, Malina RM. Physical activity and health-related physical fitness in Taiwanese adolescents. *J Physiol Anthropol Appl Human Sci.* (2002) 21:11–9. doi: 10.2114/jpa.21.11

49. Mayorga-Vega D, Merino-Marban R, Viciana J. Criterion-related validity of sit-and-reach tests for estimating hamstring and lumbar extensibility: a meta-analysis. *J Sports Sci Med.* (2014) 13:1–14. doi: 10.4100/jhse.2014.91.18

50. Flynn JT, Kaelber DC, Baker-Smith CM, Blowey D, Carroll AE, Daniels SR, et al. Clinical practice guideline for screening and management of high blood pressure in children and adolescents. *Pediatrics.* (2017) 140:e20171904. doi: 10.1542/peds.2017-3035

51. Dormann CF, Elith J, Bacher S, Buchmann C, Carl G, Carré G, et al. Collinearity: a review of methods to deal with it and a simulation study evaluating their performance. *Ecography.* (2013) 36:27–46. doi: 10.1111/j.1600-0587.2012.07348.x

52. Hayes AF. *Introduction to Mediation, Moderation and Conditional Process Analysis: A Regression-Based Approach*. New York: Guilford Press. (2022).

53. Mazicioglu MM, Yalcin BM, Ozturk A, Ustunbas HB, Kurtoglu S. Anthropometric risk factors for elevated blood pressure in adolescents in Turkey aged 11–17. *Pediatric Nephrol.* (2010) 25:2327–34. doi: 10.1007/s00467-010-1623-x

54. Gishti O, Gaillard R, Durmus B, Abrahamse M, van der Beek EM, Hofman A, et al. Total and abdominal fat distribution, and cardiovascular risk factors in school-age children. *Pediatr Res.* (2015) 77:710–8. doi: 10.1038/pr.2015.29

55. Styne DM, Arslanian SA, Connor EL, Farooqi IS, Murad MH, Silverstein JH, et al. Pediatric obesity-assessment, treatment, and prevention: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab.* (2017) 102:709–57. doi: 10.1210/jc.2016-2573

56. Cohen DD, Lopez-Jaramillo P, Fernandez-Santos JR, Castro-Pinero J, Sandercock G. Muscle strength is associated with lower diastolic blood pressure in schoolchildren. *Prev Med.* (2017) 95:1–6. doi: 10.1016/j.ypmed.2016.11.006

57. Diaz EC, Weber JL, Adams SH, Young CG, Bai S, Borsheim E. Cardiorespiratory fitness associates with blood pressure and metabolic health of children-the arkansas active kids study. *Med Sci Sports Exerc.* (2021) 53:2225–32. doi: 10.1249/MSS.0000000000002701

58. Zaqout M, Michels N, Bammann K, Ahrens W, Sprengeler O, Molnar D, et al. Influence of physical fitness on cardio-metabolic risk factors in European children. The IDEFICS study. *Int J Obes.* (2016) 40:1119–25. doi: 10.1038/ijo.2016.22

59. Garcia-Hermoso A, Alonso-Martinez AM, Ramirez-Velez R, Izquierdo M. Effects of exercise intervention on health-related physical fitness and blood pressure in preschool children: a systematic review and meta-analysis of randomized controlled trials. *Sports Med.* (2020) 50:187–203. doi: 10.1007/s40279-019-01191-w

60. Kochli S, Endes K, Steiner R, Engler L, Infanger D, Schmidt-Trucksass A, et al. Obesity, high blood pressure, and physical activity determine vascular phenotype in young children. *Hypertension.* (2019) 73:153–61. doi: 10.1161/HYPERTENSIONAHA.118.11872

61. De Moraes ACF, Vilanova-Campelo RC, Torres-Leal FL, Carvalho HB. Is self-reported physical fitness useful for estimating fitness levels in children and adolescents? A reliability and validity study. *Medicina.* (2019) 55:286. doi: 10.3390/medicina55060286

62. Agostinis-Sobrinho CA, Moreira C, Abreu S, Lopes L, Sardinha LB, Oliveira-Santos J, et al. Muscular fitness and metabolic and inflammatory biomarkers in adolescents: results from LabMed physical activity study. *Scand J Med Sci Sports.* (2017) 27:1873–80. doi: 10.1111/sms.12805

63. Takken T, Bongers BC, van Brussel M, Haapala EA, Hulzebos EHJ. Cardiopulmonary exercise testing in pediatrics. *Ann Am Thorac Soc.* (2017) 14:S123–8. doi: 10.1513/AnnalsATS.201611-912FR

64. Wiklander J, Lysholm J. Simple tests for surveying muscle strength and muscle stiffness in sportsmen. *Int J Sports Med.* (1987) 8:50–4. doi: 10.1055/s-2008-1025640

65. Bolton L. Exercise and chronic wound healing. *Wounds.* (2019) 31:65–7.

66. Welkie JF, Comerota AJ, Katz ML, Aldridge SC, Kerr RP, White JV. Hemodynamic deterioration in chronic venous disease. *J Vasc Surg.* (1992) 16:733–40. doi: 10.1016/0741-5214(92)90228-Z

67. Delgado Floody PA, Caamano Navarrete F, Palomino-Devia C, Jerez-Mayorga D, Martinez-Salazar C. Relationship in obese Chilean schoolchildren between physical fitness, physical activity levels and cardiovascular risk factors. *Nutr Hosp.* (2019) 36:13–9. doi: 10.20960/nh.1932

68. Chrysant SG. The clinical significance of isolated diastolic hypertension. *Postgrad Med.* (2020) 132:624–8. doi: 10.1080/00325481.2020.1788294

69. Seo YG, Lim H, Kim Y, Ju YS, Lee HJ, Jang HB, et al. The effect of a multidisciplinary lifestyle intervention on obesity status, body composition, physical fitness, and cardiometabolic risk markers in children and adolescents with obesity. *Nutrients.* (2019) 11:137. doi: 10.3390/nu11010137

70. Wellman RJ, Sylvestre MP, Abi Nader P, Chiolero A, Mesidor M, Dugas EN, et al. Intensity and frequency of physical activity and high blood pressure in adolescents: a longitudinal study. *J Clin Hypertens.* (2020) 22:283–90. doi: 10.1111/jch.13806

71. Chavarrias M, Carlos-Vivas J, Barrantes-Martin B, Perez-Gomez J. Effects of 8-week of fitness classes on blood pressure, body composition, and physical fitness. *J Sports Med Phys Fitness.* (2019) 59:2066–74. doi: 10.23736/S0022-4707.19.09886-4

72. Cao M, Quan M, Zhuang J. Effect of high-intensity interval training versus moderate-intensity continuous training on cardiorespiratory fitness in children and adolescents: a meta-analysis. *Int J Environ Res Public Health.* (2019) 16:1533. doi: 10.3390/ijerph16091533

73. Chaput JP, Willumsen J, Bull F, Chou R, Ekelund U, Firth J, et al. 2020 WHO guidelines on physical activity and sedentary behaviour for children and adolescents aged 5-17 years: summary of the evidence. *Int J Behav Nutr Phys Act.* (2020) 17:141. doi: 10.1186/s12966-020-01037-z

74. Gambardella J, Morelli MB, Wang XJ, Santulli G. Pathophysiological mechanisms underlying the beneficial effects of physical activity in hypertension. *J Clin Hypertens.* (2020) 22:291–5. doi: 10.1111/jch.13804

75. Bakker EA, Sui X, Brellenthin AG, Lee DC. Physical activity and fitness for the prevention of hypertension. *Curr Opin Cardiol.* (2018) 33:394–401. doi: 10.1097/HCO.0000000000000526

76. Momma H, Sawada SS, Sloan RA, Gando Y, Kawakami R, Miyachi M, et al. Frequency of achieving a "fit" cardiorespiratory fitness level and hypertension: a cohort study. *J Hypertens.* (2019) 37:820–6. doi: 10.1097/HJH.0000000000001935

77. Wu SJ, Pan WH, Yeh NH, Chang HY. Dietary nutrient intake and major food sources: the Nutrition and Health Survey of Taiwan Elementary School Children 2001–2002. *Asia Pac J Clin Nutr.* (2007) 2:518–33.

78. Health Promotion Administration. *Nutrition and Health Survey in Taiwan, 2013–2016*. (2022). Epub July 12, 2019. Available online at: https://www.hpa.gov.tw/Pages/ashx/File.ashx?FilePath$=\sim$/File/Attach/11145/File_12788.pdf (accessed March 13, 2023).

79. Awazu M. Isolated nocturnal hypertension in children. *Front Pediatrics*. (2022) 10:54. doi: 10.3389/fped.2022.823414

frontiers | Frontiers in Public Health

TYPE Original Research
PUBLISHED 27 April 2023
DOI 10.3389/fpubh.2023.1097675

OPEN ACCESS

EDITED BY
Shikai Yu,
Tongji University, China

REVIEWED BY
Susma Vaidya,
Children's National Hospital, United States
Claudio Maffeis,
University of Verona, Italy

*CORRESPONDENCE
Muhammad Yazid Jalaludin
✉ yazidj@ummc.edu.my

SPECIALTY SECTION
This article was submitted to Children and Health, a section of the journal Frontiers in Public Health

RECEIVED 14 November 2022
ACCEPTED 14 March 2023
PUBLISHED 27 April 2023

CITATION
Nur Zati Iwani AK, Jalaludin MY, Roslan FA, Mansor F, Md Zain F, Hong JYH, Zin RMWM, Yahya A, Ishak Z, Selamat R and Mokhtar AH (2023) Cardiometabolic risk factors among children who are affected by overweight, obesity and severe obesity.
Front. Public Health 11:1097675.
doi: 10.3389/fpubh.2023.1097675

Cardiometabolic risk factors among children who are affected by overweight, obesity and severe obesity

Ahmad Kamil Nur Zati Iwani[1], Muhammad Yazid Jalaludin[2]*, Farah Aqilah Roslan[1], Fazliana Mansor[1], Fuziah Md Zain[3], Janet Yeow Hua Hong[3], Ruziana Mona Wan Mohd Zin[1], Abqariyah Yahya[4], Zahari Ishak[5], Rusidah Selamat[6] and Abdul Halim Mokhtar[7]

[1]Endocrine and Metabolic Unit, Institute for Medical Research, Ministry of Health Malaysia, Setia Alam, Malaysia, [2]Department of Paediatrics, Faculty of Medicine, University Malaya, Kuala Lumpur, Malaysia, [3]Department of Paediatrics, Hospital Putrajaya, Ministry of Health Malaysia, Putrajaya, Malaysia, [4]Department of Social and Preventive Medicine, Faculty of Medicine, University Malaya, Kuala Lumpur, Malaysia, [5]Department of Educational Psychology and Counselling, Faculty of Education, University Malaya, Kuala Lumpur, Malaysia, [6]Nutrition Division, Ministry of Health Malaysia, Putrajaya, Malaysia, [7]Department of Sports Medicine, Faculty of Medicine, University Malaya, Kuala Lumpur, Malaysia

Background: The increasing severity of obesity is expected to lead to more serious health effects. However, there is limited information on the prevalence and clinical characteristics of cardiometabolic risk factors in severely children affected by obesity in Malaysia. This baseline study aimed to investigate the prevalence of these factors and their association with obesity status among young children.

Methods: In this study, a cross-sectional design was employed using the baseline data obtained from the My Body Is Fit and Fabulous at school (MyBFF@school) intervention program involving obese school children. Obesity status was defined using the body mass index (BMI) *z*-score from the World Health Organization (WHO) growth chart. Cardiometabolic risk factors presented in this study included fasting plasma glucose (FPG), triglycerides (TGs), total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), blood pressure, acanthosis nigricans, insulin resistance (IR), and MetS. MetS was defined using the International Diabetes Federation (IDF) 2007 criteria. Descriptive data were presented accordingly. The association between cardiometabolic risk factors, such as obesity status, and acanthosis nigricans with MetS was measured using multivariate logistic regression, which was adjusted for gender, ethnicity, and strata.

Results: Out of 924 children, 38.4% ($n = 355$) were overweight, 43.6% ($n = 403$) were obese, and 18% ($n = 166$) were severely obese. The overall mean age was 9.9 ± 0.8 years. The prevalence of hypertension, high FPG, hypertriglyceridemia, low HDL-C, and the presence of acanthosis nigricans among severely children affected by obesity was 1.8%, 5.4%, 10.2%, 42.8%, and 83.7%, respectively. The prevalence of children affected by obesity who were at risk of MetS in <10-year-old and MetS >10-year-old was observed to be similar at 4.8%. Severely children affected by obesity had higher odds of high FPG [odds ratio (OR) = 3.27; 95% confdence interval (CI) 1.12, 9.55], hypertriglyceridemia (OR = 3.50; 95%CI 1.61, 7.64), low HDL-C (OR = 2.65; 95%CI 1.77, 3.98), acanthosis nigricans (OR = 13.49; 95%CI 8.26, 22.04), IR (OR = 14.35; 95%CI 8.84, 23.30), and MetS (OR = 14.03; 95%CI 3.97, 49.54) compared to overweight and children affected by obesity. The BMI z-score, waist circumference (WC), and percentage body fat showed a significant correlation with triglycerides, HDL-C, the TG: HDL-C ratio, and the homeostatic model assessment for IR (HOMA-IR) index.

Conclusions: Severely children affected by obesity exhibit a higher prevalence of and are more likely to develop cardiometabolic risk factors compared to overweight and children affected by obesity. This group of children should be monitored closely and screened periodically for obesity-related health problems to institute early and comprehensive intervention.

KEYWORDS

childhood obesity, severely obese, cardiometabolic risks, metabolic syndrome, acanthosis nigricans

1. Introduction

There is a high prevalence of obesity worldwide, affecting both adults and children (1, 2). The most recent national prevalence of overweight and obesity among Malaysian children aged 5–17 years was 15.0% and 14.8%, respectively (3). Despite an increase in the prevalence of obesity over the past 15 years, data on the impact of overweight, obesity, and severe obesity in young children in the world, including Malaysia, are still scarce. In some countries, the increase in childhood obesity preceded the increase in adult obesity (4). This high prevalence of obesity has led to heightened awareness and concerns relevant to many significant health problems, such as type 2 diabetes mellitus (T2DM), liver disease, hyperlipidemia, and cardiovascular disease (CVD), which consequently increase healthcare costs (5, 6). Several studies have shown that severe obesity was associated with a greater risk of weight-related complications, including abnormal lipid levels, blood glucose levels, and increased blood pressure (7, 8).

A systematic review and meta-analysis of 63 studies examining 49,200 children found that obesity was associated with significantly worse risk parameters for CVD in school-aged children (9). However, the finding was obtained from studies conducted in a highly developed country. Studies on cardiometabolic risk factors and their association with obesity status in school-aged children are still insufficiently explored in low- and middle-income countries, such as Malaysia. Cardiometabolic risk factors associated with obesity may include acanthosis nigricans, insulin resistance (IR), elevated blood pressure, and dyslipidemia, which may later lead to CVD and T2DM. A recent study by Garcia et al. (10) found that children affected by obesity with grade 3 acanthosis nigricans (the degree of severity in the neck by Burke's scale) were associated with increased waist circumference (WC), triglycerides (TGs), low-density lipoprotein cholesterol (LDL-C), total cholesterol, and homeostatic model assessment for IR (HOMA-IR), which might lead to vascular alterations. Similarly, our group also previously found that the majority of children with acanthosis nigricans (43%) were in the upper tertiles of the ratio of triglycerides to high-density lipoprotein cholesterol (TG: HDL-C) (11).

In addition to acanthosis nigricans, the metabolic syndrome (MetS), which encloses the clustering of cardiometabolic disorders, such as abdominal obesity, elevated fasting plasma glucose (FPG), dyslipidemia, and hypertension, is also an important tool for identifying individuals who are at a high risk of T2DM and CVD (12, 13). A previous study showed that the prevalence of obesity among Malaysian children diagnosed with MetS was 10% (14). The individual risk factors of MetS (abdominal obesity, high triglycerides, low HDL-C, high blood pressure, and high FPG) were found to be higher in children affected by obesity than in children with normal weight (14). The findings of this current study may provide a comparison of obesity status among school-aged children in Malaysia to previous studies and help develop effective policy measures to prevent obesity. Therefore, this study aimed to determine the prevalence of cardiometabolic risk factors and their association with obesity status among children who participated in My Body Is Fit and Fabulous at school (MyBFF@school) programs.

2. Methods

2.1. Study design and sampling

This study was a cross-sectional study, which used the baseline data of overweight, obesity, and severe obesity among young children who participated in the MyBFF@school phase II program. This programs was a school-based lifestyle intervention program that included nutritional–physical activity and psychology modules specifically designed for children affected by obesity (15). Between January and early March 2016, children and adolescents from 23 Malaysian Public Schools were screened. Eligible children were invited to participate in the intervention program. A written informed consent was obtained from parents or guardians, and the assent form was signed by the participating child.

2.2. Study participants

All children affected by obesity classified as overweight, obese, and severely obese according to the World Health Organization (WHO) body mass index (BMI) chart (16) using the BMI z-score criteria were eligible for this study. Children affected by obesity with a physical or mental impairment, with medical conditions that prevent him/her from participating in moderate-to-vigorous physical activity, with comorbidities that may interfere with the study (such as diagnosed T2DM, hypertension, nephritic syndrome, epilepsy, congenital heart disease, and skeletal anomalies), and on steroids, anti-epileptics, and methylphenidate were excluded from this study.

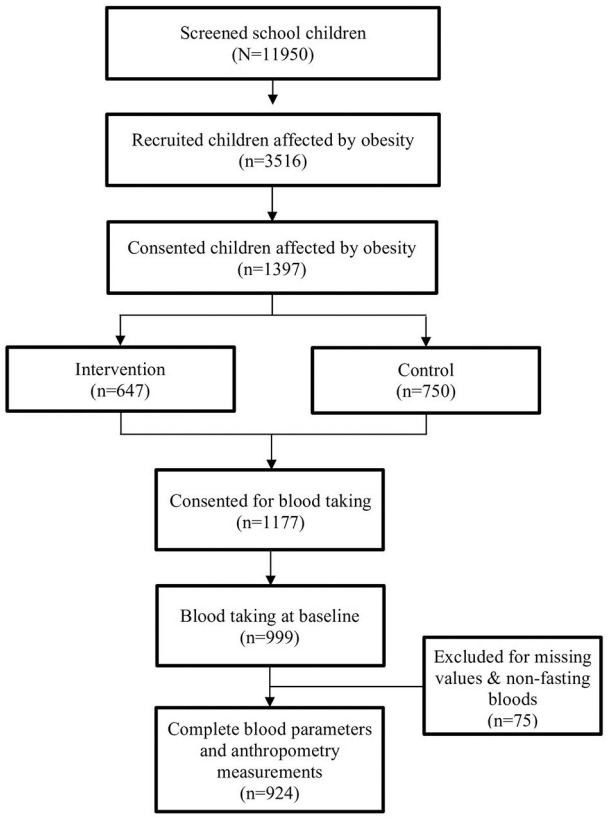


FIGURE 1
Flow chart for My Body is Fit and Fabulous at School (MyBFF@school) study at baseline.

A total of 11,950 primary school children aged 8–11 years were screened, and 3,516 (29.4%) children were eligible to participate. Of the 3,516 children, 1,397 (39.7%) gave their consent to participate in this study, with 647 of them in the intervention group and the remaining 750 children in the control group. At baseline, children in both groups underwent a similar screening that was performed in the morning because children were assessed during fasting. In this paper, 924 children with complete anthropometric measurements and fasting blood parameters at baseline were analyzed (Figure 1).

2.3. Anthropometric measurements

These measurements were taken two times, and their average was used in the data analysis. BMI was calculated by dividing weight in kilograms by the square of height in meters (kg/m^2). The weight category was grouped based on the WHO BMI chart (16) using the BMI z-score criteria, which is overweight, obese, and severely obese. The BMI *z*-score was calculated using the WHO AnthroPlus 2007 software, with an indication of overweight > +1.0 standard deviation (SD), obese > +2.0 SD, and severely obese > +3.0 SD (an extended cutoff from the WHO growth curve) (17, 18). WC was measured using a non-extensible tape (Seca 201, Germany) to the nearest 0.1 cm at the midpoint between the lowest rib and the iliac crest. Body weight and the percentage of body fat (PBF) were measured using a bioelectrical impedance analysis (InBody 720, BioSpace, Korea). Children were required to stand barefoot on the body composition analyzer while holding electrode hand holders for 3 min.

2.4. Clinical measurements

Blood pressure reading was gathered manually by trained staff using a mercury sphygmomanometer (Accoson, UK) with an appropriate cuff size for each individual. Children were in a sitting position with their right upper arm positioned at the heart level and their feet flat on the ground. The reading was taken two times at 5-min intervals to improve accuracy, and the mean was recorded. Physical examination for acanthosis nigricans at the nape of the neck was performed by trained medical officers/pediatricians.

A venous blood sample (after a minimum of 8 h fasting) was collected by trained nurses/medical officers. To measure blood glucose, 2 ml of blood was collected in a sodium fluoride tube, and to measure the lipid profile (total cholesterol, triglycerides, HDL-C, and LDL-C), another 5 ml in a plain tube test tube was collected. All blood samples were labeled and transported in an ice box to the central laboratory of the Institute for Medical Research within 2 h of collection. Serum total cholesterol, triglycerides, HDL-C, and LDL-C were assessed by the enzymatic colorimetric method, while the FPG level was determined by the enzymatic oxidation colorimetric method. All samples were analyzed by Randox Laboratories (Antrim, UK) using an autochemical analyzer, Dirui CS-400.

Children with MetS were determined according to the International Diabetes Federation (IDF) 2007 definition, which was defined as having a WC of more than the 90th percentile with the presence of at least 2 other clinical characteristics (triglycerides ≥ 1.7 mmol/L, HDL-C < 1.03 mmol/L, blood pressure ≥ 130/85 mmHg, and FPG ≥ 5.6 mmol/L) (19). These criteria are set for children over 10 years of age. Therefore, children who were <10 years of age and fulfilled the above criteria were classified as being at risk of MetS.

The IR status was based on the HOMA-IR calculated by multiplying the value of fasting plasma insulin and FPG and then dividing the multiplied value by 22.5 (20). In prepubertal children, a score of HOMA-IR of ≥2.6 (21) was classified as IR and of <2.6 as insulin sensitive. In pubertal children, a score of HOMA-IR of ≥ 4.0 was categorized as IR, while a score of <4.0 was categorized as insulin sensitive (22).

2.5. Statistical analysis

All data analyses were performed using the IBM Statistical Package for the Social Sciences (SPSS) version 22. The normality test of continuous data was determined using the Kolmogorov–Smirnov test. Continuous data were presented as mean and SD, while categorical data were presented as frequency and percentage. Comparison of the means was determined using the Kruskal–Wallis test for non-normally distributed variables. The chi-squared test was used to compare differences between the categorical

TABLE 1 Sociodemographic at baseline by obesity status.

Features	Overweight ($n = 355$)	Obese ($n = 403$)	Severely obese ($n = 166$)	*P*-value	Total ($N = 924$)
Total (%)	38.4	43.6	18.0	–	100.0
Sociodemographic					
Age					
Overall, mean ± SD	9.9 ± 0.9	9.9 ± 0.8	9.7 ± 0.9	0.009	9.9 ± 0.8
<10 years old, median (p25, p75)	9.0 (8.6, 9.6)	9.3 (8.8, 9.7)	8.9 (8.6, 9.4)	0.024	9.1 (8.7, 9.6)
≥10 years old, median (p25, p75)	10.6 (10.3, 10.9)	10.5 (10.2, 10.8)	10.5 (10.2, 10.7)	NS	10.5 (10.3, 10.8)
Gender, *n* (%)					
Boys	159 (44.8)	212 (52.6)	114 (68.7)	<0.001	485 (52.5)
Girls	196 (55.2)	191 (47.4)	52 (31.3)		439 (47.5)
Pubertal status, *n* (%)					
Boys					
Pre-pubertal	137 (85.6)	191 (90.5)	98 (86.0)	NS	426 (87.8)
Pubertal	23 (14.4)	20 (9.5)	16 (14.0)		59 (12.2)
Girls					
Pre-pubertal	137 (85.6)	191 (90.5)	98 (86.0)	NS	426 (87.8)
Pubertal	23 (14.4)	20 (9.5)	16 (14.0)		59 (12.2)
Ethnicity, *n* (%)					
Malay	263 (74.1)	301 (74.7)	133 (80.1)	NS	697 (75.4)
Chinese	46 (13.0)	53 (13.2)	16 (9.6)		115 (12.4)
Indian	41 (11.5)	42 (10.4)	13 (7.8)		96 (10.4)
Others	5 (1.4)	7 (1.7)	4 (2.4)		16 (1.7)
School location, *n* (%)					
Urban	186 (52.4)	242 (60)	96 (57.8)	NS	524 (56.7)
Rural	169 (47.6)	161 (40)	70 (42.2)		400 (43.3)

NS, not significant; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

data. The association between cardiometabolic risk factors by obesity status and acanthosis nigricans with MetS was measured using multivariate logistic regression and adjusted for gender, ethnicity, and strata. Spearman's correlation test was used to correlate anthropometry (BMI z-score, WC, and PBF) with MetS components and IR. A *p*-value of <0.05 was considered statistically significant for all analyses.

3. Results

Baseline sociodemographics by obesity status are presented in Table 1. The final number of children with complete data was 924, ranging in age from 8.0 to 11 years, with a mean (SD) age of 9.8 (0.84) and a median age of 9.9 years. In total, 52.5% were men and 47.5% were women. The majority of children were Malay (75.4%), followed by Chinese (12.4%), Indians (10.4%), and other ethnic groups (1.7%). Of the 924 children, 38.4% were overweight, 43.6% were obese, and 18.0% of them were severely obese. No significant differences were observed between school locations.

Table 2 presents anthropometric, clinical, and biochemical profiles at baseline by obesity status. As data on continuous variables were not normally distributed, median results were reported. The median of both BMI and the BMI z-score increased as a function of obesity status. Similarly, median WC and PBF increased as a function of obesity status. There was no significant difference in the blood pressure measurement. From the biochemical profile, severely children affected by obesity demonstrated higher triglycerides, higher median (0.9 mmol/l) and lower HDL-C, and lower median levels (1.0 mmol/l) compared to overweight and children affected by obesity.

Table 3 presents the prevalence of cardiometabolic risk factors by obesity status. It was found that the prevalence of all cardiometabolic risks was significantly higher with a greater degree of obesity. Severely children affected by obesity had a significantly higher prevalence of hypertension, high FPG, high triglycerides, and low HDL-C with frequencies of 1.8%, 5.4%, 10.2%, and 42.8%,

TABLE 2 Anthropometric measures, clinical measures, and biochemical profile at baseline by obesity status.

Features	Overweight ($n = 355$)	Obese ($n = 403$)	Severely obese ($n = 166$)	*P*-value	Total ($N = 924$)
Anthropometric measures					
BMI (kg/m^2), median (p25, p75)	20.4 (19.5, 21.3)	24.0 (22.9, 25.7)	29.1 (27.3, 31.3)	<0.001	23.2 (20.8, 25.9)
BMI z score median (p25, p75)	1.53 (1.29, 1.78)	2.44 (2.21, 2.74)	3.49 (3.24, 4.01)	<0.001	2.23 (1.69, 2.83)
Waist circumference (cm), median (p25, p75)	66.6 (63.4, 71.0)	77.0 (72.9, 81.2)	87.2 (81.4, 94.4)	<0.001	74.3 (68.0, 81.2)
Percentage of body fat (%), median (p25, p75)	32.6 (28.8, 35.7)	39.8 (36.7, 42.6)	45.7 (43.2, 48.3)	<0.001	37.8 (33.3, 42.8)
Clinical measures					
Blood pressure					
Systolic (mmHg), median (p25, p75)	100.0 (91.0, 105.0)	100.0 (92.0, 104.0)	100.9 (91.0, 105.0)	NS	100.0 (92.0, 104.0)
Diastolic (mmHg), median (p25, p75)	60.0 (57.0, 69.0)	61.0 (55.0, 69.0)	60.0 (57.8, 69.0)	NS	60.0 (57.0, 69.0)
Biochemical profile					
Fasting plasma glucose (mmol/L), median (p25, p75)	4.7 (4.5, 4.9)	4.7 (4.5, 4.9)	4.7 (4.5, 5.0)	NS	4.7 (4.5, 4.9)
Total cholesterol (mmol/L), median (p25, p75)	4.1 (3.7, 4.6)	4.1 (3.7, 4.6)	4.0 (3.6, 4.5)	NS	4.1 (3.7, 4.6)
Triglycerides (mmol/L), median (p25, p75)	0.7 (0.5, 1.0)	0.9 (0.7, 1.2)	0.9 (0.7, 1.2)	<0.001	0.8 (0.6, 1.1)
HDL-C (mmol/L), median (p25, p75)	1.1 (1.0, 1.3)	1.1 (0.9, 1.2)	1.0 (0.9, 1.2)	<0.001	1.1 (0.9, 1.2)
LDL-C (mmol/L), median (p25, p75)	2.8 (2.4, 3.3)	2.8 (2.4, 3.4)	2.9 (2.4,3.4)	NS	2.8 (2.4, 3.4)

NS, not significant; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

respectively, compared to overweight and children affected by obesity. The presence of acanthosis nigricans was significantly more common in severely children affected by obesity, which was 83.7% as compared to 58.8% in children affected by obesity and 31.3% in overweight children. Severely children affected by obesity also had the highest prevalence of IR using the HOMA-IR calculation, which was 72.8% and exhibited the highest value of the TG: HDL-C ratio. All severely children affected by obesity had WC above the 90th percentile ($p < 0.001$). Severely children affected by obesity had the highest PBF (45.5%), followed by 39.8% in children affected by obesity and 32.6% in overweight children. For children over 10 years of age, the prevalence of MetS increased significantly with the degree of obesity, which was 0.3%, 2.7%, and 4.8% in overweight, obese, and severely children affected by obesity, respectively. A similar prevalence of being at risk of MetS was also observed among children <10 years of age of 0.6%, 2.0%, and 4.8% in overweight, obese, and severely children affected by obesity, respectively.

The association between cardiometabolic risk factors and obesity status is shown in Table 4. Severely children affected by obesity had significantly higher odds (OR = 3.27; 95% confidence interval (CI) 1.12, 9.55) of having abnormal FPG levels compared to children affected by obesity. They also had higher odds of hypertriglyceridemia (OR = 3.50; 95%CI 1.61, 7.64), lower HDL-C (OR = 2.65; 95%CI 1.77, 3.98), the presence of acanthosis nigricans (OR = 13.49; 95%CI 8.26, 22.07), IR (OR = 14.35; 95%CI 8.84, 23.30), and MetS (OR = 14.03; 95%CI 3.97, 49.54). However, there was no significant difference in the odds of having high levels of total cholesterol and LDL-C.

Table 5 presents the association between adiposity measures (BMI z-score, WC, and PBF) and MetS components and IR. A higher correlation was observed between adiposity measures and IR surrogate markers (HOMA-IR and TG: HDL-C ratio) compared to MetS components ($r \approx 0.4$, $p < 0.001$ and $r \approx 0.2$, $p < 0.001$). Additionally, a significant correlation was found between adiposity measures and triglycerides and HDL-C. All three adiposity measures were not significantly correlated with blood pressure and FPG.

According to Table 6, children affected by obesity affected by acanthosis nigricans were two times as likely to develop MetS, i.e., 2.22 (95%CI 1.09, 4.52), after adjusting for gender, ethnicity, and strata.

TABLE 3 Prevalence of cardiometabolic risk factors by obesity status.

Features	Overweight ($n = 355$), n (%)	Obese ($n = 403$), n (%)	Severely obese ($n = 166$), n (%)	P-value
Waist circumference (cm) $\geq 90^{th}$ percentile	126 (35.5)	343 (85.1)	166 (100.0)	<0.001
Percentage body fat, mean (sd)	32.2 (4.8)	39.8 (4.4)	45.5 (4.2)	<0.001[a]
Hypertension (≥130/85 mmHg)	0	2 (0.5)	3 (1.8)	0.032
Fasting plasma glucose (≥5.6 mmol/L)	6 (1.7)	8 (2.0)	9 (5.4)	0.027
Total cholesterol (≥5.2 mmol/L)	32 (9.0)	37 (9.2)	12 (7.2)	NS
Triglycerides (≥1.7 mmol/L)	12 (3.4)	36 (8.9)	17 (10.2)	0.002
HDL-C (<1.03 mmol/L)	87 (24.5)	149 (37.0)	71 (42.8)	<0.001
LDL-C (≥3.36 mmol/L)	89 (25.1)	118 (29.3)	52 (31.3)	NS
Presence of acanthosis nigricans	111 (31.3)	237 (58.8)	139 (83.7)	<0.001
Insulin resistance by pubertal stage	63 (19.6)	158 (43.2)	107 (72.8)	<0.001
TG:HDL-C ratio, mean (sd)	0.78 (0.45)	0.98 (0.56)	1.02 (0.50)	<0.001[a]
Metabolic syndrome	1 (0.3)	11 (2.7)	8 (4.8)	<0.001
At risk of metabolic syndrome	2 (0.6)	8 (2.0)	8 (4.8)	

Chi-squared test.
[a]One-way analysis of variance (ANOVA).
NS, not significant; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.
Insulin resistance is calculated using the homeostatic model assessment for IR (HOMA-IR).

4. Discussion

My Body Is Fit and Fabulous at school is a school-based lifestyle intervention program to combat obesity among overweight, obese, and severely children affected by obesity. We studied the prevalence of cardiometabolic risk factors and their association with obesity status among children using the baseline information from this intervention program. To our knowledge, this is one of the large-scale studies in Southeast Asia to embark on understanding the health-related problems among severely children affected by obesity aged 8–11 years in the community. Alarmingly, severely obese young children was almost in the proportion of 20%, which means that they were more likely to remain obese in adulthood and develop complications, such as high LDL, hypertension, and T2DM (23). A similar trend was reported in the USA. According to the National Health and Nutrition Examination Survey, the rates of obesity among children and teenage have increased to more than threefold since the 1970s, along with the rates of severe obesity increasing more than fivefold in the same period (24, 25). Therefore, it is vital to determine the clinical characteristics of this group of children. This information will give more insights into the health risk of these children. Then, the obesity strategy could be governed from prevention to early diagnosis and treatment.

It is not surprising to note that severely children affected by obesity had the highest prevalence and a greater likelihood of having cardiometabolic risk factors compared with overweight and children affected by obesity. For example, a study of 8,579 obese American children and young adults demonstrated that the mean for cardiometabolic variables and the prevalence of abnormal values were higher with greater severity of obesity, particularly triglycerides and HDL-C (26). According to a follow-up study by Morrison et al. (27), the occurrence of CVD in adulthood was highly predicted by individuals with hypertriglyceridemia in childhood. Furthermore, the association between atherosclerosis in young children and elevated BMIs was long proven by the autopsy of children and young adults from the Bogalusa Heart Study (28). Additionally, youth with traditional CVD risk factors associated with childhood hypertension (e.g., homozygous or heterozygous familial hypercholesterolemia), severe obesity, and T2DM are at a higher risk of CVD (29). Our study highlighted that a high proportion of young but obese healthy children (8–11 years) already demonstrated a poor cardiometabolic profile, which could potentially lead to premature cardiovascular events if left unattended (18).

We also found a higher prevalence and greater likelihood of having acanthosis nigricans among severely children affected by obesity. The increase in adipose tissues during childhood

TABLE 4 Association between cardiometabolic risk factors and obesity status.

Obesity status	OR (95%CI)			
	Fasting plasma glucose (≥5.6 mmol/L)	Total cholesterol (≥5.2 mmol/L)	Triglycerides (≥1.7 mmol/L)	HDL-C (<1.03 mmol/L)
Overweight	1	1	1	1
Obese	1.20 (0.41, 3.51)	1.01 (0.61, 1.67)	2.90 (1.48, 5.69)[b]	1.91 (1.38, 2.62)[c]
Severely obese	3.27 (1.12, 9.55)[a]	0.70 (0.35, 1.42)	3.50 (1.61, 7.64)[b]	2.65 (1.77, 3.98)[c]
Obesity status	OR (95%CI)			
	LDL-C (≥3.36 mmol/L)	Presence of acanthosis nigricans	Insulin resistance according to pubertal stages	At risk of metabolic syndrome and metabolic syndrome
Overweight	1	1	1	1
Obese	1.26 (0.91, 1.74)	3.53 (2.57, 4.85)[c]	3.37 (2.37, 4.81)[c]	6.03 (1.76, 20.60)[b]
Severely obese	1.46 (0.96, 2.22)	13.49 (8.26, 22.04)[c]	14.35 (8.84, 23.30)[c]	14.03 (3.97, 49.54)[c]

Multivariate logistic regression (adjusted for gender, ethnicity, and strata).
[a]Significant at $p < 0.05$; [b]Significant at $p < 0.01$; [c]Significant at $p < 0.001$.
OR, odds ratio; CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

TABLE 5 The correlation between adiposity (BMI z-score, WC, and PBF) and metabolic syndrome components and insulin resistance.

Metabolic syndrome components	BMI *z*-score		WC (cm)		PBF (%)	
	r	*p*-value	*R*	*p*-value	*r*	*p*-value
Systolic blood pressure (mmHg)	−0.0002	0.995	0.029	0.377	0.017	0.604
Diastolic blood pressure (mmHg)	0.003	0.921	0.002	0.952	0.032	0.334
Fasting plasma glucose (mmol/L)	0.068	0.040	0.0648	0.049	0.036	0.278
Triglycerides (mmol/L)	0.197	<0.001	0.252	<0.001	0.211	<0.001
HDL-C (mmol/L)	−0.177	<0.001	−0.174	<0.001	−0.155	<0.001
HOMA-IR index	0.424	<0.001	0.472	<0.001	0.414	<0.001
TG:HDL-C ratio	0.240	<0.001	0.283	<0.001	0.241	<0.001

Spearman's correlation.
BMI, body mass index; WC, waist circumference; PBF, percentage of body fat; HDL-C, high-density lipoprotein cholesterol.

is a plausible starter to develop abnormal glucose metabolism associated with IR (30). This supports the presence of acanthosis nigricans as one of the clinical markers of IR in children affected by obesity (31). Our study showed that children affected by obesity with acanthosis nigricans were two times as likely to have MetS, which was consistent with a few other reported studies among children (32, 33). This observation is important as a cohort study by Morrison et al. (34) found that 10-year-old girls diagnosed with both MetS and hyperinsulinemia had a high frequency of progression to T2DM 14 years later.

Along with obesity, the prevalence of MetS has increased worldwide. Its prevalence affects not only adults but also children (4). In this study, we chose the IDF 2007 definition as the definition of MetS for children that are currently being used worldwide, stratified by age with fixed cutoffs for blood pressure, lipids, glycemia, and abdominal circumferential points assessed by percentile (35). Additionally, the presence of MetS using this definition is predictive of an increased cardiometabolic risk (36). Surprisingly, 4.8% of severely children affected by obesity younger than 10 years of age were already at risk of having MetS. The percentage was comparable to that of severely children affected by obesity who were 10 years of age and over and had MetS. Fortunately, this prevalence is much lower than that reported in a school-based study by Palhares et al. (37), with 13.6% of obese Brazilian children having MetS (using the same definition of MetS).

In addition, our findings showed that all adiposity markers, i.e., BMI, WC, and PBF, were significantly correlated with the HOMA-IR, TG: HDL-C ratio, triglycerides, and HDL-C. Interestingly, although there was no correlation with FPG, the highest correlation was observed with HOMA-IR, suggesting that childhood obesity studies should venture into IR beyond glucose measurements. Previous studies also showed that most obese and IR individuals did not develop hyperglycemia (38). However, the association between IR and childhood obesity is beyond the scope of this article. Moreover, a non-significant

TABLE 6 The association between acanthosis nigricans and metabolic syndrome.

	Metabolic syndrome and at risk of metabolic syndrome, *n* (%)	No metabolic syndrome, *n* (%)	OR (95%CI)	*P*-value
Presence of acanthosis nigricans	26 (68.4)	461 (52.0)	2.22 (1.09, 4.52)	0.028
Absence of acanthosis nigricans	12 (31.6)	425 (48.0)	1	

Adjusted for gender, ethnicity, and strata.
OR, odds ratio; CI, confidence interval.

correlation with MetS components, such as high LDL-C and hypertension, could be explained by the age of the children involved in this study. This study involved young children in the early years of obesity. Therefore, complications such as high LDL-C, hypertension, and diabetes were not yet observed as these diseases were time-sensitive (depending on the chronic level of obesity).

The major strength of this study is that it is a community-based study with a large data set, with a huge number of students being screened, and with ages as early as 8 years old. In addition, our study included severely children affected by obesity, while other studies tended to exclude them. As proven in the present study, severely children affected by obesity were more likely to have cardiometabolic risk factors. Additionally, the HOMA-IR cutoff was adopted based on pubertal stages, considering the influence of the pubertal state with IR (39, 40). Another strength of this study was that proportionate random sampling was used to select schools to ensure sufficient representation of multiethnic and socioeconomically diverse populations in Malaysia. An adjustment for potential confounding factors was also done for the association between cardiometabolic risk factors and obesity status.

Nevertheless, this study has some limitations. One limitation is that we do not have adequate information on the socioeconomic status despite attempting our best to obtain the parental monthly income. However, we do have the information on strata, either from the urban or rural school, which broadly indicates their socioeconomic background. Hypertension could not be further analyzed as there were very few children with hypertension. It is impossible to explain the causal relationship between obesity markers and a cardiometabolic risk as this study only used the baseline data from an intervention study. In essence, we recommend initiating a cohort study to investigate the association further.

5. Conclusion

This study has demonstrated that severely obese young children aged 8–11 years have a significantly greater cardiometabolic risk, which may lead to premature cardiovascular complications, such as myocardial infarction, or cerebrovascular accidents. This finding is particularly important in managing childhood obesity, and it is therefore essential to implement effective intervention programs for severely children affected by obesity. These young children require early and targeted intervention. Additionally, obesity-related health problems should be monitored closely and screened periodically to evaluate both prevention and treatment strategies.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Medical Research and Ethics Committee (MREC), Ministry of Health Malaysia. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin. The assent form was signed by the participating child.

Author contributions

AHM as a principal investigator and coordinator of this study. AHM, MYJ, FMZ, RS, and ZI contributed to the overall concept and design of the study. MYJ, FMZ, JYHH, and FM contributed to the concept of the clinical part of the study. FM, RMWMZ, AKNZI, and FAR contributed to the logistics and sample collection. FAR contributed to the laboratory analysis. FAR, AY, RMWMZ, and AKNZI contributed to the data management and analysis. All authors read and approved the manuscript.

Funding

This study was funded by the National Institutes of Health, Ministry of Health Malaysia (NMMR-13-439-16563). The funders had no role in study design, data collection and analysis, the decision to publish, or preparation of the manuscript.

Acknowledgments

The authors would like to thank the Director General of Health Malaysia for granting his permission to publish this paper, the Ministry of Education Malaysia for approval to undertake this study, all research team members, staff of the Ministry of Health Malaysia, participants, and teachers for their help in data collection. We acknowledge the special contribution of Dr. Hj. Tahir Bin Aris as a coordinator of the MyBFF@school programme.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Alfano R, Robinson O, Handakas E, Nawrot TS, Vineis P, Plusquin M. Perspectives and challenges of epigenetic determinants of childhood obesity: a systematic review. *Obesity Rev.* (2022) 23:e13389. doi: 10.1111/obr.13389

2. Abarca-Gómez L, Abdeen ZA, Hamid ZA, Abu-Rmeileh NM, Acosta-Cazares B, Acuin C, et al. Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128·9 million children, adolescents, and adults. *Lancet.* (2017) 390:2627–42. doi: 10.1016/s0140-6736(17)32129-3

3. Institute for Public Health. *National Health and Morbidity Survey (NHMS) 2019: Vol. I: NCDs-Non-Communicable Diseases: Risk Factors and Other Health Problem; Technical Report*. Washington, DC: Institute For Public Health (2019).

4. Forouzanfar MH, Afshin A, Alexander LT, Anderson HR, Bhutta ZA, Biryukov S, et al. Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990–2015: a systematic analysis for the global burden of disease study 2015. *Lancet.* (2016) 388:1659–724. doi: 10.1016/S0140-6736(16)31679-8

5. Lipshultz SE, Messiah SE, Miller TL. *Pediatric Metabolic Syndrome: Comprehensive Clinical Review and Related Health Issues*. New York, NY: Springer Science and Business Media (2012).

6. Finkelstein EA, Trogdon JG, Cohen JW, Dietz W. Annual medical spending attributable to obesity: payer-and service-specific estimates: amid calls for health reform, real cost savings are more likely to be achieved through reducing obesity and related risk factors. *Health Aff.* (2009) 28(Suppl1):w822–w31. doi: 10.1377/hlthaff.28.5.w822

7. Bendor CD, Bardugo A, Pinhas-Hamiel O, Afek A, Twig G. Cardiovascular morbidity, diabetes and cancer risk among children and adolescents with severe obesity. *Cardiovasc Diabetol.* (2020) 19:1–14. doi: 10.1186/s12933-020-01052-1

8. Lee J, Kim JH. Endocrine comorbidities of pediatric obesity. *Clin Exp Pediatr.* (2021) 64:619. doi: 10.3345/cep.2021.00213

9. Friedemann C, Heneghan C, Mahtani K, Thompson M, Perera R, Ward AM. Cardiovascular disease risk in healthy children and its association with body mass index: systematic review and meta-analysis. *BMJ.* (2012) 345:e4759. doi: 10.1136/bmj.e4759

10. Burguete-García AI, Ramírez Valverde AG, Espinoza-León M, Vázquez IS, Estrada Ramírez EY, Maldonado-López I, et al. Severe quantitative scale of acanthosis nigricans in neck is associated with abdominal obesity, Homa-Ir, and hyperlipidemia in obese children from Mexico City: a cross-sectional study. *Dermatol Res Pract.* (2022) 2022:9. doi: 10.1155/2022/2906189

11. Iwani NAKZ, Jalaludin MY, Zin RMWM, Fuziah MZ, Hong JYH, Abqariyah Y, et al. Triglyceride to Hdl-C ratio is associated with insulin resistance in overweight and obese children. *Sci Rep.* (2017) 7:1–7. doi: 10.1038/srep40055

12. DeBoer MD, Gurka MJ, Woo JG, Morrison JA. Severity of the metabolic syndrome as a predictor of type 2 diabetes between childhood and adulthood: the princeton lipid research cohort study. *Diabetologia.* (2015) 58:2745–52. doi: 10.1007/s00125-015-3759-5

13. Bjerregaard LG, Jensen BW, Ängquist L, Osler M, Sørensen TI, Baker JL. Change in overweight from childhood to early adulthood and risk of type 2 diabetes. *N Engl J Med.* (2018) 378:1302–12. doi: 10.1056/NEJMoa1713231

14. Fadzlina AA, Harun F, Nurul Haniza MY, Al Sadat N, Murray L, Cantwell MM, et al. Metabolic syndrome among 13 year old adolescents: prevalence and risk factors. *BMC Public Health.* (2014) 14:S7. doi: 10.1186/1471-2458-14-S3-S7

15. Selamat R, Raib J, Abdul Aziz NA, Zulkafly N, Ismail AN WNA WM, et al. Dietary practices and meal patterns among overweight and obese school children in Malaysia: baseline data from a school-based intervention study. *Ecol Food Nutr.* (2019) 44:1–16. doi: 10.1080/03670244.2019.1694922

16. World Health Organization. *Training Course on Child Growth Assessment Who Child Growth Standards*. Geneva: World Health Organization (2008). Available online at: https://www.who.int/nutrition/publications/childgrowthstandards_trainingcourse/en/ (accessed September 14, 2022).

17. Onis M, Onyango AW, Borghi E, Siyam A, Nishida C, Siekmann J. Development of a who growth reference for school-aged children and adolescents. *Bull World Health Organ.* (2007) 85:660–7. doi: 10.2471/blt.07.043497

18. Spinelli A, Buoncristiano M, Kovacs VA, Yngve A, Spiroski I, Obreja G, et al. Prevalence of severe obesity among primary school children in 21 European countries. *Obes Facts.* (2019) 12:244–58. doi: 10.1159/000500436

19. International Diabetes Federation. *The IDF Consensus Definition of the Metabolic Syndrome in Children and Adolescents*. Brussels: International Diabetes Federation (2007). Available online at: https://www.idf.org/e-library/consensus-statements/61-idf-consensus-definition-of-metabolic-syndrome-in-children-and-adolescents.html (accessed September 14, 2022).

20. Burke JP, Hale DE, Hazuda HP, Stern MP, A. quantitative scale of acanthosis nigricans. *Diabetes Care.* (1999) 22:1655–9. doi: 10.2337/diacare.22.10.1655

21. Singh Y, Garg MK, Tandon N, Marwaha RK, A. study of insulin resistance by Homa-Ir and its cut-off value to identify metabolic syndrome in urban Indian adolescents. *J Clin Res Pediatr Endocrinol.* (2013) 5:245–51. doi: 10.4274/Jcrpe.1127

22. Reinehr T, Andler W. Changes in the atherogenic risk factor profile according to degree of weight loss. *Arch Dis Child.* (2004) 89:419–22. doi: 10.1136/adc.2003.028803

23. Caprio S, Santoro N, Weiss R. Childhood obesity and the associated rise in cardiometabolic complications. *Nat Metab.* (2020) 2:223–32. doi: 10.1038/s42255-020-0183-z

24. Warren M, Beck S, Rayburn J. *The State of Obesity: Better Policies for a Healthier America 2018*. Princeton: Robert Wood Johnson Foundation (2018).

25. Fryar CD, Carroll MD, Ogden CL. *Prevalence of Overweight, Obesity, and Severe Obesity among Children and Adolescents Aged 2–19 Years: United States, 1963–1965 Through 2015–2016* (2018). Available online at: https://www.cdc.gov/nchs/data/hestat/obesity_child_13_14/obesity_child_13_14.htm (accessed January 1, 2023).

26. Skinner AC, Perrin EM, Moss LA, Skelton JA. Cardiometabolic risks and severity of obesity in children and young adults. *N Engl J Med.* (2015) 373:1307–17. doi: 10.1056/NEJMoa1502821

27. Morrison JA, Glueck CJ, Woo JG, Wang P. Risk factors for cardiovascular disease and type 2 diabetes retained from childhood to adulthood predict adult outcomes: the Princeton Lrc follow-up study. *Int J Pediatr Endocrinol.* (2012) 2012:6. doi: 10.1186/1687-9856-2012-6

28. Berenson GS, Srinivasan SR, Bao W, Newman WP, Tracy RE, Wattigney WA. Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults. *N Engl J Med.* (1998) 338:1650–6. doi: 10.1056/nejm199806043382302

29. De Ferranti SD, Steinberger J, Ameduri R, Baker A, Gooding H, Kelly AS, et al. Cardiovascular risk reduction in high-risk pediatric patients: a scientific statement from the American Heart Association. *Circulation.* (2019) 139:e603–e34. doi: 10.1161/CIR.0000000000000618

30. Hershkop K, Besor O, Santoro N, Pierpont B, Caprio S, Weiss R. Adipose insulin resistance in obese adolescents across the spectrum of glucose tolerance. *J Clin Endocrinol Metab.* (2016) 101:2423–31. doi: 10.1210/jc.2016-1376

31. Lopez-Alvarenga JC, Chittoor G, Paul SFD, Puppala S, Farook VS, Fowler SP, et al. Acanthosis nigricans as a composite marker of cardiometabolic risk and its complex association with obesity and insulin resistance in Mexican American children. *PLoS ONE.* (2020) 15:e0240467. doi: 10.1371/journal.pone.0240467

32. Daye M, Eklioglu BS, Atabek ME. Relationship of acanthosis nigricans with metabolic syndrome in obese children. *J Pediatr Endocrinol Metab.* (2020) 33:1563–8. doi: 10.1515/jpem-2020-0154

33. Velazquez-Bautista M, Lopez-Sandoval JJ, Gonzalez-Hita M, Vazquez-Valls E, Cabrera-Valencia IZ, Torres-Mendoza BM. Association of metabolic syndrome with low birth weight, intake of high-calorie diets and acanthosis nigricans in children and adolescents with overweight and obesity. *Endocrinol Diabetes Nutr.* (2017) 64:11–7. doi: 10.1016/j.endinu.2016.09.004

34. Morrison JA, Glueck CJ, Umar M, Daniels S, Dolan LM, Wang P. Hyperinsulinemia and metabolic syndrome at mean age of 10 years in black and white schoolgirls and development of impaired fasting glucose and type 2 diabetes mellitus by mean age of 24 years. *Metabolism.* (2011) 60:24–31. doi: 10.1016/j.metabol.2009.12.013

35. Sharma V, Coleman S, Nixon J, Sharples L, Hamilton-Shield J, Rutter H, et al. A systematic review and meta-analysis estimating the population prevalence of

comorbidities in children and adolescents aged 5–18 years. *Obes Rev.* (2019) 20:1341–9. doi: 10.1111/obr.12904

36. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, et al. Harmonizing the metabolic syndrome: a joint interim statement of the international diabetes federation task force on epidemiology and prevention; national heart, lung, and blood institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation.* (2009) 120:1640–5. doi: 10.1161/CIRCULATIONAHA.109.192644

37. Palhares HM, da Silva AP, Resende DC, Pereira GA, Rodrigues VJ, Borges MF. Evaluation of clinical and laboratory markers of cardiometabolic risk in overweight and obese children and adolescents. *Clinics.* (2017) 72:36–43. doi: 10.6061/clinics/2017(01)07

38. Freeman AM PN. *Insulin Resistance*. Washington, DC: StatPearls Publishing (2020).

39. Pilia S, Casini MR, Foschini ML, Minerba L, Musiu MC, Marras V, et al. The effect of puberty on insulin resistance in obese children. *J Endocrinol Invest.* (2009) 32:401–5. doi: 10.1007/BF03346475

40. Reinehr T. Metabolic syndrome in children and adolescents: a critical approach considering the interaction between pubertal stage and insulin resistance. *Curr Diabetes Rep.* (2016) 16:8. doi: 10.1007/s11892-015-0695-1

frontiers | Frontiers in Pediatrics

TYPE Review
PUBLISHED 04 May 2023
DOI 10.3389/fped.2023.1147362

OPEN ACCESS

EDITED BY
Shikai Yu,
Tongji University, China

REVIEWED BY
Akshay Shekhar,
Regeneron Pharmaceuticals, Inc., United States
Michele Lioncino,
University of Campania Luigi Vanvitelli, Italy

*CORRESPONDENCE
Ce Wang
crease.sy@163.com

RECEIVED 18 January 2023
ACCEPTED 19 April 2023
PUBLISHED 04 May 2023

CITATION
Li D and Wang C (2023) Advances in symptomatic therapy for left ventricular non-compaction in children.
Front. Pediatr. 11:1147362.
doi: 10.3389/fped.2023.1147362

Advances in symptomatic therapy for left ventricular non-compaction in children

Dong Li and Ce Wang*

Department of Pediatrics, Shengjing Hospital of China Medical University, Shenyang, China

Left ventricular non-compaction is a complex cardiomyopathy and the third largest childhood cardiomyopathy, for which limited knowledge is available. Both pathogenesis and prognosis are still under investigation. Currently, no effective treatment strategy exists to reduce its incidence or severity, and symptomatic treatment is the only clinical treatment strategy. Treatment strategies are constantly explored in clinical practice, and some progress has been made in coping with the corresponding symptoms because the prognosis of children with left ventricular non-compaction is usually poor if there are complications. In this review, we summarized and discussed the coping methods for different left ventricular non-compaction symptoms.

KEYWORDS

left ventricular non-compaction (LVNC), therapy, children, myocardiopathy, heart failiure

Introduction

With the advancements in diagnosis and treatment techniques, the detection rate of myocardial insufficiency in children has increased. Left ventricular non-compaction (LVNC) is a rare and complex condition in children with cardiomyopathy. It is characterized by the presence of thick and reticulated myocardial trabeculae in the ventricular cavity with deep, sunken fossae connecting to the left ventricular cavity. In recent Australian retrospective studies, the incidence of LVNC in children was reported to be approximately 0.11/100,000 (1), and several investigations demonstrated that the majority of pediatric patients with LVNC have a poor prognosis, especially those with comorbidities other than cardiomyopathies (1–4).

At present, LVNC is the most commonly used diagnostic method to detect the morphological characteristics of left ventricle by echocardiography. In the past cohort studies, specific echocardiographic criteria were established, including Jenni, Chin and Stollberger (5–7). And the widely used LVNC diagnostic criteria are mainly Jenni diagnostic criteria. Mainly in these aspects: (a) it includes dense layer and non-dense layer, and the ratio of the thickness of non-dense layer myocardium to the thickness of dense layer myocardium is more than 2 (children are more than 1.4), so it is necessary to pay attention to the measurement time in systole. (b) The lesion area is generally located at the apex of the heart (>80%), and some patients' lateral walls and inferior walls will be involved. (c) Color Doppler can see that there is blood flow communication, but it should be noted that blood flow is not connected with coronary circulation.

It is worth mentioning that, in recent studies, LVNC is not usually recognized and LV hypertrabeculation is perhaps more accurate (8). This is because in studies of some adult

Abbreviations
LCNC, left ventricular non-compaction; ECG, electrocardiogram; iPSCs, induced pluripotent stem cells; ACEI, Angiotensin converting enzyme Inhibitors; SGLT2, sodium-dependent glucose transporters 2; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy (HCM).

cases, it has been found that the degree of myocardial trabecular densification varies from one person to another and from one site to another in the same individual. For some adult myocardial tissue, the degree of myocardial non-dense on imaging may meet the diagnostic criteria, but the patient does not show any symptoms. In addition, myocardial nondensification is usually accompanied by other cardiac diseases such as dilated cardiomyopathy or hypertrophic cardiomyopathy, but there is no clinical evidence that their outcome and prognosis are affected by the degree of myocardial nondensification. When these patients are diagnosed with LVNC, perhaps overdiagnosis is involved, and this may be normal in some patients, such as pregnant women or athletes. Therefore, the use of LV hypertrabeculation, more inclined to describe the imaging phenotype, is more recommended in studies than easily as a clinical diagnosis.

However, in pediatric cases, the use of LV hypertrabeculation in children still requires caution due to the paucity of relevant studies and the fact that, as a congenital heart disease, it is not easy to determine differences in the degree of myocardial trabecular densification in children given the relatively short time of cardiac development in children compared to adults. In this article, we tentatively follow the diagnosis of LVNC because of the inability to obtain strong support.

The clinical symptoms of LVNC in children are complex. LVNC may be clinically asymptomatic or present with a variety of symptoms such as chest pain, dyspnea, and palpitations; however, three main clinical symptoms require urgent attention (9–12). The most common and the most important is heart failure, which is associated with most of the other clinical symptoms (13–16). Thromboembolism and arrhythmias are also common complications of high clinical concern in patients with LVNC. In addition, these patients often have a neuromuscular disease and may experience fatigue (17, 18), muscle aches and pains, and elevated creatine kinase levels (19). The relevant data are compiled in **Table 1**. Moreover, even though several children with LVNC have adverse outcomes, to date, no clinically targeted treatment exists, and only symptomatic or prophylactic treatment is available (20–23).

Generally speaking, left ventricular noncompaction is a congenital disease with unknown etiology (26). At present, there is no literature to prove that adult myocardial noncompaction has an acquired trend or mechanism. Some patients with left ventricular noncompaction are asymptomatic from birth to onset, and it is not discovered until they have heart-related symptoms or physical examination. This is called myocardial noncompaction in adults. Therefore, both adults and children with myocardial noncompaction are congenital diseases, but the time of discovery or symptoms is different (27).

In this review, we discuss current advances in the clinical management of the different symptoms of LVNC to further the search for more effective treatments for the various related complications and facilitate the progress of clinical research. The latest treatment strategy, indications and contraindications are compiled in **Figures 1–3**. Simultaneously, our review provides potential insight for clinical discoveries in the treatment of LVNC.

Heart failure

Patients with LVNC can show many symptoms or no symptoms. To be sure, LVNC can lead to heart failure (9, 15). However, according to the researchers' data, among LVNC patients, patients with heart failure symptoms have worse prognosis and higher mortality than those with isolated LVNC (28, 29). However, some researchers think that heart failure is not a high-risk factor for LVNC (1, 30, 31). Under any circumstances, prevention and treatment of heart failure should be prioritized (32) (**Figure 1**).

However, prevention and treatment of heart failure in children still require improvements. The etiology of heart failure in children, usually caused by congenital heart disease, is different from that in adults, which is usually ischemic. Therefore, the therapeutic management of heart failure in children also differs from that in adults in some respects. The onset of heart failure in children is usually associated with symptoms such as fatigue, shortness of breath, exercise intolerance, and sometimes more serious

TABLE 1 Clinical findings in pediatric patients with isolated non-compaction cardiomyopathy.

Pediatric patients	Ichida F et al. (7)	Wald R et al. (24)	Koh C et al. (8)	Brescia ST et al. (25)	Wang C et al. (21)		van Waning JI et al. (12)	Shi WY et al. (1)	Sabatino J et al. (9)
					Infanitile type	Juvenile type			
Number of patients	27	22	10	242	108	97	52	29	23
Male patients, *n* (%)	15 (56%)	40%	7 (70%)	145 (60%)	59 (55%)	51 (53%)	—	20 (69%)	12 (52%)
Age range, years	1–15	—	0.019–12	0.3–13.9	0–1	1–15	0–15	0.08–1.3	0–18
Length of follow-up (median)	17 years	16 years	8 years	4 years	3.5 years	5.9 years	4.2 years	6.8 years	5.4 years
Age at diagnosis (median)	—	3.9 years	—	7.2 ± 6.9 years	2.7 months	7.3 years	—	0–1 years	—
Family history of cardiomyopathy	12 (44%)	18%	—	33 (14%)	37 (34%)	36 (37%)	8 (15%)	9 (31%)	3 (13%)
Death in follow-up	2 (7%)	14%	3 (30%)	31 (13%)	14 (13%)	9 (10%)	8 (15%)	14 (48%)	—
Clinical characteristic (at the time of diagnosis)									
Asymptomatic	—	—	1 (10%)	89 (37%)	21 (19%)	52 (54%)	9 (17%)	—	—
Heart failure	6 (22%)	54%	8 (80%)	60 (25%)	65 (60%)	22 (23%)	13 (27%)	24 (83%)	—
Arrhythmia	6 (22%)	—	3 (30%)	80 (33%)	9 (8%)	11 (11%)	9 (17%)	—	2 (9%)
Thromboembolism	2 (7%)	—	0(0%)	—	5(5%)	5(5%)	2(4%)	—	0(0%)

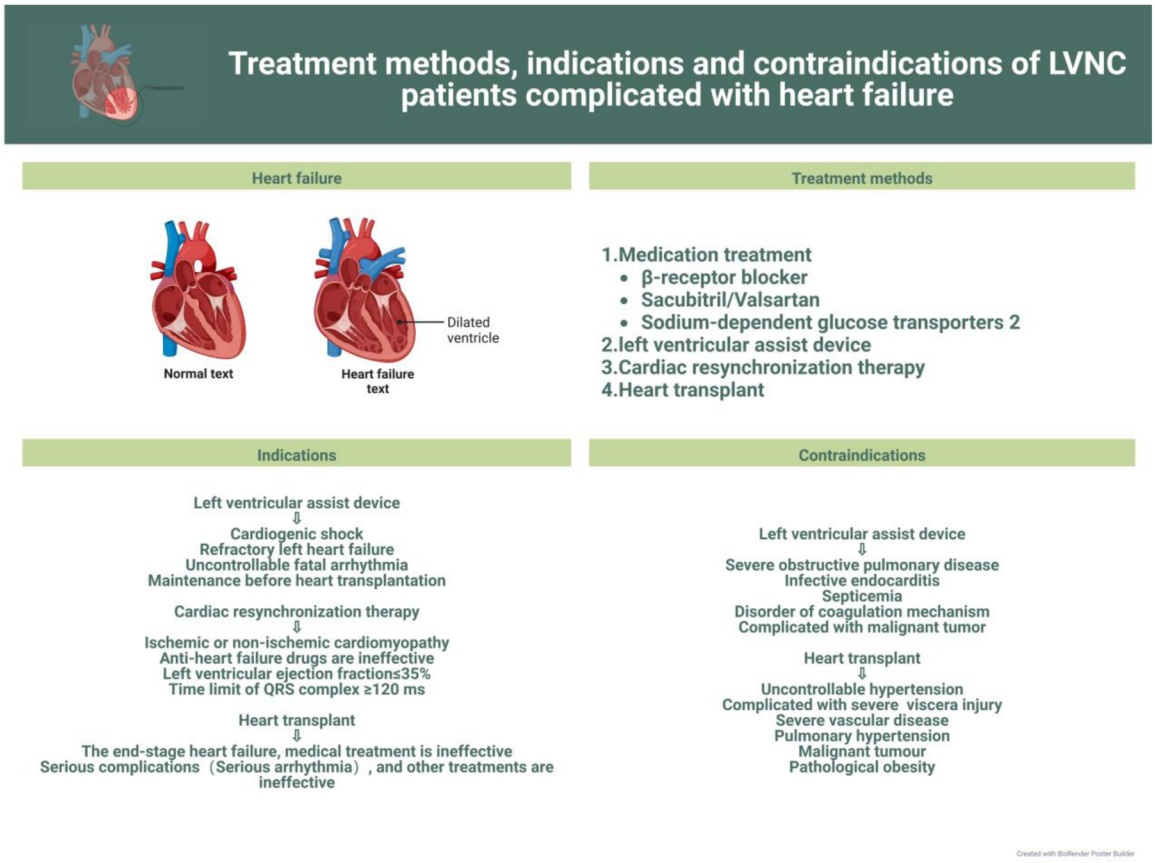


FIGURE 1
Treatment of LVNC complicated with heart failure.

symptoms, therefore necessitating prompt and effective treatment. There are two widely accepted clinical principles of treatment: elimination of the cause and control of symptoms and disease progression (33, 34). The primary goal of managing children with heart failure is to closely monitor their general condition and arrange nutritional support rationally. For children with LVNC, close attention should be paid to changes in oxygen partial pressure and provide ventilation support if necessary. Additionally, digoxin should be administered to enhance myocardial contractility in children with LVNC and left heart systolic dysfunction. Other clinically recognized and recommended drugs include β-blockers and those of the ACEI class (33, 35, 36).

Ivabradine is a selective inhibitor of sinus node If current, which can specifically reduce the heart rate, but has no obvious effect on cardiac conduction time, myocardial contractility and ventricular repolarization (37). Clinical studies show that heart rate is significantly related to the prognosis of heart failure, and ivabradine can reduce the hospitalization rate and mortality rate of HF (25, 38, 39). Many authoritative heart failure guidelines strongly recommend HF (heart failure with reduced ejection fraction) for adults as Class IIa (38, 40–42), and pediatric heart failure guidelines are recommended as promising drugs for HF (chronic heart failure (CHF) in children (43). At present, only tablets are approved for adult CHF in China, and the Food and Drug Administration (FDA) has supplemented and approved oral liquid and tablets for children with stable HF caused by DCM for 6 months and above, which provides evidence-based evidence for clinical use in pediatrics. Specific usage and dosage are as follows: (1) for children over 6 months old and weighing less than <40 kg, the initial dosage is 0.05 mg/kg, twice a day, taken with meals, and the dosage is adjusted every two weeks according to the tolerance to reduce the heart rate by at least 20%; the maximum dose is 0.2 mg/(kg/times) (children aged 6 months to <1 year) or 0.3 mg/(kg/times) (children aged ≥1 year), and the total dose does not exceed 7.5 mg/time. (2) Children with body weight ≥40 kg: the initial dose is 2.5 mg, twice a day, and the dose is adjusted every two weeks according to the tolerance to reduce the heart rate by at least 20%, and the maximum dose is 7.5 mg/time (44).

Phase II/III clinical studies show that ivabradine can safely and effectively reduce the resting heart rate of children, and the left ventricular ejection fraction, clinical cardiac function classification and quality of life have a good improvement trend (24). At the same time, because it is dose-dependent, its activity depends on the opening and closing of If current channel, which can reach saturation state and prevent the adverse events of infinite decrease of heart rate (45, 46). It provides a new drug

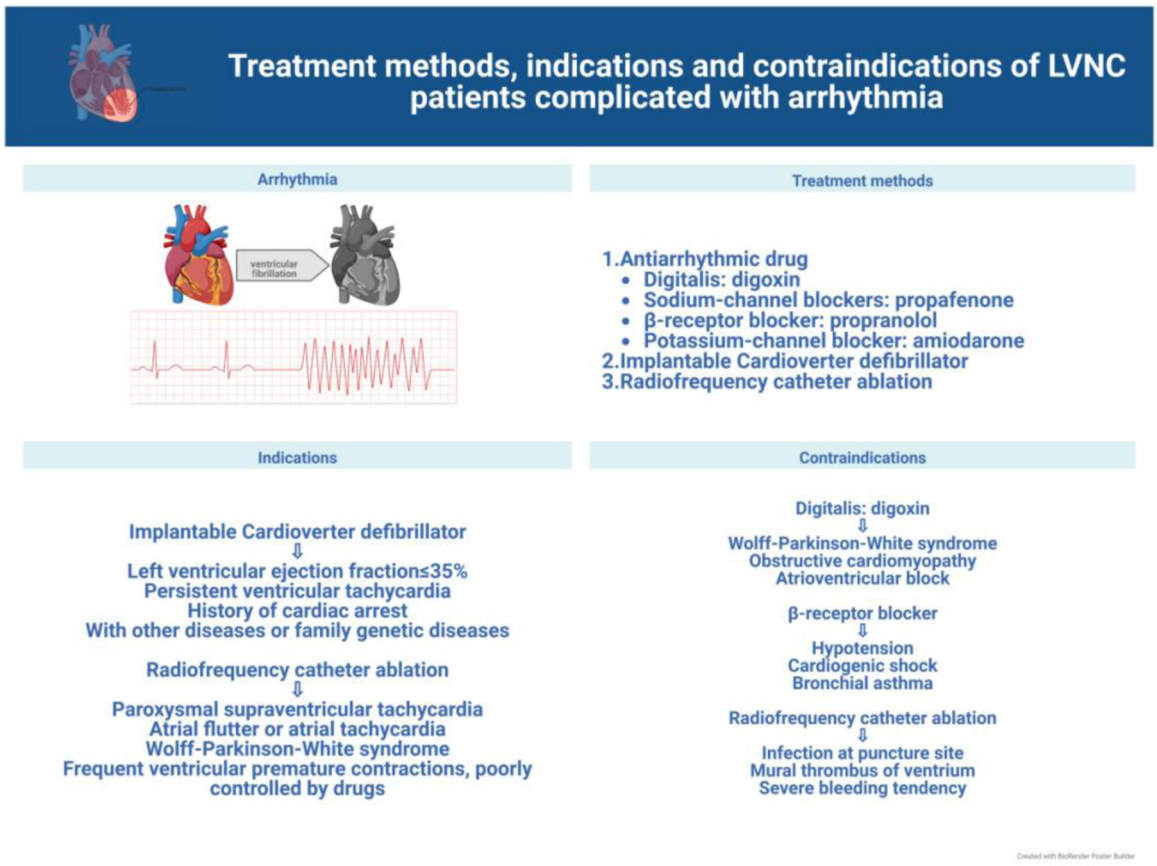


FIGURE 2
Treatment of LVNC complicated with arrhythmia.

treatment idea for children with heart failure who still have symptoms, reduced left ventricular ejection fraction (LVEF), sinus rhythm and resting heart rate of not less than 70 beats/min after using traditional anti-heart failure drugs simultaneously, and can be used as an alternative. At the same time, considering its characteristics of direct action on sinus node and few adverse reactions, it has a good application prospect for the treatment of heart failure in children with sinus tachycardia.

Long-term use of β-blockers can improve the symptoms and quality of life of adults with heart failure, and reduce the risk of death and hospitalization. However, children's studies show that carvedilol can improve the echocardiographic parameters and serum brain natriuretic peptide (BNP) level to some extent, but it has only a tendency to improve the prognosis of clinical heart failure (47–49). Therefore, there is not enough data to recommend or prevent it for children with congestive HF.

Some studies demonstrate the effectiveness of using drugs such as sacubitril/valsartan and SGLT2 inhibitors for the treatment of heart failure (34); however, this drug has only been proved to be applicable to the treatment of heart failure in adults, and no study has proved that this drug can be applied to children. Therefore, the safety and effectiveness of this drug in children patients are unknown. Besides, although the research on the efficacy of diuretics in pediatric HF population is limited at present, it can be confirmed that diuretics play an important role in the acute management of symptomatic HF patients. Through the review of adult diuretic treatment, it is confirmed that the use of diuretics can effectively alleviate symptoms, reduce the onset of HF deterioration and improve living conditions (50). Through these data and empirical evidence, it is enough to prove that their routine use in the emergency of HF children is reasonable. Diuretics can reduce the fluid accumulation in children and reduce the burden on the heart (51).

However, although these studies suggest that their use in patients with heart failure is warranted, it is unknown whether they can improve the condition of patients with LVNC. Therefore, after clinical trials and evaluation, these drugs may be promising (52, 53).

Although pharmacological therapy can significantly improve the quality of life in children with heart failure, there is still a large proportion of children with poor prognosis owing to disease progression or other factors; therefore, these children should be considered for cardiac assist device implantation or even heart transplantation (33, 54). The implantation of a left ventricular assist device (LVAD) has been shown to be effective when medications fail to improve LV systolic and diastolic function in patients with LVNC (55). In an Italian study (56), researchers concluded that cardiac resynchronization therapy

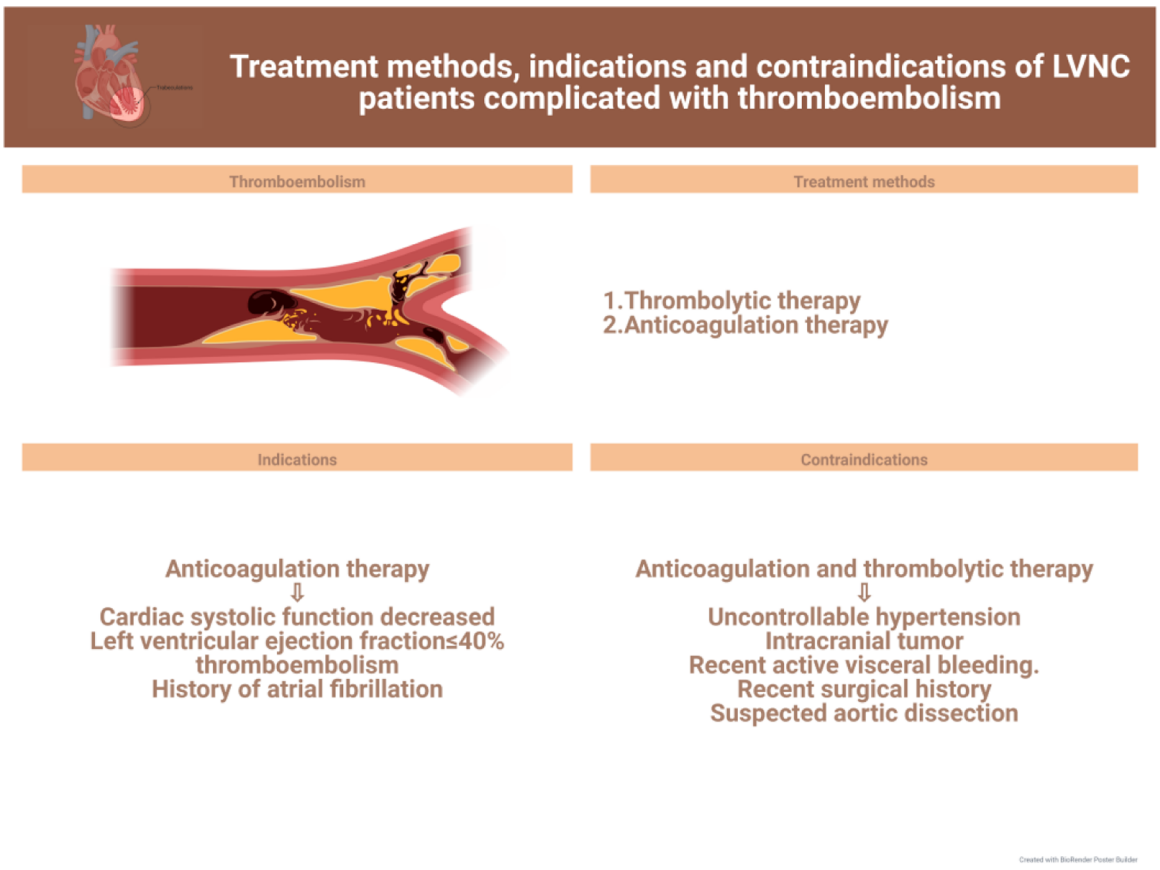


FIGURE 3
Treatment of LVNC complicated with thromboembolism.

(CRT) was effective in improving LV function in 52 heart failure volunteers (20 with DCM plus LVNC and 32 with DCM alone) using cardiac resynchronization therapy and was more effective in patients with LVNC than in those with DCM alone. The efficacy becomes more evident with a larger area of myocardial densification. Heart transplantation as the ultimate treatment must be beneficial for patients with LVNC or even other cardiomyopathies (57, 58), but few cases of heart transplantation have been performed. Mexico reported the first case of a 20-year-old LVNC patient who underwent heart transplantation (59), and the outcome was successful within 15 months with no acute rejection on intramyocardial biopsy. Its long-term prognosis needs further follow-up investigation (60–63).

Arrhythmia

Arrhythmias in patients with LVNC usually symptomatically manifest as weakness and palpitations (13, 14) and require attention and effective treatment (20, 64). All patients with LVNC who develop arrhythmias should be routinely treated with antiarrhythmic drugs. In a limited pediatric cohort study, the use of β-blockers et al. antiarrhythmic drugs was found to reduce left ventricular ejection fraction and volumes significantly in patients with LVNC (35, 65), with carvedilol having effectively improved left ventricular function; however, the long-term efficacy is unclear (66). Sotalol has been proved to be effective in the treatment of ventricular arrhythmia and atrial fibrillation in both adults and pediatrics (67, 68). It is worth mentioning that antiarrhythmic drugs should be used with caution because of their side effects and unknown risks (35, 69, 70) (**Figure 2**).

In addition, the use of implantable cardiac defibrillators can effectively prevent ventricular tachycardia and sudden death (71–73). Implantation is especially indicated when at least one of the following conditions is met: left ventricular ejection fraction ≤35% (74), sustained ventricular tachycardia or previous cardiac arrest (75), presence of comorbidities or family history of genetic disorders (76). Risk assessment by analyzing the ECG characteristics of patients with cardiomyopathy has also been performed to determine the risk of ventricular tachycardia (77) for early detection and prevention, and to provide some guidance for the use of implantable cardiac defibrillators.

A direct and effective approach for the treatment of arrhythmias is catheter radiofrequency ablation (60, 78), which has great treatment advantages as the procedure is easy to perform, does not cause damage to the heart, and is minimally invasive, while the patient bears minimal pain and recovers quickly. However, some recent investigations have found arrhythmogenic lesions in the epicardial tissue, requiring the endocardium and epicardium to be operated (19, 36, 79). In the

study by Sohns et al., 10 of 18 patients with LVNC underwent catheter radiofrequency ablation (two of them underwent endocardial and epicardial ablation) with a 90%success rate. After follow-up, the mortality rate of patients who did not undergo radiofrequency catheter ablation was approximately three times higher than that of patients who underwent radiofrequency catheter ablation; thus, it was concluded that radiofrequency catheter ablation is safe and effective for patients with LVNC (71). In addition, catheter radiofrequency ablation is contraindicated in patients with wall thrombus in the ventricular cavity, which may lead to dangerous thrombus dislodgement.

Thromboembolism

Owing to the presence of myocardial trabecular gaps in LVNC patients, there is a high risk of thrombus formation during blood flushing (36, 80). Statistically, the risk of thrombosis in patients with LVNC is about 21%–38% (52, 81). Thrombosis can be a fatal threat as it may cause complications such as stroke, pulmonary embolism, and mesenteric ischemia (**Figure 3**).

It is well known that anticoagulation and thrombolytic therapy are clinically applied for patients with LVNC who have thrombosis. However, the need for prophylactic anticoagulation in these patients is still controversial. Although there is a lack of prospective studies to make predictions, according to some recent studies and current medication guidelines (9, 82), prevention of thromboembolic complications is a clinical priority and all patients with LVNC require routine prophylaxis against thromboembolism (83, 84). In a 30-month investigation on a cohort including 17 patients with LVNC, Ritter et al. found that the incidence of thromboembolism was approximately 24%; therefore, the researchers concluded that thromboembolism occurs independent of left ventricular function and size, and that LVNC itself is a high-risk factor for it. Ultimately, the researchers supported anticoagulation for all patients with LVNC (84).

Anticoagulation is not necessary in asymptomatic patients or those with normal cardiac function and it even increases patient burden. In a mean follow-up of 229 patients with LVNC without AF by Fazio et al., the incidence of thromboembolic events was only 2.1% (85). Instead, in more severe cases, other studies found prophylactic anticoagulation in patients with heart failure to increase the risk of bleeding (86, 87).

Nonetheless, anticoagulation is clinically mandatory when LVNC patients have reduced cardiac systolic function, an ejection fraction below 40%, or thromboembolism or previous atrial fibrillation (88–90). Since the risk of thrombosis is substantially increased in patients with LVNC due to the deep grooves between myocardial trabeculae, prophylactic anticoagulation is not a problem in asymptomatic patients, although the risk of bleeding due to anticoagulation therapy cannot be ignored. In clinical practice, patients are treated according to their needs and the corresponding guideline criteria. In general, the CHADS2/CHADS2-Vasc score is commonly used as a medication guideline to analyze the risk of thromboembolism in children with LVNC (26, 91).

Unfortunately, in all anticoagulant therapy strategies, even within the normal treatment range, bleeding is inevitable, which is also a major complication of anticoagulant therapy (92, 93). The risk level of bleeding can refer to Spyropoulos' research (94). When bleeding occurs during anticoagulation, there is no way to prevent it. When bleeding occurs during anticoagulation, the location, cause and severity of bleeding should be evaluated as quickly and accurately as possible, and specific treatment should be given, including mechanical pressing and lowering the dose of anticoagulant (95). When massive bleeding occurs (the standard is that the bleeding is serious enough to require major medical intervention, such as blood transfusion or surgery, and the prognosis is extremely poor) (92, 96), generally speaking, it is necessary to stop anticoagulation treatment immediately, quickly evaluate the degree of bleeding and life state of the patient, use specific reversal agents to reverse the anticoagulation effect, and use mechanical ventilation and blood transfusion to maintain life if necessary (97–100). As long as the patient has bleeding or bleeding risk during anticoagulation, it is necessary to closely detect the patient's life state, maintain the patient's body temperature and closely detect the patient's blood gas ion stability. However, if careful anticoagulation is carried out according to the known bleeding risk factors, the risk of bleeding will be greatly reduced (101).

In addition, recent clinical case reports have shown (27) that a 65-year-old patient with LVNC in Japan suffered from worsening symptoms such as dyspnea and heart failure. After being hospitalized in an emergency department, the patient was found to have cerebral infarction. After establishing a perfect cardiopulmonary bypass, a left ventricular incision was made to remove the thrombus in the ventricle. At the same time, the protruding muscle trabecula in the patient's left ventricle was removed as much as possible. After the operation, the patient's left ventricular diastolic function and left ventricular ejection fraction were gradually improved within one year, and serious symptoms such as heart failure could be effectively solved by eliminating the cause. Therefore, excision of prominent trabeculae may be effective in improving symptoms of LVNC patients (102–104), which also provides a novel direction for the treatment of LVNC; however, its long-term prognosis still needs further follow-up.

Prospective treatment

Gene mutations, such as those involving sarcomere and ion channel genes/proteins, can lead to LVNC (91). It has been demonstrated (105) that LVNC can be induced in the mouse heart using excess All-Trans Retinoic Acid. The successful establishment of this animal model provides a completely new platform for exploring potential LVNC therapeutic approaches in the future. In 2007 Takahashi et al. (106) successfully generated iPSCs cells from adult human dermal fibroblasts. It provides a basis for cultivating LVNC animal models (107). Moreover, recent studies are gradually devoted to constructing iPSCs model to further explore the pathways that may be related to the

pathogenesis and treatment direction of LVNC. For example, some researchers have successfully established an LVNC-derived IPS cell model, and detected that the expression level of RhoA protein, a key protein of Rho pathway, is up-regulated and the degree of phosphorylation is significantly increased in the disease group (abnormal cytoskeleton changes) by Western blot, suggesting that this change may be related to Rho/ROCK pathway. Researchers believe that the imbalance of cytoskeleton and polarity may be involved in the occurrence of myocardial noncompaction, and the change of Rho/ROCK pathway activity may be its potential pathogenesis. Although there is not a lot of data to support it, it still provides a new idea for the treatment of LVNC (108).

The implementation of gene editing technologies, including zinc finger nucleases (ZFNs), transcription activator-like effector nucleases (TALENs), and clustered regularly interspaced short palindromic repeats (CRISPR) systems (109), has made the generation of LVNC cardiomyocytes a reality. Gene editing techniques have been widely utilized in cardiomyopathy research and there have been attempts to explore the role of various genes in the pathogenesis of LVNC (110, 111). There have been successful experiments using TALENs technology to introduce MYH7 mutated genes into a pig model to obtain a HCM model (112). Further, the ability to obtain LVNC animal models provides greater opportunities for treatment experimentations, including the possibility of preventing or eliminating LVNC by means of gene knockout or mutant gene repair, which should be gradually considered (113). However, the effectiveness of genetic strategies to treat LVNC and ethical considerations warrant further discussion and reviewing.

Prevention and restrictions on daily activities

In addition to the distinct symptomatic treatment described above, another potential strategy is worth exploring for patients with LVNC. It is well known that patients with symptomatic LVNC have much higher mortality and worse prognosis compared to those with an asymptomatic presentation (74, 114), especially in patients with concomitant heart failure. Although controlling LVNC symptoms' manifestation is impossible, its diagnosis before symptom development can effectively improve quality of life. In a retrospective cohort study in Japan (31) from 2000 to 2017, 44 of 105 pediatric LVNC patients (41.9%) were identified during school screening, and most of these students exhibited abnormal QRS wave segments on the electrocardiogram (ECG). With the detection of ECG abnormalities, school screening may be an important factor in the detection of patients with LVNC in the future (**Table 1**).

In addition, genetically screening families of patients with LVNC, may also elucidate whether LVNC is hereditary and determine what changes in their family's related gene is responsible and what effects this change might bring to their relatives, which could be important for future LVNC eradication and prevention (20, 115). According to statistics, the proportion of LVNC patients with family history is tremendous (**Table 1**).

Patients with LVNC can potentially engage in moderate physical activity (60, 116); this in turn can help prevent cardiovascular disease, as stated in the 2020 ESC Guidelines on sports cardiology and exercise in patients with cardiovascular disease (117); the section for patients with LVNC states that only individuals with LVEF >50% and without arrhythmias should engage in high-intensity physical activity as well as competitive sports, and only individuals with LVEF >40% should engage in appropriate physical activity. However, the expected outcome requires further clinical investigation.

Perspectives and conclusion

Although we cannot currently predict the occurrence of LVNC and no definitive treatment is yet available, we can provide patients with a better quality of life through aggressive symptomatic and preventive treatment.

Many studies have successfully identified genes associated with cardiomyopathy (118–125), and this information can be employed in genome editing technology (126); while gene therapy will progressively develop in an increasing number of genetic tests, making the future eradication of LVNC promising, researchers are constantly refining genomic and proteomic analyses through animal models. These studies provide ideas for new therapeutic strategies in the future.

However, hopes always coexist with challenges, and the safety and effectiveness of genome editing technology cannot be guaranteed (127–129). Currently, human genome editing therapy technology is still under development. Whether in the experimental design or environment different from the human body, the therapeutic effect of gene therapy on cardiomyopathy is uncertain. Although the experimental data are promising, guaranteeing its effectiveness for practical clinical application is impossible. Moreover, owing to the great unknown of genome therapy, its toxicity and side effects may also be unsustainable. The possibility that gene editing may cause other mutations or symptoms must be considered. Moreover, most current gene therapy strategies are conducted on animal models, and once they are ready to be applied to human bodies, we must ask ourselves about the potential practical and clinical problems; for instance, who is the subject of gene editing, when and under what circumstances, what might be the possible consequences, treatment measures, and expected results. The related human genome editing program must be conducted through constant research and discussion. It is necessary to ensure not only its rationality and effectiveness but also ethical proceeding. Only with the support of a multidisciplinary team of professionals can we advance human genome editing treatment strategies (130, 131).

In conclusion, patients with LVNC of any type should be closely followed up and analyzed because of the conditions' unknown nature and poor prognosis (132–134). Especially when LVEF function decreases, the prognosis of patients will be worse (28, 70, 135). We also recommend perfect genetic testing for every LVNC patient and their immediate family members, which

will be of great importance to advance our research for patients with LVNC.

Author contributions

Literature review and writing—original draft preparation, DL; writing—review and editing, CW; supervision and funding acquisition, CW. All authors contributed to the article and approved the submitted version.

Funding

This study received financial support from the National Natural Science Foundation of China (82001598) and the Natural Science Foundation of Liaoning Province (2020-BS-090).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Shi WY, Moreno-Betancur M, Nugent AW, Cheung M, Colan S, Turner C, et al. Long-term outcomes of childhood left ventricular noncompaction cardiomyopathy: results from a national population-based study. *Circulation*. (2018) 138(4):367–76. doi: 10.1161/CIRCULATIONAHA.117.032262

2. Schultze-Berndt A, Kühnisch J, Herbst C, Seidel F, Al-Wakeel-Marquard N, Dartsch J, et al. Reduced systolic function and not genetic variants determine outcome in pediatric and adult left ventricular noncompaction cardiomyopathy. *Front Pediatr*. (2021) 9:722926. doi: 10.3389/fped.2021.722926

3. Vaidya VR, Lyle M, Miranda WR, Farwati M, Isath A, Patlolla SH, et al. Long-term survival of patients with left ventricular noncompaction. *J Am Heart Assoc*. (2021) 10(2):e015563. doi: 10.1161/JAHA.119.015563

4. Jefferies JL, Wilkinson JD, Sleeper LA, Colan SD, Lu M, Pahl E, et al. Cardiomyopathy phenotypes and outcomes for children with left ventricular myocardial noncompaction: results from the pediatric cardiomyopathy registry. *J Card Fail*. (2015) 21(11):877–84. doi: 10.1016/j.cardfail.2015.06.381

5. Jenni R, Oechslin E, Schneider J, Attenhofer Jost C, Kaufmann PA. Echocardiographic and pathoanatomical characteristics of isolated left ventricular non-compaction: a step towards classification as a distinct cardiomyopathy. *Heart*. (2001) 86(6):666–71. doi: 10.1136/heart.86.6.666

6. Chin TK, Perloff JK, Williams RG, Jue K, Mohrmann R. Isolated noncompaction of left ventricular myocardium. A study of eight cases. *Circulation*. (1990) 82 (2):507–13. doi: 10.1161/01.cir.82.2.507

7. Stollberger C, Finsterer J, Blazek G. Left ventricular hypertrabeculation/noncompaction and association with additional cardiac abnormalities and neuromuscular disorders. *Am J Cardiol*. (2002) 90(8):899–902. doi: 10.1016/s0002-9149(02)02723-6

8. Petersen SE, Jensen B, Aung N, Friedrich MG, McMahon CJ, Mohiddin SA, et al. Excessive trabeculation of the left ventricle: JACC: cardiovascular imaging expert panel paper. *JACC Cardiovasc Imaging*. (2023) 16(3):408–25. doi: 10.1016/j.jcmg.2022.12.026

9. Gerecke BJ, Engberding R. Noncompaction cardiomyopathy-history and current knowledge for clinical practice. *J Clin Med*. (2021) 10(11):2457. doi: 10.3390/jcm10112457

10. Ichida F, Hamamichi Y, Miyawaki T, Ono Y, Kamiya T, Akagi T, et al. Clinical features of isolated noncompaction of the ventricular myocardium: long-term clinical course, hemodynamic properties, and genetic background. *J Am Coll Cardiol*. (1999) 34(1):233–40. doi: 10.1016/s0735-1097(99)00170-9

11. Koh C, Lee PW, Yung TC, Lun KS, Cheung YF. Left ventricular noncompaction in children. *Congenit Heart Dis*. (2009) 4(4):288–94. doi: 10.1111/j.1747-0803.2009.00269.x

12. Sabatino J, Di Salvo G, Krupickova S, Fraisse A, Prota C, Bucciarelli V, et al. Left ventricular twist mechanics to identify left ventricular noncompaction in childhood. *Circ Cardiovasc Imaging*. (2019) 12(4):e007805. doi: 10.1161/CIRCIMAGING.118.007805

13. Hotta VT, Tendolo SC, Rodrigues ACT, Fernandes F, Nastari L, Mady C. Limitations in the diagnosis of noncompaction cardiomyopathy by echocardiography. *Arq Bras Cardiol*. (2017) 109(5):483–8. doi: 10.5935/abc.20170152

14. Bekheit S, Karam B, Daneshvar F, Zaidan J, Tabet R, Spagnola J, et al. Sudden cardiac death in isolated right ventricular hypertrabeculation/noncompaction cardiomyopathy. *Ann Noninvasive Electrocardiol*. (2018) 23(4):e12487. doi: 10.1111/anec.12487

15. van Waning JI, Caliskan K, Hoedemaekers YM, van Spaendonck-Zwarts KY, Baas AF, Boekholdt SM, et al. Genetics, clinical features, and long-term outcome of noncompaction cardiomyopathy. *J Am Coll Cardiol*. (2018) 71(7):711–22. doi: 10.1016/j.jacc.2017.12.019

16. Ojemolon PE, Evbayekha EO, Odion J, Bello J, Shaka H. Left ventricular noncompaction as a rare cause of syncope. *Cureus*. (2021) 13(11):e19409. doi: 10.7759/cureus.19409

17. Stöllberger C, Finsterer J. The relationship between takotsubo syndrome, left ventricular hypertrabeculation/noncompaction, neurologic and neuromuscular disorders. *Rev Cardiovasc Med*. (2021) 22(4):1413–20. doi: 10.31083/j.rcm2204146

18. Stöllberger C, Finsterer J. Understanding left ventricular hypertrabeculation/noncompaction: pathomorphologic findings and prognostic impact of neuromuscular comorbidities. *Expert Rev Cardiovasc Ther*. (2019) 17(2):95–109. doi: 10.1080/14779072.2019.1561280

19. Towbin JA, Jefferies JL. Cardiomyopathies due to left ventricular noncompaction, mitochondrial and storage diseases, and inborn errors of metabolism. *Circ Res*. (2017) 121(7):838–54. doi: 10.1161/CIRCRESAHA.117.310987

20. Finsterer J. Left ventricular non-compaction and its cardiac and neurologic implications. *Heart Fail Rev*. (2010) 15(6):589–603. doi: 10.1007/s10741-010-9175-5

21. Udeoji DU, Philip KJ, Morrissey RP, Phan A, Schwarz ER. Left ventricular noncompaction cardiomyopathy: updated review. *Ther Adv Cardiovasc Dis*. (2013) 7(5):260–73. doi: 10.1177/1753944713504639

22. Zuccarino F, Vollmer I, Sanchez G, Navallas M, Pugliese F, Gayete A. Left ventricular noncompaction: imaging findings and diagnostic criteria. *AJR Am J Roentgenol*. (2015) 204(5):W519–30. doi: 10.2214/AJR.13.12326

23. Song ZZ. The treatment of noncompaction of ventricular myocardium. *Cardiovasc Ther*. (2011) 29(5):315–21. doi: 10.1111/j.1755-5922.2010.00174.x

24. Bonnet D, Berger F, Jokinen E, Kantor PF, Daubeney PEF. Ivabradine in children with dilated cardiomyopathy and symptomatic chronic heart failure. *J Am Coll Cardiol*. (2017) 70(10):1262–72. doi: 10.1016/j.jacc.2017.07.725

25. Bocchi EA, Salemi VMC. Ivabradine for treatment of heart failure. *Expert Opin Drug Saf*. (2019) 18(5):393–402. doi: 10.1080/14740338.2019.1612873

26. Stöllberger C, Wegner C, Finsterer J. CHADS2- and CHA2DS2VASc scores and embolic risk in left ventricular hypertrabeculation/noncompaction. *J Stroke Cerebrovasc Dis*. (2013) 22(6):709–12. doi: 10.1016/j.jstrokecerebrovasdis.2011.10.014

27. Takamatsu M, Kamohara K, Sato M, Koga Y. Effect of noncompacted myocardial resection on isolated left ventricular noncompaction. *Ann Thorac Surg*. (2020) 110(5):e387–9. doi: 10.1016/j.athoracsur.2020.03.071

28. Wang C, Takasaki A, Watanabe Ozawa S, Nakaoka H, Okabe M, Miyao N, et al. Long-term prognosis of patients with left ventricular noncompaction–comparison between infantile and juvenile types. *Circ J*. (2017) 81(5):694–700. doi: 10.1253/circj.CJ-16-1114

29. Hirono K, Hata Y, Miyao N, Okabe M, Takarada S, Nakaoka H, et al. Left ventricular noncompaction and congenital heart disease increases the risk of congestive heart failure. *J Clin Med*. (2020) 9(3):785. doi: 10.3390/jcm9030785

30. Gan Y, Luo L, Tian J, Liu L, Lu T. Do children with left ventricular noncompaction and a noncompaction-to-compaction ratio <2 have a better prognosis? *BMC Pediatr*. (2020) 20(1):430. doi: 10.1186/s12887-020-02312-5

31. Hirono K, Miyao N, Yoshinaga M, Nishihara E, Yasuda K, Tateno S, et al. A significance of school screening electrocardiogram in the patients with ventricular noncompaction. *Heart Vessels*. (2020) 35(7):985–95. doi: 10.1007/s00380-020-01571-7

32. Engberding R, Yelbuz TM, Breithardt G. Isolated noncompaction of the left ventricular myocardium—a review of the literature two decades after the initial case description. *Clin Res Cardiol*. (2007) 96(7):481–8. doi: 10.1007/s00392-007-0528-6

33. Masarone D, Valente F, Rubino M, Vastarella R, Gravino R, Rea A, et al. Pediatric heart failure: a practical guide to diagnosis and management. *Pediatr Neonatol*. (2017) 58(4):303–12. doi: 10.1016/j.pedneo.2017.01.001

34. Toyono M, Kondo C, Nakajima Y, Nakazawa M, Momma K, Kusakabe K. Effects of carvedilol on left ventricular function, mass, and scintigraphic findings in isolated left ventricular non-compaction. *Heart*. (2001) 86(1):E4. doi: 10.1136/heart.86.1.e4

35. Parent JJ, Towbin JA, Jefferies JL. Medical therapy leads to favorable remodeling in left ventricular non-compaction cardiomyopathy: dilated phenotype. *Pediatr Cardiol*. (2016) 37(4):674–7. doi: 10.1007/s00246-015-1330-2

36. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Colvin MM, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American college of cardiology/American heart association task force on clinical practice guidelines and the heart failure society of America. *Circulation*. (2017) 136(6):e137–61. doi: 10.1161/CIR.0000000000000509

37. 杜朝阳 高路, 崔娘 等. 伊伐布雷定治疗儿童心力衰竭的研究现状[J]. 中国临床药理学杂志. (2020) 36(15):2373–6. doi: 10.13699/j.cnki.1001-6821.2020.15.060

38. Swedberg K, Komajda M, Böhm M, Borer JS, Ford I, Dubost-Brama A, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. *Lancet*. (2010) 376(9744):875–85; Erratum in: *Lancet*. (2010);**376** (9757):1988. Lajnscak, M [corrected to Lainscak, M]; Rabanedo, I Roldan [corrected to Rabadán, I Roldan]; Leva, M [corrected to Ieva, M]. doi: 10.1016/S0140-6736(10)61198-1

39. Lechat P, Hulot JS, Escolano S, Mallet A, Leizorovicz A, Werhlen-Grandjean M, et al. Heart rate and cardiac rhythm relationships with bisoprolol benefit in chronic heart failure in CIBIS II trial. *Circulation*. (2001) 103(10):1428–33. doi: 10.1161/01.cir.103.10.1428

40. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Colvin MM, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American college of cardiology/American heart association task force on clinical practice guidelines and the heart failure society of America. *J Card Fail*. (2017) 23(8):628–51. doi: 10.1016/j.cardfail.2017.04.014

41. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the task force for the diagnosis and treatment of acute and chronic heart failure of the European society of cardiology (ESC)Developed with the special contribution of the heart failure association (HFA) of the ESC. *Eur Heart J*. (2016) 37(27):2129–200; Erratum in: *Eur Heart J*. (2016). doi: 10.1093/eurheartj/ehw128

42. Ezekowitz JA, O'Meara E, McDonald MA, Abrams H, Chan M, Ducharme A, et al. 2017 Comprehensive update of the Canadian cardiovascular society guidelines for the management of heart failure. *Can J Cardiol*. (2017) 33(11):1342–433. doi: 10.1016/j.cjca.2017.08.022

43. Klugman D, Goswami ES, Berger JT. Pediatric cardiac intensive care society 2014 consensus statement: pharmacotherapies in cardiac critical care antihypertensives. *Pediatr Crit Care Med*. (2016) 17(3 Suppl 1):S101–8. doi: 10.1097/PCC.0000000000000621

44. US FOOD AND DRUG ADMINISTRATION (FDA). *Corlanor (ivabradine)[EB/OL]*. Washington, DC: FDA. (2019). Available at: https://www.accessdata.fda.gov/drugsatfda_docs/lable/2019/209964lbl.pdf (January 10, 2017).

45. Deedwania P. Selective and specific inhibition of if with ivabradine for the treatment of coronary artery disease or heart failure. *Drugs*. (2013) 73(14):1569–86. doi: 10.1007/s40265-013-0117-0

46. Badu-Boateng C, Jennings R, Hammersley D. The therapeutic role of ivabradine in heart failure. *Ther Adv Chronic Dis*. (2018) 9(11):199–207. doi: 10.1177/2040622318784556

47. Shaddy RE, Boucek MM, Hsu DT, Boucek RJ, Canter CE, Mahony L, et al. Carvedilol for children and adolescents with heart failure: a randomized controlled trial. *JAMA*. (2007) 298(10):1171–9. doi: 10.1001/jama.298.10.1171

48. Huang M, Zhang X, Chen S, Sun Y, Xiao Y, Sun J, et al. The effect of carvedilol treatment on chronic heart failure in pediatric patients with dilated cardiomyopathy: a prospective, randomized-controlled study. *Pediatr Cardiol*. (2013) 34(3):680–5. doi: 10.1007/s00246-012-0527-x

49. Recla S, Schmidt D, Logeswaran T, Esmaeili A, Schranz D. Pediatric heart failure therapy: why β1-receptor blocker, tissue ACE-I and mineralocorticoid-receptor-blocker? *Transl Pediatr*. (2019) 8(2):127–32. doi: 10.21037/tp.2019.04.08

50. Felker GM, Ellison DH, Mullens W, Cox ZL, Testani JM. Diuretic therapy for patients with heart failure: JACC state-of-the-art review. *J Am Coll Cardiol*. (2020) 75(10):1178–95. doi: 10.1016/j.jacc.2019.12.059

51. Channer KS, McLean KA, Lawson-Matthew P, Richardson M. Combination diuretic treatment in severe heart failure: a randomised controlled trial. *Br Heart J*. (1994) 71(2):146–50. doi: 10.1136/hrt.71.2.146

52. Stöllberger C, Blazek G, Dobias C, Hanafin A, Wegner C, Finsterer J. Frequency of stroke and embolism in left ventricular hypertrabeculation/noncompaction. *Am J Cardiol*. (2011) 108(7):1021–3. doi: 10.1016/j.amjcard.2011.05.039

53. Wu M. Mechanisms of trabecular formation and specification during cardiogenesis. *Pediatr Cardiol*. (2018) 39(6):1082–9. doi: 10.1007/s00246-018-1868-x

54. Law YM, Lal AK, Chen S, Čiháková D, Cooper LT Jr, Deshpande S, et al. Diagnosis and management of myocarditis in children: a scientific statement from the American heart association. *Circulation*. (2021) 144(6):e123–35. doi: 10.1161/CIR.0000000000001001

55. Hashemi H, Raza FS, Harmon DM, Alias T, Felius J, Sherwood MJ. Usefulness of a left ventricular assist device in patients with left ventricular noncompaction. *Proc (Bayl Univ Med Cent)*. (2018) 31(1):61–3. doi: 10.1080/08998280.2017.1401342

56. Bertini M, Ziacchi M, Biffi M, Biagini E, Rocchi G, Martignani C, et al. Effects of cardiac resynchronisation therapy on dilated cardiomyopathy with isolated ventricular non-compaction. *Heart*. (2011) 97(4):295–300. doi: 10.1136/hrt.2010.211607

57. Conraads V, Paelinck B, Vorlat A, Goethals M, Jacobs W, Vrints C. Isolated non-compaction of the left ventricle: a rare indication for transplantation. *J Heart Lung Transplant*. (2001) 20(8):904–7. doi: 10.1016/s1053-2498(01)00264-9

58. Strüber M, Meyer AL, Malehsa D, Kugler C, Simon AR, Haverich A. The current status of heart transplantation and the development of "artificial heart systems". *Dtsch Arztebl Int*. (2009) 106(28-29):471–7. doi: 10.3238/arztebl.2009.0471

59. Zetina-Tun HJ, Careaga-Reyna G, Galván-Díaz J, Sánchez-Uribe M. Trasplante cardiaco: una opción para tratamiento del miocardio no compactado aislado de ventrículo izquierdo. Primer caso en México [Heart transplantation for the treatment of isolated left ventricular myocardial noncompaction. First case in Mexico]. *Cir Cir*. (2017) 85(6):539–43. doi: 10.1016/j.circir.2016.09.001

60. Brescia ST, Rossano JW, Pignatelli R, Jefferies JL, Price JF, Decker JA, et al. Mortality and sudden death in pediatric left ventricular noncompaction in a tertiary referral center. *Circulation*. (2013) 127(22):2202–8. doi: 10.1161/CIRCULATIONAHA.113.002511

61. Stöllberger C, Wegner C, Benatar A, Chin TK, Dangel J, Majoor-Krakauer D, et al. Postnatal outcome of fetal left ventricular hypertrabeculation/noncompaction. *Pediatr Cardiol*. (2016) 37(5):919–24. doi: 10.1007/s00246-016-1369-8

62. Al-Kindi SG, El-Amm C, Ginwalla M, Hoit BD, Park SJ, Oliveira GH. Heart transplant outcomes in patients with left ventricular non-compaction cardiomyopathy. *J Heart Lung Transplant*. (2015) 34(6):761–5. doi: 10.1016/j.healun.2014.11.005

63. Lakdawala NK. Big data for a rare disease: examining heart transplantation for left ventricular noncompaction in the united network of organ sharing registry. *J Heart Lung Transplant*. (2015) 34(6):759–60. doi: 10.1016/j.healun.2015.03.019

64. Fazio G, Corrado G, Zachara E, Rapezzi C, Sulafa AK, Sutera L, et al. Ventricular tachycardia in non-compaction of left ventricle: is this a frequent complication? *Pacing Clin Electrophysiol*. (2007) 30(4):544–6. doi: 10.1111/j.1540-8159.2007.00706.x

65. Kida K, Yoneyama K, Kobayashi Y, Takano M, Akashi YJ, Miyake F. Late gadolinium enhancement on cardiac magnetic resonance images predicts reverse remodeling in patients with nonischemic cardiomyopathy treated with carvedilol. *Int J Cardiol*. (2013) 168(2):1588–9. doi: 10.1016/j.ijcard.2013.01.043

66. Wald R, Veldtman G, Golding F, Kirsh J, McCrindle B, Benson L. Determinants of outcome in isolated ventricular noncompaction in childhood. *Am J Cardiol*. (2004) 94(12):1581–4. doi: 10.1016/j.amjcard.2004.08.047

67. Haverkamp W, Martinez-Rubio A, Hief C, Lammers A, Mühlenkamp S, Wichter T, et al. Efficacy and safety of d,l-sotalol in patients with ventricular tachycardia and in survivors of cardiac arrest. *J Am Coll Cardiol*. (1997) 30(2):487–95. doi: 10.1016/s0735-1097(97)00190-3

68. Valdés SO, Miyake CY, Niu MC, de la Uz CM, Asaki SY, Landstrom AP, et al. Early experience with intravenous sotalol in children with and without congenital heart disease. *Heart Rhythm*. (2018) 15(12):1862–9. doi: 10.1016/j.hrthm.2018.07.010.

69. Cuculich PS, Schill MR, Kashani R, Mutic S, Lang A, Cooper D, et al. Noninvasive cardiac radiation for ablation of ventricular tachycardia. *N Engl J Med*. (2017) 377(24):2325–36. doi: 10.1056/NEJMoa1613773

70. Li Q, Miao L, Xia L, Abdelnasser HY, Zhang F, Lu Y, et al. Left ventricular noncompaction is associated with valvular regurgitation and a variety of arrhythmias. *J Cardiovasc Dev Dis*. (2022) 9(2):49. doi: 10.3390/jcdd902004

71. Sohns C, Ouyang F, Volkmer M, Metzner A, Nürnberg JH, Ventura R, et al. Therapy of ventricular arrhythmias in patients suffering from isolated left ventricular non-compaction cardiomyopathy. *Europace*. (2019) 21(6):961–9. doi: 10.1093/europace/euz016

72. Epstein AE, DiMarco JP, Ellenbogen KA, Estes NA 3rd, Freedman RA, Gettes LS, et al. ACC/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American college of cardiology/American heart association task force on practice guidelines (writing committee to revise the ACC/AHA/NASPE 2002 guideline update for implantation of cardiac pacemakers and antiarrhythmia devices) developed in collaboration with the American association for thoracic surgery and society of thoracic surgeons. *J Am Coll Cardiol.* (2008) 51(21):e1–62. doi: 10.1016/j.jacc.2008.02.032

73. Sato Y, Matsumoto N, Takahashi H, Imai S, Yoda S, Kasamaki Y, et al. Cardioverter defibrillator implantation in an adult with isolated noncompaction of the ventricular myocardium. *Int J Cardiol.* (2006) 110(3):417–9. doi: 10.1016/j.ijcard.2005.08.056

74. Grupa Robocza Europejskiego Towarzystwa Kardiologicznego (ESC) do spraw rozpoznawania i postepowania w kardiomiopatii przerostowej, Elliott PM, Anastasakis A, Borger MA, Borggrefe M, Cecchi F, Charron P, et al. Wytyczne ESC dotyczące rozpoznawania i postępowania w kardiomiopatii przerostowej w 2014 roku [2014 ESC guidelines on diagnosis and management of hypertrophic cardiomyopathy]. *Kardiol Pol.* (2014) 72(11):1054–126. doi: 10.5603/KP.2014.0212

75. Petersen SE, Selvanayagam JB, Wiesmann F, Robson MD, Francis JM, Anderson RH, et al. Left ventricular non-compaction: insights from cardiovascular magnetic resonance imaging. *J Am Coll Cardiol.* (2005) 46(1):101–5. doi: 10.1016/j.jacc.2005.03.045

76. Caliskan K, Szili-Torok T, Theuns DA, Kardos A, Geleijnse ML, Balk AH, et al. Indications and outcome of implantable cardioverter-defibrillators for primary and secondary prophylaxis in patients with noncompaction cardiomyopathy. *J Cardiovasc Electrophysiol.* (2011) 22(8):898–904. doi: 10.1111/j.1540-8167.2011.02015.x

77. Cetin MS, Ozcan Cetin EH, Canpolat U, Cay S, Topaloglu S, Temizhan A, et al. Usefulness of fragmented QRS complex to predict arrhythmic events and cardiovascular mortality in patients with noncompaction cardiomyopathy. *Am J Cardiol.* (2016) 117(9):1516–23. doi: 10.1016/j.amjcard.2016.02.022

78. Derval N, Jais P, O'Neill MD, Haissaguerre M. Apparent idiopathic ventricular tachycardia associated with isolated ventricular noncompaction. *Heart Rhythm.* (2009) 6(3):385–8. doi: 10.1016/j.hrthm.2008.11.020

79. Grigoratos C, Barison A, Ivanov A, Andreini D, Amzulescu MS, Mazurkiewicz L, et al. Meta-analysis of the prognostic role of late gadolinium enhancement and global systolic impairment in left ventricular noncompaction. *JACC Cardiovasc Imaging.* (2019) 12(11 Pt 1):2141–51. doi: 10.1016/j.jcmg.2018.12.029

80. Jenni R, Oechslin EN, van der Loo B. Isolated ventricular non-compaction of the myocardium in adults. *Heart.* (2007) 93(1):11–5. doi: 10.1136/hrt.2005.082271

81. Muser D, Nucifora G, Gianfagna E, Pavoni D, Rebellato L, Facchin D, et al.. Clinical spectrum of isolated left ventricular noncompaction: thromboembolic events, malignant left ventricular arrhythmias, and refractory heart failure. *J Am Coll Cardiol.* (2014) 63(16):e39. doi: 10.1016/j.jacc.2013.11.063

82. Engberding R, Stöllberger C, Ong P, Yelbuz TM, Gerecke BJ, Breithardt G. Isolated non-compaction cardiomyopathy. *Dtsch Arztebl Int.* (2010) 107(12):206–13. doi: 10.3238/arztebl.2010.0206

83. Oechslin EN, Attenhofer Jost CH, Rojas JR, Kaufmann PA, Jenni R. Long-term follow-up of 34 adults with isolated left ventricular noncompaction: a distinct cardiomyopathy with poor prognosis. *J Am Coll Cardiol.* (2000) 36(2):493–500. doi: 10.1016/s0735-1097(00)00755-5

84. Ritter M, Oechslin E, Sütsch G, Attenhofer C, Schneider J, Jenni R. Isolated noncompaction of the myocardium in adults. *Mayo Clin Proc.* (1997) 72(1):26–31. doi: 10.4065/72.1.26

85. Fazio G, Corrado G, Zachara E, Rapezzi C, Sulafa AK, Sutera L, et al. Anticoagulant drugs in noncompaction: a mandatory therapy? *J Cardiovasc Med (Hagerstown).* (2008) 9(11):1095–7. doi: 10.2459/JCM.0b013e328308da04

86. Homma S, Thompson JL, Pullicino PM, Levin B, Freudenberger RS, Teerlink JR, et al. Warfarin and aspirin in patients with heart failure and sinus rhythm. *N Engl J Med.* (2012) 366(20):1859–69. doi: 10.1056/NEJMoa1202299

87. Rengo G, Pagano G, Squizzato A, Moja L, Femminella GD, de Lucia C, et al. Oral anticoagulation therapy in heart failure patients in sinus rhythm: a systematic review and meta-analysis. *PLoS One.* (2013) 8(1):e52952. doi: 10.1371/journal.pone.0052952

88. Bocchi EA, Marcondes-Braga FG, Bacal F, Ferraz AS, Albuquerque D, Rodrigues Dde A, et al. Sociedade Brasileira de Cardiologia. III Diretriz brasileira de insuficiência cardíaca crnica. *Arq Bras Cardiol.* (2009) 93(1):1–71. doi: 10.1590/S0066-782X2012001000001

89. Murphy RT, Thaman R, Blanes JG, Ward D, Sevdalis E, Papra E, et al. Natural history and familial characteristics of isolated left ventricular non-compaction. *Eur Heart J.* (2005) 26(2):187–92. doi: 10.1093/eurheartj/ehi025

90. Weiford BC, Subbarao VD, Mulhern KM. Noncompaction of the ventricular myocardium. *Circulation.* (2004) 109(24):2965–71. doi: 10.1161/01.CIR.0000132478.60674.D0

91. Finsterer J, Stöllberger C, Towbin JA. Left ventricular noncompaction cardiomyopathy: cardiac, neuromuscular, and genetic factors. *Nat Rev Cardiol.* (2017) 14(4):224–37. doi: 10.1038/nrcardio.2016.207

92. Levine MN, Raskob G, Beyth RJ, Kearon C, Schulman S. Hemorrhagic complications of anticoagulant treatment: the seventh ACCP conference on antithrombotic and thrombolytic therapy. *Chest.* (2004) 126(3 Suppl):287S–310S. doi: 10.1378/chest.126.3_suppl.287S

93. Ng HJ, Crowther MA. New anti-thrombotic agents: emphasis on hemorrhagic complications and their management. *Semin Hematol.* (2006) 43(1 Suppl 1):S77–83. doi: 10.1053/j.seminhematol.2005.11.023

94. Spyropoulos AC, Brohi K, Caprini J, Samama CM, Siegal D, Tafur A, et al. Scientific and standardization committee communication: guidance document on the periprocedural management of patients on chronic oral anticoagulant therapy: recommendations for standardized reporting of procedural/surgical bleed risk and patient-specific thromboembolic risk. *J Thromb Haemost.* (2019) 17(11):1966–72. doi: 10.1111/jth.14598

95. Crowther MA, Warkentin TE. Bleeding risk and the management of bleeding complications in patients undergoing anticoagulant therapy: focus on new anticoagulant agents. *Blood.* (2008) 111(10):4871–9. doi: 10.1182/blood-2007-10-120543

96. Turpie AG, Bauer KA, Eriksson BI, Lassen MR. Fondaparinux vs enoxaparin for the prevention of venous thromboembolism in major orthopedic surgery: a meta-analysis of 4 randomized double-blind studies. *Arch Intern Med.* (2002) 162 (16):1833–40. doi: 10.1001/archinte.162.16.1833

97. Dzik WS. Reversal of drug-induced anticoagulation: old solutions and new problems. *Transfusion.* (2012) 52 Suppl 1:45S–55S. doi: 10.1111/j.1537-2995.2012.03690.x

98. Bijsterveld NR, Moons AH, Boekholdt SM, van Aken BE, Fennema H, Peters RJ, et al. Ability of recombinant factor VIIa to reverse the anticoagulant effect of the pentasaccharide fondaparinux in healthy volunteers. *Circulation.* (2002) 106 (20):2550–4. doi: 10.1161/01.cir.0000038501.87442.02

99. Bijsterveld NR, Vink R, van Aken BE, Fennema H, Peters RJ, Meijers JC, et al. Recombinant factor VIIa reverses the anticoagulant effect of the long-acting pentasaccharide idraparinux in healthy volunteers. *Br J Haematol.* (2004) 124 (5):653–8. doi: 10.1111/j.1365-2141.2003.04811.x

100. Lethagen S. Desmopressin in mild hemophilia A: indications, limitations, efficacy, and safety. *Semin Thromb Hemost.* (2003) 29(1):101–6. doi: 10.1055/s-2003-37944

101. Dreijer AR, Diepstraten J, Brouwer R, Croles FN, Kragten E, Leebeek FWG, et al. Risk of bleeding in hospitalized patients on anticoagulant therapy: prevalence and potential risk factors. *Eur J Intern Med.* (2019) 62:17–23. doi: 10.1016/j.ejim.2019.01.008

102. Gan C, Hu J, Luo S, An Q, Lin K. Surgical restoration of left ventricular diastolic function: possible treatment for noncompaction cardiomyopathy. *J Card Surg.* (2014) 29(6):827–8. doi: 10.1111/jocs.12339

103. Agmon Y, Connolly HM, Olson LJ, Khandheria BK, Seward JB. Noncompaction of the ventricular myocardium. *J Am Soc Echocardiogr.* (1999) 12 (10):859–63. doi: 10.1016/s0894-7317(99)70192-6

104. Stöllberger C, Finsterer J. Is surgical removal of the noncompacted layer the clue to treat left ventricular hypertrabeculation/noncompaction? *J Card Surg.* (2014) 29(6):837–8. doi: 10.1111/jocs.12438

105. Cao F, Yang Z, Yin L. A fetal mouse model of ventricular non-compaction using retinoic acid. *Pathol Res Pract.* (2019) 215(8):152496. doi: 10.1016/j.prp.2019.152496

106. Takahashi K, Tanabe K, Ohnuki M, Narita M, Ichisaka T, Tomoda K, et al. Induction of pluripotent stem cells from adult human fibroblasts by defined factors. *Cell.* (2007) 131(5):861–72. doi: 10.1016/j.cell.2007.11.019

107. van Mil A, Balk GM, Neef K, Buikema JW, Asselbergs FW, Wu SM, et al. Modelling inherited cardiac disease using human induced pluripotent stem cell-derived cardiomyocytes: progress, pitfalls, and potential. *Cardiovasc Res.* (2018) 114 (14):1828–42. doi: 10.1093/cvr/cvy208

108. Lawson CD, Ridley AJ. Rho GTPase signaling complexes in cell migration and invasion. *J Cell Biol.* (2018) 217(2):447–57. doi: 10.1083/jcb.201612069

109. Strong A, Musunuru K. Genome editing in cardiovascular diseases. *Nat Rev Cardiol.* (2017) 14(1):11–20. doi: 10.1038/nrcardio.2016.139

110. Zou J, Tran D, Baalbaki M, Tang LF, Poon A, Pelonero A, et al. An internal promoter underlies the difference in disease severity between N- and C-terminal truncation mutations of Titin in zebrafish. *Elife.* (2015) 4:e09406. doi: 10.7554/eLife.09406

111. Jaffré F, Miller CL, Schänzer A, Evans T, Roberts AE, Hahn A, et al. Inducible pluripotent stem cell-derived cardiomyocytes reveal aberrant extracellular regulated kinase 5 and mitogen-activated protein kinase kinase 1/2 signaling concomitantly promote hypertrophic cardiomyopathy in RAF1-associated noonan syndrome. *Circulation.* (2019) 140(3):207–24. doi: 10.1161/CIRCULATIONAHA.118.037227

112. Montag J, Petersen B, Flögel AK, Becker E, Lucas-Hahn A, Cost GJ, et al. Successful knock-in of hypertrophic cardiomyopathy-mutation R723G into the

MYH7 gene mimics HCM pathology in pigs. *Sci Rep*. (2018) 8(1):4786. doi: 10.1038/s41598-018-22936-z

113. Ma H, Marti-Gutierrez N, Park SW, Wu J, Lee Y, Suzuki K, et al. Correction of a pathogenic gene mutation in human embryos. *Nature*. (2017) 548(7668):413–9. doi: 10.1038/nature23305

114. Greutmann M, Mah ML, Silversides CK, Klaassen S, Attenhofer Jost CH, Jenni R, et al. Predictors of adverse outcome in adolescents and adults with isolated left ventricular noncompaction. *Am J Cardiol*. (2012) 109(2):276–81. doi: 10.1016/j.amjcard.2011.08.043

115. Towbin JA, Lorts A, Jefferies JL. Left ventricular non-compaction cardiomyopathy. *Lancet*. (2015) 386(9995):813–25. doi: 10.1016/S0140-6736(14)61282-4

116. Towbin JA, Beasley G. Left ventricular noncompaction and vigorous physical activity: what is the connection? *J Am Coll Cardiol*. (2020) 76(15):1734–6. doi: 10.1016/j.jacc.2020.08.051

117. Pelliccia A, Sharma S, Gati S, Bäck M, Börjesson M, Caselli S, et al. 2020 ESC guidelines on sports cardiology and exercise in patients with cardiovascular disease. *Eur Heart J*. (2021) 42(1):17–96. doi: 10.1093/eurheartj/ehaa605

118. Miszalski-Jamka K, Jefferies JL, Mazur W, Głowacki J, Hu J, Lazar M, et al. Novel genetic triggers and genotype-phenotype correlations in patients with left ventricular noncompaction. *Circ Cardiovasc Genet*. (2017) 10(4):e001763. doi: 10.1161/CIRCGENETICS.117.001763

119. Akhtar T, Bandyopadhyay D, Ghosh RK, Mondal S. Left ventricular noncompaction cardiomyopathy: recent update on genetics, usefulness of biomarker, and speckle imaging. *J Cardiol*. (2019) 73(1):94–5. doi: 10.1016/j.jjcc.2018.05.016

120. Alawani SS, Paul A, Krishna MR, Ahamed H. Familial left ventricular noncompaction cardiomyopathy due to a novel mutation in the MYH 7 gene. *Ann Pediatr Cardiol*. (2021) 14(4):544–6. doi: 10.4103/apc.APC_92_20

121. Parent JJ, Towbin JA, Jefferies JL. Left ventricular noncompaction in a family with lamin A/C gene mutation. *Tex Heart Inst J*. (2015) 42(1):73–6. doi: 10.14503/THIJ-13-3843

122. Wang J, Guo Y, Huang M, Zhang Z, Zhu J, Liu T, et al. Identification of TAZ mutations in pediatric patients with cardiomyopathy by targeted next-generation sequencing in a Chinese cohort. *Orphanet J Rare Dis*. (2017) 12(1):26. doi: 10.1186/s13023-016-0562-4

123. Wang C, Hata Y, Hirono K, Takasaki A, Ozawa SW, Nakaoka H, et al. A wide and specific spectrum of genetic variants and genotype-phenotype correlations revealed by next-generation sequencing in patients with left ventricular noncompaction. *J Am Heart Assoc*. (2017) 6(9):e006210. doi: 10.1161/JAHA.117.006210

124. Miyao N, Hata Y, Izumi H, Nagaoka R, Oku Y, Takasaki I, et al. TBX5 R264k acts as a modifier to develop dilated cardiomyopathy in mice independently of T-box pathway. *PLoS One*. (2020) 15(4):e0227393. doi: 10.1371/journal.pone.0227393

125. Samudrala SSK, North LM, Stamm KD, Earing MG, Frommelt MA, Willes R, et al. Novel KLHL26 variant associated with a familial case of Ebstein's anomaly and left ventricular noncompaction. *Mol Genet Genomic Med*. (2020) 8(4):e1152. doi: 10.1002/mgg3.1152

126. Tariq M, Ware SM. Importance of genetic evaluation and testing in pediatric cardiomyopathy. *World J Cardiol*. (2014) 6(11):1156–65. doi: 10.4330/wjc.v6.i11.1156

127. Wang D, Tai PWL, Gao G. Adeno-associated virus vector as a platform for gene therapy delivery. *Nat Rev Drug Discov*. (2019) 18(5):358–78. doi: 10.1038/s41573-019-0012-9

128. Maule G, Arosio D, Cereseto A. Gene therapy for cystic fibrosis: progress and challenges of genome editing. *Int J Mol Sci*. (2020) 21(11):3903. doi: 10.3390/ijms21113903

129. Ylä-Herttuala S, Baker AH. Cardiovascular gene therapy: past, present, and future. *Mol Ther*. (2017) 25(5):1095–106. doi: 10.1016/j.ymthe.2017.03.027

130. Keeler AM, ElMallah MK, Flotte TR. Gene therapy 2017: progress and future directions. *Clin Transl Sci*. (2017) 10(4):242–8. doi: 10.1111/cts.12466

131. Ishikawa K, Weber T, Hajjar RJ. Human cardiac gene therapy. *Circ Res*. (2018) 123(5):601–13. doi: 10.1161/CIRCRESAHA.118.311587

132. Finsterer J, Stöllberger C, Bonner E. Left ventricular hypertrabeculation/noncompaction associated with coronary heart disease and myopathy. *Int J Cardiol*. (2011) 148(3):e53–5. doi: 10.1016/j.ijcard.2009.03.007

133. Sengupta PP, Mohan JC, Mehta V, Jain V, Arora R, Pandian NG, et al. Comparison of echocardiographic features of noncompaction of the left ventricle in adults versus idiopathic dilated cardiomyopathy in adults. *Am J Cardiol*. (2004) 94(3):389–91. doi: 10.1016/j.amjcard.2004.04.046

134. Madnawat H, Atallah I, Ahmad A, Harjai K. Biventricular noncompaction cardiomyopathy in a patient presenting with a new cerebrovascular event. *Am J Cardiol*. (2023) 190:110–2. doi: 10.1016/j.amjcard.2022.11.047

135. Ivanov A, Dabiesingh DS, Bhumireddy GP, Mohamed A, Asfour A, Briggs WM, et al. Prevalence and prognostic significance of left ventricular noncompaction in patients referred for cardiac magnetic resonance imaging. *Circ Cardiovasc Imaging*. (2017) 10(9):e006174. doi: 10.1161/CIRCIMAGING.117.006174

frontiers | Frontiers in Public Health

TYPE Original Research
PUBLISHED 02 June 2023
DOI 10.3389/fpubh.2023.1105163

OPEN ACCESS

EDITED BY
Shikai Yu,
Tongji University, China

REVIEWED BY
Katrien Vandoorne,
Technion Israel Institute of Technology, Israel
Mathilde Sengoelge,
Karolinska Institutet (KI), Sweden

*CORRESPONDENCE
Fiona M. Wood
✉ fiona.wood@health.wa.gov.au
Jeremy K. Nicholson
✉ j.nicholson@imperial.ac.uk

RECEIVED 22 November 2022
ACCEPTED 11 May 2023
PUBLISHED 02 June 2023

CITATION
Begum S, Lodge S, Hall D, Johnson BZ, Bong SH, Whiley L, Gray N, Fear VS, Fear MW, Holmes E, Wood FM and Nicholson JK (2023) Cardiometabolic disease risk markers are increased following burn injury in children. *Front. Public Health* 11:1105163. doi: 10.3389/fpubh.2023.1105163

Cardiometabolic disease risk markers are increased following burn injury in children

Sofina Begum[1,2,3,4,5], Samantha Lodge[4], Drew Hall[4], Blair Z. Johnson[5], Sze How Bong[4], Luke Whiley[4,6,7], Nicola Gray[4,7], Vanessa S. Fear[8], Mark W. Fear[5], Elaine Holmes[3,4,7], Fiona M. Wood[5,9]* and Jeremy K. Nicholson[4,7,10]*

[1]Harvard Medical School, Harvard University, Boston, MA, United States, [2]Channing Division of Network Medicine, Brigham and Women's Hospital, Boston, MA, United States, [3]Department of Metabolism, Digestion and Reproduction, Faculty of Medicine, Imperial College London, London, United Kingdom, [4]Australian National Phenome Centre, Computational and Systems Medicine, Health Futures Institute, Perth, WA, Australia, [5]School of Biomedical Sciences, The University of Western Australia, Perth, WA, Australia, [6]Perron Institute for Neurological and Translational Science, Nedlands, WA, Australia, [7]Centre for Computational and Systems Medicine, Health Futures Institute, Murdoch University, Perth, WA, Australia, [8]Translational Genetics, Telethon Kids Institute, Perth, WA, Australia, [9]WA Department of Health, Burns Service of Western Australia, Perth, WA, Australia, [10]Faculty of Medicine, Institute of Global Health Innovation, London, United Kingdom

Introduction: Burn injury in children causes prolonged systemic effects on physiology and metabolism leading to increased morbidity and mortality, yet much remains undefined regarding the metabolic trajectory towards specific health outcomes.

Methods: A multi-platform strategy was implemented to evaluate the long-term immuno-metabolic consequences of burn injury combining metabolite, lipoprotein, and cytokine panels. Plasma samples from 36 children aged 4–8 years were collected 3 years after a burn injury together with 21 samples from non-injured age and sex matched controls. Three different ^{1}H Nuclear Magnetic Resonance spectroscopic experiments were applied to capture information on plasma low molecular weight metabolites, lipoproteins, and α-1-acid glycoprotein.

Results: Burn injury was characterized by underlying signatures of hyperglycaemia, hypermetabolism and inflammation, suggesting disruption of multiple pathways relating to glycolysis, tricarboxylic acid cycle, amino acid metabolism and the urea cycle. In addition, very low-density lipoprotein sub-components were significantly reduced in participants with burn injury whereas small-dense low density lipoprotein particles were significantly elevated in the burn injured patient plasma compared to uninjured controls, potentially indicative of modified cardiometabolic risk after a burn. Weighted-node Metabolite Correlation Network Analysis was restricted to the significantly differential features ($q < 0.05$)between the children with and without burn injury and demonstrated a striking disparity in the number of statistical correlations between cytokines, lipoproteins, and small molecular metabolites in the injured groups, with increased correlations between these groups.

Discussion: These findings suggest a 'metabolic memory' of burn defined by a signature of interlinked and perturbed immune and metabolic function. Burn injury is associated with a series of adverse metabolic changes that persist chronically and are independent of burn severity and this study demonstrates increased risk of cardiovascular disease in the long-term. These findings highlight a crucial need for improved longer term monitoring of cardiometabolic health in a vulnerable population of children that have undergone burn injury.

KEYWORDS

metabolomics, precision medicine, cardiometabolic disease risk, child health, burn injury, NMR, inflammation, cytokines

1. Introduction

Non-severe burn injury, defined as less than 20% total body surface area (TBSA), is a common childhood medical insult, accounting for over 85% of pediatric burn cases in Australia (1). Recent research has demonstrated that even non-severe childhood burns are associated with a significant increase in hospitalization for a range of morbidities, including cardiovascular diseases, suggestive of a sustained systemic response to this type of injury (2). However, non-severe burn injury has traditionally been less well-studied than severe burns (2). Severe burn injury induces a global multisystemic effect, far beyond the initial site of injury, and the subsequent hypermetabolic response has been shown to persist for several years post-injury, even when no scarring remains (3). However, the extent and nature of this response in non-severe burns is less well established.

The burn-induced hypermetabolic response is thought to result from a physiological drive toward healing, which causes elevated catabolism (4), inflammation and sustained stress hormone release (5). The hypermetabolic state has been found to be persistent in many patients with severe burns, with its resolution linked to the longevity and duration of exposure to elevated levels of catecholamines, cortisol and glucagons (6). Serum cortisol measurements, and a range of cytokines including IL-6 and TNF-α have been reported to remain significantly increased for up to 3 years post-burn injury in children (7). This heightened proinflammatory state is typically accompanied by hyperglycemia and increased insulin resistance, independent of burn severity (8). Post-burn dysregulation of metabolism and immune regulation has also been associated with increased production of reactive oxygen species (ROS) and reactive nitrogen species such as nitric oxide and peroxynitrite (9). While severe burns have been well documented to induce this chronic inflammatory and hypermetabolic response, the mechanisms behind these chronic aberrations and whether these changes persist after non-severe burns, is less clear (10, 11).

One of the hallmarks of burn injury is the high rate of hospital admissions for cardiovascular disease (CVD) compared to the general population within the first few years post-injury (12). However, some researchers report no such elevation in CVD risk (13). Our prior work, deploying targeted metabolic phenotyping strategies to map the hypermetabolic state present in children long after recovery from a non-severe burn injury, demonstrated increased plasma levels of multiple amino acids and the neurotoxic metabolite quinolinic acid (14) but did not assess whether there are sustained metabolic changes that might be associated with the observed increased risk of cardiovascular disease (15). In order to address this substantial research gap, here we utilize ^{1}H Nuclear Magnetic Resonance (NMR) spectroscopy to measure a wide panel of plasma metabolites. We apply three different pulse sequences to capture different molecular panels including lipoproteins (quantified based on the standard 1D NMR pulse sequence); small molecules (spin echo pulse sequence to attenuate contributions of macromolecules) and the JEDI pulse sequence (combining three spectroscopic editing techniques: diffusion; relaxation; J-editing to suppress small molecules and large proteins/lipoproteins) to capture biomarkers of inflammation. Together these pulse sequences enabled assessment of the metabolic landscape associated with the risk and incidence of cardiovascular disease (16). We identify a systemic signature of dysregulated lipoproteins associated with prior burn injury that may be linked to altered CVD risk post burn-injury.

Abbreviations: TBSA, Total Body Surface Area; NMR, Nuclear Magnetic Resonance; CPMG, Carr-Purcell Meiboom-Gill; JEDI-PGPE, J-Edited DiFFusional Pulsed Gradient Echo Experiment; PCA, Principal Component Analysis; OPLS-DA, Orthogonal Partial Least Squares-Discriminant Analysis; SD, Standard Deviation; GlycA, α-1-acid glycoprotein signal A; GlycB, α-1-acid glycoprotein signal B; SPC, Supramolecular Phospholipid Composite; STOCSY, Statistical TOtal Correlation SpectroscopY.

2. Results

2.1. Metabolic phenotypes indicate persistent metabolic effects of burn injury in children

Differentiation of children with prior burn injury versus no burn injury was apparent for all three data sets focusing on lipoproteins, small molecules, and the inflammatory NMR panel (17). Orthogonal Partial Least Squares-Discriminant Analysis (OPLS-DA) is a robust statistical strategy to interrogate features in high-dimensional data, utilizing supervised regression analysis to define variation for class discrimination (18). The OPLS-DA models of all three sets of spectral data indicated there were significant metabolic differences between the prior burn injury and the control groups. The strongest classifier of burn injury was based on the standard 1D NMR pulse sequence dataset suggesting that burn injury was defined by a broad metabolic response as the standard profile contains contributions from low molecular weight molecules, lipoproteins, and glycoproteins. The cross-validated OPLS-DA model yielded a predictive value (Q^2Y) of 0.52 and was predominantly driven by higher relative concentrations of glucose, amino acids (with the exception of glutamate and glycine), pyruvate, creatine, *N*-acetyl signals from α-1-acid glycoproteins (GlycA and GlycB) representing the burn injury group, with lower concentrations of acetate, acetoacetate, glutamate, and 3-methyl histidine (Figures 1A,B). The contribution of these low molecular weight metabolites differentiating the prior burn injury group from controls was further assessed using metabolite concentrations quantified using B.I.-LISA™ software (19). Glutamine, alanine, creatine, phenylalanine, and glucose were found to be directly correlated with burn injury, based on Student's t test, while controlling the false-discovery rate ($p < 0.05$) and the Cliff's delta value (Supplementary Figure S2B), whereas glutamic acid and 3-D-hydroxybutyric acid were inversely associated (Table 1). 3-D-hydroxybutyric acid was higher in the control group plasma samples but did not retain significance after controlling the false discovery rate (Figures 1C,D). There was a trend toward higher levels

10.3389/fpubh.2023.1105163

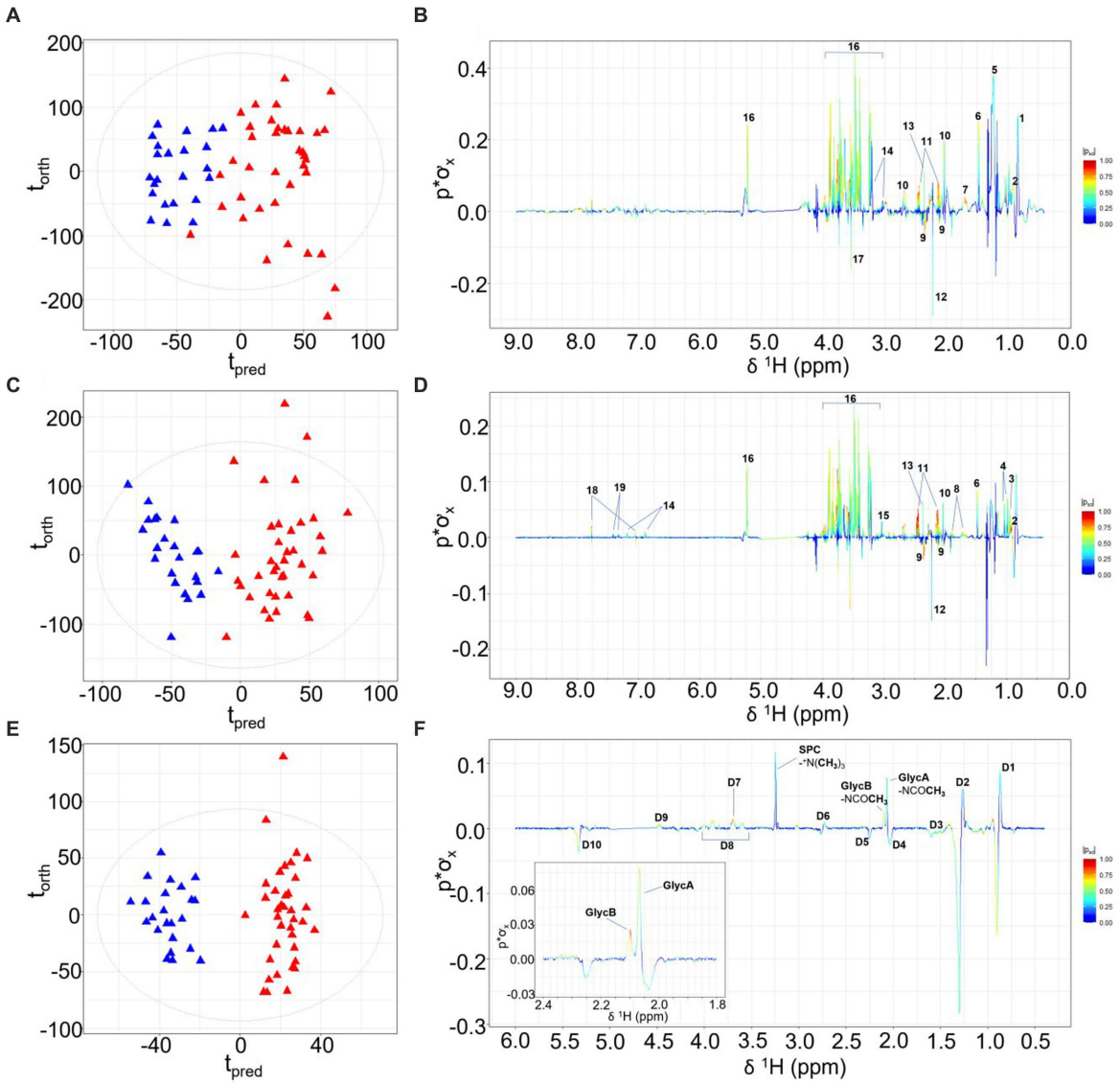


FIGURE 1
OPLS-DA scores plots, with t_{orth} (orthogonal) representing the greatest amount of systematic variation in the data set uncorrelated to Y (burn injury or healthy control groups), and t_{pred} (predictive) representing the greatest amount of correlated variation to Y. Corresponding model loadings coefficients are shown, differentiating the NMR plasma spectra from children with prior burn injury (red) from the control group (blue) based on the standard 1D NMR pulse sequence **(A,B)**; the CPMG pulse sequence **(C,D)** and the JEDI-PGPE pulse sequence **(E,F)**. Key: 1- Lipid: -CH_2CH_3, 2-Isoleucine, 3-Leucine, 4-Valine, 5- Lipid: -$CH_2CH_2CH_2$–6-Alanine, 7- Lipid: -CH_2CH_2CO 8-Lysine 9-Glutamate, 10-Methioine, 11-Glutamine, 12-Acetone, 13-Pyruvate, 14-Tyrosine, 15-Creatine, 16-Glucose, 17-Glycine, 18-3-methylhistidine, 19-Phenylalanine, D1-Lipid: -CH_2CH_3 D2- Lipid: -$CH_2CH_2CH_2$- D3- Lipid: -CH_2CH_2CO D4- Lipid: -CH_2CH=CH- D5- Lipid: -CH_2CO D6- Lipid: -CH=CH-CH_2-CH=CH- D7- SPC: $^+NCH_2CH_2OP$- D8-GlycA/GlycB *N*-acetyl sugar moieties, D9- SPC:-$^+NCH_2CH_2OP$- D10- Lipid: -CH=CH-.

of other ketone bodies (acetone and acetoacetate) in the control group, but these were not statistically significant.

Whereas the standard 1-Dimensional (1D) NMR experiment reflects the global molecular signature and composition, the Carr-Purcell Meiboom-Gill (CPMG) spin-echo experiment, effects spectral editing based on the proton T_2 relaxation properties of proton signals by attenuating peaks from large molecules with slow rotational correlation times such as lipoproteins (20). In contrast JEDI-PGPE pulse sequences use pulsed field gradients to enhance signals from molecules with high segmental motional freedom but slow translational diffusion molecules that are contained within certain lipoprotein sub-compartments (21). Since the OPLS-DA model constructed from the standard 1D NMR spectra ($Q^2Y = 0.52$) was stronger than either the CPMG (Q^2Y 0.46; Figures 1C,D) or JEDI-PGPE (Q^2Y 0.26; Figures 1E,F) models, this suggests that a broad range of low molecular weight molecules (most prevalent through 1D NMR spectral resolution), lipoproteins and glycoproteins are disrupted in children who have suffered prior burn injury. The CPMG model loadings (Figure 1D) further highlighted the association of citrate and formate with thermal injury whereas GlycA and GlycB were the strongest discriminatory signals differentiating burn from control group in the JEDI-PGPE data set (Figure 1F). The signals arising from the supramolecular phospholipid composite (SPC) peak were reduced in the burn injury group, but were not significantly

TABLE 1 Quantified metabolites differentiating children with prior burn injury from control.

Compound	Mean concentration [SD] Control group	Mean concentration [SD] Burn injury group	Cliff's Delta[a]	value of *p* (univariate)	*q*-value[b]
Glutamine: glutamate ratio	2.190 [2.762]	5.565 [3.595]	0.56	0.0003***	0.004**
Glutamine	0.503 [0.090]	0.638 [0.100]	0.53	5.30×10^{-3}***	5.88×10^{-3}***
Alanine	0.278 [0.058]	0.348 [0.095]	0.48	0.0017**	0.013*
GlycA[c]	4.386×10^{3}	4.518×10^{3}	0.45	0.037*	0.104
Creatine	0.046 [0.017]	0.054 [0.009]	0.37	0.017*	0.097
Phenylalanine	0.034 [0.043]	0.039 [0.020]	0.35	0.022*	0.098
Glucose	4.607 [0.962]	4.966 [1.179]	0.34	0.027*	0.106
GlycB[c]	0.986×10^{3} [0.110×10^{3}]	1.087×10^{3} [0.174×10^{3}]	0.31	2.78×10^{-4}***	0.016*
3-D- Hydroxybutyric acid	0.086 [0.278]	0.061 [0.299]	−0.30	0.047*	0.150
Glutamate	0.213 [0.108]	0.101 [0.077]	−0.55	3.80×10^{-3}***	5.88×10^{-3}***

[a]Ranked in order of the magnitude of the Cliff's Delta statistic.
[b]Value of *p* corrected for multiple testing (FDR, BH), *$p<0.05$, **$p<0.01$, ***$p<0.001$.
[c]GlycA (α-1-acid glycoprotein signal A) and GlycB (α-1-acid glycoprotein signal B) are imputed integrals of spectral peaks.

differential. The corresponding PCA scores plots are provided in Supplementary Figure S1.

Metabolite-metabolite correlations were explored for key metabolites characteristic of prior burn injury using STOCSY (22) (Supplementary Figure S3). To investigate the association between 3-D-hydroxybutyric acid and ketogenesis, a correlation analysis driven from the apex of the acetoacetate peak (Supplementary Figure S3A) demonstrated a strong association between the three ketone bodies and 3-D-hydroxybutyric acid, further suggesting that burn injury was associated with a systematic decrease in plasma ketone bodies. Glucose was directly associated with GlycA and HDL lipoproteins (Supplementary Figure S3B); pyruvate was weakly associated with alanine and lactate (Supplementary Figure S3C); creatine was positively associated with multiple amino acids (Supplementary Figure S3D) and glutamine and glutamate were strongly inversely correlated (Supplementary Figure S3E).

2.2. Prior burn injury affects the plasma lipoprotein composition

PCA modeling of lipoproteins, quantified according to the Bruker iVDR B.I.-LISA™ method (19), showed a cluster of burn injury patients in the lower left-hand quadrant of the scores plot (Figure 2A). The differential signature of the plasma lipoprotein parameters was further defined in the OPLS-DA model (R^2X 0.437, R^2Y 0.492, Q^2Y 0.321) and the eruption plot based on the model loadings versus Cliff's delta statistic (Figures 2B,D). Prior burn injury was characterized by relatively higher plasma concentrations of LDL subfractions 5 and 6, particularly particle number, total cholesterol, free cholesterol, triglycerides, and Apolipoprotein B. Total LDPN and LDAB were also elevated in the burn injury group although this association was not significant after adjusting for multiple testing. In contrast, multiple VLDL5 subfractions were present in lower concentrations in the prior burn injury group in comparison to the controls as were L1TG and L4TG (Figures 2C,D; Table 2). Although the group size was small, the prior burn injury group was subdivided into burns caused by scalds versus flame. LDL-1 and LDL-4 triglyceride fractions were associated with scalds whereas the L6PL subfraction was associated with flame burns (Supplementary Figure S4).

2.3. Correlation of and other inflammatory markers lipoproteins with cytokines

α-1-acid glycoprotein *N*-acetyl signals (GlycA and GlycB) have long been known to be associated with systemic inflammation (23), Spearman's correlation of lipoprotein parameters and JEDI-PGPE integrals for GlycA, GlycB and SPC were calculated and presented two distinct profiles corresponding to non-burn controls (Figure 3A) and burn injury (Figure 3B). In the control group there were negative correlations between GlycA and IL-7, IL-10 and GM-CSF (Figure 4A), whereas GlycB was positively correlated with several cytokines including IFN-γ, IL-13, IL-17a, IL-13, IL-6 and TNF-α, signatures absent in burn injury children(Figure 4B). In contrast, in the burn injury group both GlycA and GlycB showed strong direct correlations for IL-2, IL-6, IL-10, IL-13, TNF-α and IFN-γ reflecting the hyperinflammatory consequences associated with previous burn injury (7). Of these cytokines, IL-2, TNF-α and IFN-γ showed independent association with burn injury.

The same contrasting correlation profile for the control and prior burn (Figures 3C,D) groups was also evident in the correlation structure between the significant lipoprotein parameters and the cytokines. The cytokine correlation map for the full list of lipoproteins is provided in Supplementary Figure S5. The small dense LDL lipoprotein parameters from subclasses 5 and 6 were weakly anticorrelated with most measured cytokines in the control group, particularly GM-CSF, IL-7, IL-10, and IL-12, whereas the VLDL subfraction 5 parameters (V5PL, V5CH, V5FC) were weakly directly associated with most cytokines, particularly IL-2, IL-10 and IL-12. This pattern largely reversed in the prior burn injury group with a general positive correlation between cytokines and LDL-6 lipoprotein parameters with notable correlations with IL-7 and IL-12. VLDL5 sub-particles were inversely related with the global cytokine profile for the burn group. Plasma HDTG concentrations were lower in the burn group. Interestingly, H2TG, H3TG, H3A1 and H3A2

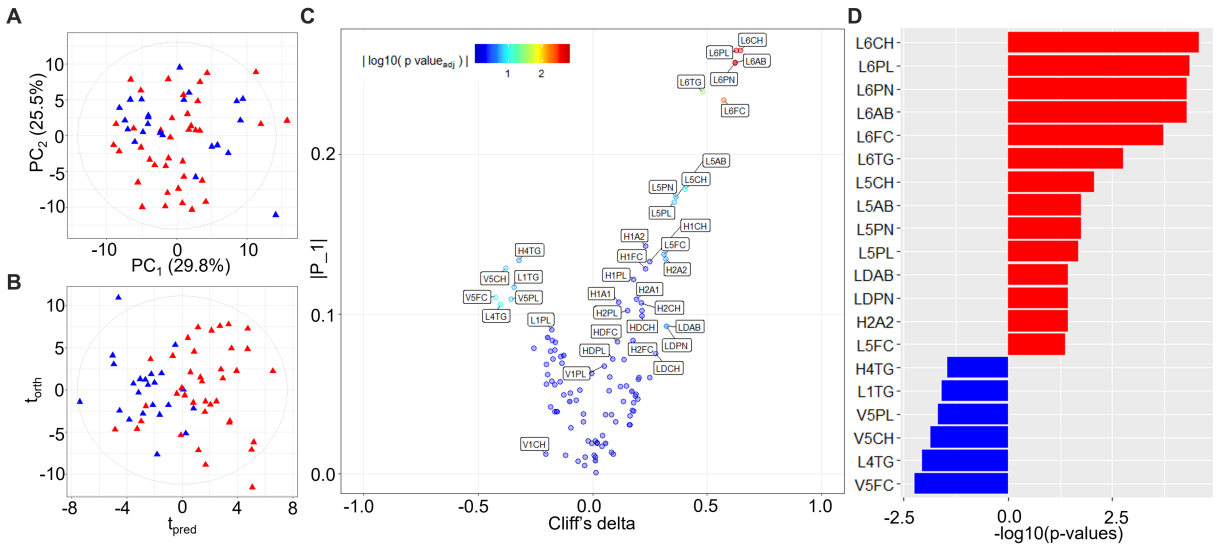


FIGURE 2
PCA and OPLS-DA models of quantified lipoprotein subfractions. **(A)** PCA scores plot of burn injury patients and healthy control profiles (R^2Y 0.987, Q^2Y 0.933); **(B)** Scores plot of the equivalent OPLS-DA model (R^2X 0.437, R^2Y 0.492, Q^2Y 0.321); **(C)** Variable importance eruption plot of predictive lipoprotein parameters based on OPLS-DA component loadings (t_{pred}) and univariate effect sizes (Cliff's delta). Co-ordinates are colored by the FDR-adjusted value of *p* (<0.05) from the statistical group comparison; **(D)** Significant lipoprotein parameters ranked by Cliff's delta. Significant lipoprotein parameters distinguishing burn injury source (scald vs. flame) from multivariate linear regression modeling can be found in Supplementary Figure S4. L6CH, Low-Density Lipoprotein- 6 Subclass Cholesterols; L6PL, Low-Density Lipoprotein- 6 Subclass Phospholipids; L6PN, Low-Density Lipoprotein- 6 Subclass Particle Number; L6AB, Low-Density Lipoprotein- 6 Subclass Apolipoprotein-B100; L6FC, Low-Density Lipoprotein- 6 Subclass Free Cholesterol; L6TG, Low-Density Lipoprotein- 6 Subclass Triglycerides; L5CH, Low-Density Lipoprotein- 5 Subclass Cholesterols; L5AB, Low-Density Lipoprotein- 5 Subclass Apolipoprotein-B100; L5PN, Low-Density Lipoprotein- 5 Subclass Particle Number; L5PL, Low-Density Lipoprotein- 5 Subclass Phospholipids; LDPN, Low-Density Lipoprotein- Particle Number; LDAB, Low-Density Lipoprotein- Apolipoprotein-B100; H2A2, High-Density Lipoprotein- 2 Subclass Apolipoprotein-A2; L5FC, Low-Density Lipoprotein- 5 Subclass Free Cholesterol; H4TG, High-Density Lipoprotein- 4 Subclass Triglycerides; L1TG, Low-Density Lipoprotein- 1 Subclass Triglycerides; V5PL, Very Low-Density Lipoprotein- 5 Subclass Phospholipids; V5CH, Very Low-Density Lipoprotein- 5 Subclass Cholesterols; L4TG, Low-Density Lipoprotein- 4 Subclass Triglycerides; V5FC, Very Low-Density Lipoprotein- 5 Subclass Free Cholesterols.

were positively correlated to GlycA in burn injury but showed no correlation in non-burn signatures.

The global correlation structure in these data can be visualized as circular correlation maps, illustrating Spearman's correlations for the panels of metabolites, lipoproteins and cytokines that significantly differentiate the prior burn participants from the control group (Figure 4). Additionally, IL-6 and IL-8 were included in the network based on their previous reported sustained association with burn injury (7). A contrasting correlation pattern between cytokines and metabolites/lipoproteins was observed when the control group was compared to the prior burn injury group. Whereas the overall correlation between individual cytokines and metabolites/lipoproteins was slightly weaker in the prior burn injury group due to the presence of sub-phenotypes within this group (Supplementary Figure S6), the number of connections between nodes for the correlation networks was substantially greater for most metabolites and cytokines in the burn injury group, indicating a co-ordinated immune-driven systemic response to burn injury. The notable exceptions were H4TG and glucose, which demonstrated a greater number of connections to cytokines in the control group. Phenylalanine was the node with the greatest number of weighted correlations ($n=15$), linked with LDL and VLDL parameters, TNF-α, IL-6, IL-8, glutamate, alanine, creatine and 3-D-hydroxybutyrate in the prior burn injury group, whereas for the control group, there was a lower number of significant associations ($n=6$), losing the association with the LDL parameters, TNF-α and IL-8 correlation, despite a cluster of strong immuno-metabolic connections presented in the circular correlation map (Figure 4A). GlycB correlated with 9 parameters, including 3 cytokines in the burn injury group, while in the control group, GlycB only mapped to glutamine, alanine and creatine (all elevated following burn injury). Similarly, the small dense lipoprotein parameters (e.g., L6PN) had higher weighted node correlations with cytokines and alanine and phenylalanine in the burn group.

3. Discussion

3.1. Immuno-inflammatory signatures of burn injury

We identified an inflammatory signature in the plasma profile of children with prior burn injury based on elevated concentrations of GlycB. This is consistent with our previous observation of elevated cytokines TNF-α (1.31-fold), IL-2 (1.18-fold), IL-7 (1.63-fold), and IFN-γ indicating that children with prior burns manifested low grade chronic inflammation. GlycA, and GlycB, represent glycosylated amino sugars in sidechains of a composite of five main acute phase glycoproteins: α-1-acid glycoprotein, α-1-antichymotrypsin, α-1-antitrypsin, haptoglobin and transferrin. GlycA and GlycB are robust markers of inflammation, found to be superior in accuracy to traditional pathology measures such as C-Reactive Protein (CRP) (24). Elevations in these *N*-acetylated glycoproteins have been reported in association with non-ischemic heart failure (25), vascular aging (26), rheumatoid

TABLE 2 Quantified plasma lipoproteins significantly differentiating children with prior burn injury from healthy controls ($p<0.05$).

Lipoprotein subfraction[a]	Mean concentration [SD] control	Mean concentration [SD] Burn injury	Cliff's Delta[b]	p-value	q-value[c]
L6CH	11.86 [3.39]	17.61 [4.24]	0.65	1.10×10^{-5}***	1.50×10^{-3}***
L6PL	7.46 [1.69]	10.16 [2.21]	0.63	4.60×10^{-5}***	1.50×10^{-3}***
L6PN	174.52 [46.07]	248.11 [60.73]	0.62	2.50×10^{-5}***	1.50×10^{-3}***
L6AB	9.60 [2.53]	13.65 [3.34]	0.62	5.50×10^{-5}***	1.50×10^{-3}***
L6FC	3.80 [0.94]	5.14 [1.09]	0.57	2.00×10^{-4}***	4.33×10^{-3}***
L6TG	2.50 [0.58]	3.15 [0.92]	0.48	1.80×10^{-3}***	3.31×10^{-2}***
L5CH	7.66 [2.34]	10.41 [2.58]	0.4	8.80×10^{-2}***	0.11
L5AB	5.37 [1.56]	7.06 [1.69]	0.36	0.018*	0.17
L5PN	97.70 [28.44]	128.34 [30.78]	0.36	0.018*	0.17
L5PL	4.72 [1.16]	5.92 [1.29]	0.35	0.021*	0.17
LDPN	790.10 [181.46]	935.38 [167.27]	0.32	0.036*	0.22
LDAB	43.45 [9.98]	51.45 [9.20]	0.32	0.036*	0.22
H2A2	2.89 [0.63]	3.15 [0.87]	0.32	0.038*	0.22
L5FC	3.01 [0.63]	3.60 [0.65]	0.31	0.043*	0.24
H4TG	3.02 [0.60]	2.75 [0.78]	−0.32	0.036*	0.22
L1TG	3.83 [1.34]	3.20 [1.28]	−0.34	0.026*	0.19
V5PL	1.26 [0.34]	1.07 [0.50]	−0.36	0.021*	0.17
V5CH	0.84 [0.34]	0.63 [0.48]	−0.38	0.014*	0.15
L4TG	1.33 [0.42]	1.07 [0.57]	−0.4	9.00×10^{-3}***	0.11
V5FC	0.64 [0.23]	0.41 [0.26]	−0.42	5.90×10^{-3}***	0.09

[a]L6CH, Low-Density Lipoprotein- 6 Subclass Cholesterols; L6PL, Low-Density Lipoprotein- 6 Subclass Phospholipids; L6PN, Low-Density Lipoprotein- 6 Subclass Particle Number; L6AB, Low-Density Lipoprotein- 6 Subclass Apolipoprotein-B100; L6FC, Low-Density Lipoprotein- 6 Subclass Free Cholesterol; L6TG, Low-Density Lipoprotein- 6 Subclass Triglycerides; L5CH, Low-Density Lipoprotein- 5 Subclass Cholesterols; L5AB, Low-Density Lipoprotein- 5 Subclass Apolipoprotein-B100; L5PN, Low-Density Lipoprotein- 5 Subclass Particle Number; L5PL, Low-Density Lipoprotein- 5 Subclass Phospholipids; LDPN, Low-Density Lipoprotein- Particle Number; LDAB, Low-Density Lipoprotein- Apolipoprotein-B100; H2A2, High-Density Lipoprotein- 2 Subclass Apolipoprotein-A2; L5FC, Low-Density Lipoprotein- 5 Subclass Free Cholesterol; H4TG, High-Density Lipoprotein- 4 Subclass Triglycerides; L1TG, Low-Density Lipoprotein- 1 Subclass Triglycerides; V5PL, Very Low-Density Lipoprotein- 5 Subclass Phospholipids; V5CH, Very Low-Density Lipoprotein- 5 Subclass Cholesterols; L4TG, Low-Density Lipoprotein- 4 Subclass Triglycerides; V5FC, Very Low-Density Lipoprotein- 5 Subclass Free Cholesterols.
[b]p-value corrected for multiple testing (FDR, BH), *$p<0.05$, **$p<0.01$, ***$p<0.001$.
[c]Ranked in order of the magnitude of the Cliff's Delta statistic.

arthritis (27), SARS-CoV-2 infection (21), insulin resistance (28) and atherosclerosis (29). Glycosylation patterns of serum proteins are typically expected during acute phase injury. Connelly et al., found in children suffering acute Kawasaki disease, elevated GlycA, increased total and small LDL particle numbers and decreased HDL particle numbers ($p<0.001$) (30). Similar signatures were observed in this cohort of children, with elevated GlycA and GlycB and elevated small dense LDL particle numbers (mainly L6PN). GlycB also demonstrated significant correlations with TNF-α, IFN-γ, IL-2, IL-6, IL-7 and IL-8 exclusively in burn injury children, suggesting that it is associated with the systemic response to inflammation post burn injury (due to overlap with lipoprotein peaks, the higher concentrations of GlycA in the prior burn injury group did not reach statistical significance). Burn-induced increase in TNF-α concentrations can increase the rate of lipolysis and hence production of free fatty acids (31), which can contribute to the hyperglycemia and increased insulin resistance associated with post burn injury (32).

Johnston et al., demonstrated elevated levels of TNF-α (1.31-fold), IL-2 (1.18-fold), IL-7 (1.63-fold), and IFN-γ (1.18-fold) 3 years post injury in the pediatric burn injury patients in comparison to healthy controls and described a significantly reduced antibody response to diphtheria, tetanus, and pertussis vaccine antigens (7). Numerous studies have reported high levels of serum cytokines and chemokines post burn injury including IL-7, IL-10, IL-12, macrophage inflammatory protein-1b with some studies noting the sustained elevation of these cytokines for at least 3 years post injury (33). Sustained elevation of cytokines such as TNF-α, IL-2 and IL-17 at 3 years post burn may suggest a transition from a Th1 response in acute burn injury toward a Th2 dominated immune response in the chronic phase (6).

3.2. The metabolic 'memory' of prior burn injury is associated with distinctive lipoprotein signatures

Multiple plasma lipoproteins were systematically altered in participants with prior burn injury. Specifically, we found higher concentrations of small dense LDL subfractions (LDL5 and LDL6) to be associated with burn injury. These small dense LDL particles are known to have greater atherogenic potential than larger LDL subfractions (LDL1-4) and in particular, small dense LDL cholesterol is more predictive of cardiovascular disease than that of total LDL-C (34). A large population-based study also found that increased long-term risk of ischemic heart disease in men was related to preferential accumulation of small dense LDL particles but not large LDL particles (35). This raises the question as

FIGURE 3
Spearman's correlation between lipoproteins and JEDI-PGPE quantified integrals for **(A)** non-burn controls and **(B)** burn injury patients; and between cytokines and differential lipoproteins **(C)** non-burn controls and **(D)** burn injury patients. GlycA, α-1-acid glycoprotein signal A; GlycB, α-1-acid glycoprotein signal B; SPC1, Supramolecular Phospholipid Composite Integral 1; SPC2, Supramolecular Phospholipid Composite Integral 2; SPC3, Supramolecular Phospholipid Composite Integral 3; TotalSPC, Total Supramolecular Phospholipid Composite; GM-CSF, Granulocyte-macrophage colony-stimulating factor; IFNγ, Interferon γ; IL-10, Interleukin 10, IL-12(p70), Interleukin 12 heterodimeric 70kDA; IL-13, Interleukin 13; IL-17A, Interleukin 17A; IL-1B, Interleukin 1B; IL-2, Interleukin 2; IL-5, Interleukin 5; IL-6, Interleukin 6; IL-7, Interleukin 7; IL-8, Interleukin 8; TNF-α, Tumour Necrosis Factor-α.

to whether the association of LDL5 and LDL6 cholesterol and particle number could have implications with respect to increased risk of cardiovascular disease following burn injury. In one study, higher LDL particle number was consistently associated with increased risk for cardiovascular disease, independent of other lipid measurements, but other LDL parameters were not associated with cardiovascular disease after adjustment for cholesterol concentrations (36). There is substantial evidence demonstrating associations between burn injury and cardiometabolic diseases (37). Hypertriglyceridemia, hypocholesterolemia, and hypophospholipidemia have been reported to occur following thermal injury (38) with excessive accumulation of triacylglycerols in liver tissue (39). Concentrations of both low- and high-density lipoprotein have been reported to be reduced following burn injury, which is consistent with depleted blood cholesterol and phospholipid levels that occur following burn injury (40). While the altered lipid profiles may certainly contribute the increased risk of cardiometabolic disease, the systemic effect of burn injury is complex and it is likely that immune dysfunction and inflammatory mediators, also modulate cardiac damage (41).

3.3. Burn injury causes persistent changes in metabolite profiles reflecting hypermetabolism and hyperglycemia

Acute burn trauma is associated with long-term increased risk of developing multiple morbidities and with greater all-cause mortality

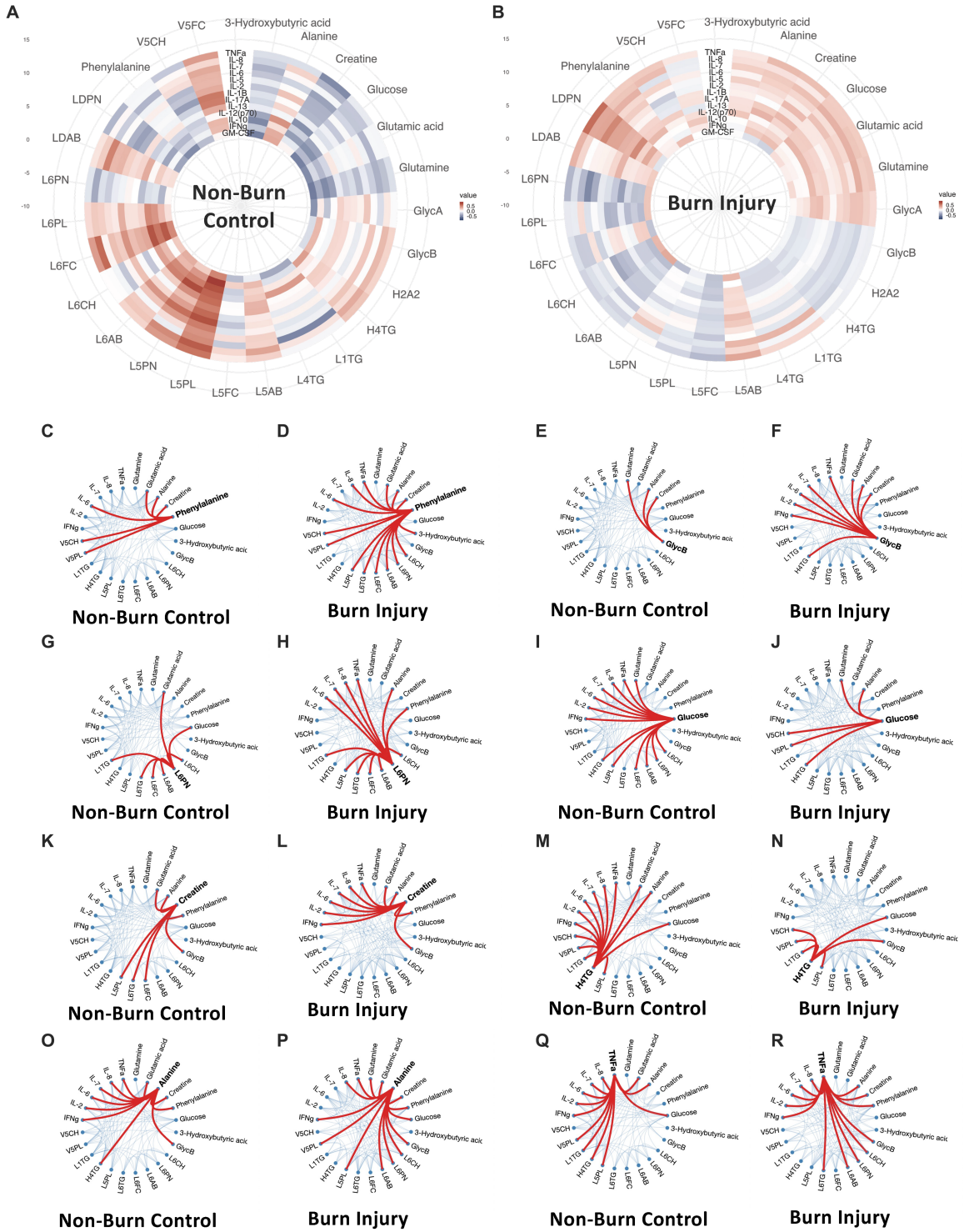


FIGURE 4
(A,B) Circular correlation map for healthy control **(A)** and prior burn injury **(B)** groups. **(C–R)** Weighted-node correlation networks showing inter-connectedness of significant parameters ($p<0.05$) from the integrated three panels (cytokine, metabolites and lipoprotein) for control and burn injury groups highlighting key nodes. Additionally, IL-6 and IL-8 are included in the correlation maps based on their importance following burn injury. L6CH, Low-Density Lipoprotein- 6 Subclass Cholesterols; L6PL, Low-Density Lipoprotein- 6 Subclass Phospholipids; L6PN, Low-Density Lipoprotein- 6 Subclass Particle Number; L6AB, Low-Density Lipoprotein- 6 Subclass Apolipoprotein-B100; L6FC, Low-Density Lipoprotein- 6 Subclass Free Cholesterol; L6TG, Low-Density Lipoprotein- 6 Subclass Triglycerides; L5CH, Low-Density Lipoprotein- 5 Subclass Cholesterols; L5AB, Low-Density Lipoprotein- 5 Subclass Apolipoprotein-B100; L5PN, Low-Density Lipoprotein- 5 Subclass Particle Number; L5PL, Low-Density Lipoprotein- 5 Subclass Phospholipids; LDPN, Low-Density Lipoprotein- Particle Number; LDAB, Low-Density Lipoprotein- Apolipoprotein-B100; H2A2, High-Density Lipoprotein- 2 Subclass Apolipoprotein-A2; L5FC, Low-Density Lipoprotein- 5 Subclass Free Cholesterol; H4TG, High-Density Lipoprotein- 4 Subclass Triglycerides; L1TG, Low-Density Lipoprotein- 1 Subclass Triglycerides; V5PL, Very Low-Density Lipoprotein- 5 Subclass Phospholipids; V5CH, Very Low-Density Lipoprotein- 5 Subclass Cholesterols; L4TG, Low-Density Lipoprotein- 4 Subclass Triglycerides; V5FC, Very Low-Density Lipoprotein- 5 Subclass Free Cholesterols; GlycA, α-1-acid glycoprotein signal A; GlycB, α-1-acid glycoprotein signal B; IFNγ, Interferon γ; IL-2, Interleukin 2; IL-6, Interleukin 6; IL-7, Interleukin 7; IL-8, Interleukin 8; TNFα, Tumor Necrosis Factor α.

(7). Burn injury exerts a profound physiological and metabolic impact resulting in raised resting energy expenditure, inflammation, altered cardiac and organ function and hypermetabolism and these effects persist for several years following the acute injury (6, 42). In the current study, we applied different NMR-based assays and integrated the metabolic response with cytokine data. All three NMR datasets indicated that prior burn injury, sustained 3 years prior to the study, induced a prolonged impact on the plasma phenotype with systematic differences in comparison with the non-injured group. These results are consistent with the known incidence of hypermetabolism and hyperglycemia, which are initiated a few days following injury and continue for several years after the burn event (43, 44), but which are not necessarily associated with the degree or severity of the burn.

We found a trend toward lower mean plasma concentrations of glucose for the control group in comparison with the burn injury group, which contributed to the differential weighting in the CPMG NMR data set (low molecular weight molecules) but was not significant for the univariate comparison using the quantified metabolite data. Burn injury stimulates insulin production and produces insulin resistance in liver, skeletal muscle, and adipose tissue, associated with post-receptor alterations such as phosphorylation of the insulin receptor substrate-1 (IRS-1) in the absence of changes in insulin receptor binding (45). Hyperglycemia during the acute phase of burn injury has been shown to be predictive of clinical outcome with high glucose levels being associated with higher incidence of infection, sepsis, and mortality (46). Similarly, abnormal insulin sensitivity indicative of peripheral and whole-body insulin resistance has been noted.

In this study, we find distinctly higher concentrations of branched chain amino acids (BCAAs) including valine, leucine, isoleucine and aromatic amino acids (AAAs: phenylalanine, tyrosine) in the prior burn injury group. Both branched chain amino acids (BCAAs) and aromatic amino acids (AAAs) have been associated with increased risk of developing type 2 diabetes with various mechanisms being proposed for their role in development of type 2 diabetes (47, 48). Leucine and other amino acids can induce pancreatic beta cells and activate the mammalian target of rapamycin (mTOR) mitogenic signaling pathway, which results in early beta cell dysfunction (49, 50). However, BCAAs can also enhance glycogen production from non-insulin dependent pathways *via* protein kinase C or phosphatidylinositol 3-kinase (51). The upregulation of BCAA and AAA production is consistent with the known 2.21-fold higher increase in developing type 2 diabetes within 5 years post burn injury (52). The subtle elevation of glucose and BCAAs along with the increase in serum phenylalanine levels may be indicative of an underlying impact on insulin sensitivity in the prior burn group.

One of the strongest changes in the burn cohort was the elevation of glutamine and depletion of glutamate, in comparison to healthy controls, with a 2.5-fold higher glutamine:glutamate ratio. In our previous targeted mass spectrometric study, we found similar evidence of hypermetabolism with significantly higher concentrations of 11 amino acids and quinolinic acid. Several of the amino acids overlapped with those measured by ^{1}H NMR spectroscopy including alanine, phenylalanine, with several other amino acids demonstrating a similar trend, although not statistically significant (14). In contrast, with our observation of a higher glutamine: glutamate ratio in the prior burn injury group, most of the literature characterizing the metabolic phenotype of metabolic dysregulation [e.g., in relation to obesity (53), type-2 diabetes (54, 55) and recovery from viral infections such as long-COVID (56)] points to higher concentrations of glutamate and a lower glutamine: glutamate ratio driving the metabolic dysfunction. Similarly in incubated enterocytes obtained from burn-injury participants, increased utilization of glutamine, has been shown to lead to the increased formation of glutamate and alanine (57). The difference between the results found in the current study and other literature is difficult to reconcile and is complicated by the fact that most of the literature studies describe adult populations. Therefore the discrepancy in glutamine: glutamate ratio may be influenced by the fact that glutamine and glutamate production differs between adults and children (58).

The generalized hypermetabolic response associated with burn injury is not dependent on the size of burn and the responses elicited by a burn covering 30% or 50% of the total body surface area are the same (48). Jeschke et al. showed that unlike the hyperinflammatory response that persists for around 6 weeks post-injury, the hypermetabolic state and hyperglycemia can persist for several years (5). Here we show that prior burn injury is characterized by higher plasma glucose concentrations for at least 3 years after non-severe burns. Statistical correlation driven from the apex of the α-anomeric glucose signal at δ5.25 showed a weak correlation with GlycA/GlycB peaks (r<0.25) indicating that the hyperglycemia may be associated with associated with inflammation since GlycA has been shown to reflect inflammation and is strongly correlated with high sensitivity C-reactive protein (hsCRP) (49). In fact, GlycA has been suggested to be a more robust marker of inflammation than C-reactive protein (CRP) (19). Following burn injury, it has been shown that metabolism shifts toward increased glycolysis, glycogenolysis, gluconeogenesis, lipolysis and proteolysis resulting from a severe energy deprivation at the cellular level promoting a hypermetabolic state (50). Altered hormone levels (increased circulating cortisol, catecholamines and glucagon) following burn injury also contribute to the hypermetabolic state (4) and serve to increase the cycling of glucose and free fatty acids (36).

Hypermetabolism induced by thermal injury has been associated with a switch from white to beige or brown fat metabolism, which may be related to increased mitochondrial mass and uncoupling protein 1 expression (59). Consistent with disrupted mitochondrial metabolism, we find prior burn injury to be associated upregulation of the tricarboxylic acid cycle as indicated by significantly higher concentrations of citrate in the multivariate models. Elevated pyruvic acid concentrations in the prior burn injury group may also impact on altered mitochondrial metabolism and has previously been reported to be increased 7 days post burn (60). It has been suggested that following burn injury, pyruvate is diverted from the TCA cycle toward lactate and alanine synthesis with Valbuena et al. finding that 60% of pyruvate, lactate and alanine carbons was glucose-derived following burn injury (61). Here we see increased plasma pyruvate and alanine without a concomitant increase in lactate concentrations. Another theory, proposed by Wolfe et al., is that there is an increased rate of substrate recycling in burn patients resulting in enhanced glycolytic-gluconeogenic and triglyceride-fatty acid cycling, which could serve to provide more metabolic flexibility to adapt efficiently to changes in burn-induced energy-substrate demands (62). Part of this energy recycling involves an upregulation of the Cahill cycle, which serves the purpose of transporting toxic nitrogenous waste from the muscles to the liver by converting L-glutamate and pyruvate into α-ketoglutarate and L-alanine (63), facilitating the transport of alanine to the liver where alanine is oxidatively deaminated to form pyruvate. The levels of alanine and aspartate aminotransferases have been shown to increase post-acute burn injury. However, Chiarelli et al. found that these transaminase levels do not always drop immediately after acute injury (64).

Phenylalanine concentrations were significantly higher in the plasma of the burn injury group than controls. Higher levels of phenylalanine have been noted in association with burn injury (primarily in the acute phase) and the elevation was associated with the hypermetabolic state (65). In severe cases of burn, even though the total free amino acids in plasma dropped, plasma phenylalanine and the phenylalanine to tyrosine ratio was consistently higher and was strongly associated with death and weight loss in both animals and patients (66). With regard to the current study, in the burn group, but not the control, phenylalanine correlated positively with multiple cytokines and small low density lipoprotein particles but negatively with 3-D-hydroxybutyrate. Collectively, there was a reduction of plasma ketone bodies in the burn injury group, although this was only significant for 3-D-hydroxybutyrate (Supplementary Figure S3A). Abbott et al. observed that in the initial phase of recovery from burn injury, patients failed to mount a ketonemic response to starvation monitored in non-burn participants following starvation (67).

3.4. Study strengths and limitations

This study utilizes novel metabolic profiling strategies to interrogate cardiometabolic risk in an overlooked vulnerable population. Here, we have demonstrated the elevated cardiometabolic risk for young children who have previously suffered from a burn injury. While prior research has established that these individuals are disproportionately affected by the development of comorbidities later in life, few follow up studies such as this exist. Although this current study was statistically underpowered for assessing if there are metabolic differences between different sources of burn, we did observe a difference between scald and flame burns scalds versus flame in the LDL lipoprotein signature with the L6PL subfraction associating with flame burns and lower density triglyceride subfractions associating with scalds. In a mouse model of thermal injury, IFN-γ was reported to be higher in scald-burned mice than in sham- and flame-burned mice suggesting that the type of burn injury may exert a differential effect on the immune-metabolic phenotypes (68). Given that there is a different chemical background to flame versus scald burns, with flame burns inducing greater formation of new protein degradation products, it is feasible that the systemic metabolic response may differ and warrants further investigation in a larger cohort. The authors recognize the limitations and constraints of capturing metabolic profiles at a single timepoint, and thus follow-up studies will be necessary.

Conclusion

The integrated multi-modal signature of plasma samples was indicative of chronic hypermetabolic and hyperinflammatory processes persisting at least 3 years post burn injury, driven by an immuno-metabolic memory. These processes were evident in the metabolic, glycoprotein, lipoprotein, and cytokine profiles. The weighted linkages between the various molecular panels underscored the systemic response to inflammation suggesting that the body mounts a prolonged response to the initial trauma with co-ordinated response between the small dense lipoprotein particles and a Th2-dominated cytokine profile. These findings support prior observation of a chronic hypermetabolic state following acute injury, driven by an immuno-metabolic memory. Further investigation of this systems response may uncover new understanding of the association of burn injury with increased long-term morbidity and mortality.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found at: https://zenodo.org/, accession number: 7344673.

Ethics statement

The studies involving human participants were reviewed and approved by Child and Adolescent Health Service WA (approval numbers: 2015219EP; 1111EP; 768EP). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

SB: conceptualization, data curation, formal analysis, data visualization and manuscript preparation. SL and BJ: investigation, methodology, and manuscript preparation. DH, LW, and NG: investigation and methodology. SHB: investigation, methodology, and resources. VF: funding acquisition and manuscript preparation. MF and FW: conceptualization and manuscript preparation. EH and JN: conceptualization, funding acquisition, formal analysis, and manuscript preparation. All authors contributed to the article and approved the submitted version.

Funding

MF is supported by the Stan Perron Center of Excellence in Childhood Burns and the Perth Children's Hospital Foundation. MRFF for funding the Australian National Phenome Center for development of methods used in this research. We thank the UK Medical Research Council (MRC), the Imperial College London MRC Doctoral Training Program and the Imperial College London Dean's Award for funding SB, the Department of Jobs, Tourism, Science and Innovation, Government of Western Australian Premier's Fellowship for funding EH, and the ARC Laureate Fellowship funding for EH.

Acknowledgments

The authors thank the Spinnaker Health Research Foundation, WA, The McCusker Foundation, WA, The Western Australian State Government. They also thank Susan L. Prescott and Debra J. Palmer for the use of control pediatric samples.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2023.1105163/full#supplementary-material

References

1. Tracy L, Rosenblum S, Gabbe B. *Burns registry of Australia and New Zealand (BRANZ) 2018/19 annual report*. (2020). Available at: https://www.monash.edu/__data/assets/pdf_file/0009/2191752/BRANZ-annual-report18_19_FINAL.pdf.

2. Krishnamoorthy V, Ramaiah R, Bhananker SM. Pediatric burn injuries. *Int J Crit Illn Inj Sci*. (2012) 2:128. doi: 10.4103/2229-5151.100889

3. Williams FN, Herndon DN, Jeschke MG. The hypermetabolic response to Burn injury and interventions to modify this response. *Clin Plast Surg*. (2009) 36:583–96. doi: 10.1016/j.cps.2009.05.001

4. Kraft R, Herndon DN, Finnerty CC, Shahrokhi S, Jeschke MG. Occurrence of multiorgan dysfunction in pediatric burn patients: incidence and clinical outcome. *Ann Surg*. (2014) 259:381–7. doi: 10.1097/SLA.0b013e31828c4d04

5. Herndon DN, Tompkins RG. Support of the metabolic response to burn injury. *Lancet*. (2004) 363:1895–902. doi: 10.1016/S0140-6736(04)16360-5

6. Jeschke MG, Gauglitz GG, Kulp GA, Finnerty CC, Williams FN, Kraft R, et al. Long-term persistance of the pathophysiologic response to severe burn injury. *PLoS One*. (2011) 6:e21245. doi: 10.1371/journal.pone.0021245

7. Johnson BZ, McAlister S, McGuire HM, Palanivelu V, Stevenson A, Richmond P, et al. Pediatric Burn survivors have Long-term immune dysfunction with diminished vaccine response. *Front Immunol*. (2020) 11:1481. doi: 10.3389/fimmu.2020.01481

8. Rehou S, Mason S, Burnett M, Jeschke MG. Burned adults develop profound glucose intolerance. *Crit Care Med*. (2016) 44:1059–66. doi: 10.1097/CCM.0000000000001605

9. Weidinger A, Kozlov AV. Biological activities of reactive oxygen and nitrogen species: oxidative stress versus signal transduction. *Biomol Ther*. (2015) 5:472–84. doi: 10.3390/biom5020472

10. Porter C, Tompkins RG, Finnerty CC, Sidossis LS, Suman OE, Herndon DN. The metabolic stress response to burn trauma: current understanding and therapies. *Lancet*. (2016) 388:1417–26. doi: 10.1016/S0140-6736(16)31469-6

11. Auger C, Samadi O, Jeschke MG. The biochemical alterations underlying post-burn hypermetabolism. *Biochim Biophys Acta (BBA) - Mol Basis Dis*. (2017) 1863:2633–44. doi: 10.1016/j.bbadis.2017.02.019

12. Duke JM, Randall SM, Fear MW, O'Halloran E, Boyd JH, Rea S, et al. Long term cardiovascular impacts after burn and non-burn trauma: a comparative population-based study. *Burns*. (2017) 43:1662–72. doi: 10.1016/j.burns.2017.08.001

13. Leung B, Younger JF, Stockton K, Muller M, Paratz J. Cardiovascular risk profile in burn survivors. *Burns*. (2017) 43:1411–7. doi: 10.1016/j.burns.2017.07.010

14. Begum S, Johnson BZ, Morillon AC, Yang R, Bong SH, Whiley L, et al. Systemic long-term metabolic effects of acute non-severe paediatric burn injury. *Sci Rep*. (2022) 12:1–10. doi: 10.1038/s41598-022-16886-w

15. O'Halloran E, Shah A, Dembo L, Hool L, Viola H, Grey C, et al. The impact of non-severe burn injury on cardiac function and long-term cardiovascular pathology. *Sci Rep*. (2016) 6:34650. doi: 10.1038/srep34650

16. Kostara CE, Papathanasiou A, Psychogios N, Cung MT, Elisaf MS, Goudevenos J, et al. NMR-based lipidomic analysis of blood lipoproteins differentiates the progression of coronary heart disease. *J Proteome Res*. (2014) 13:2585–98. doi: 10.1021/pr500061n

17. Nitschke P, Lodge S, Kimhofer T, Masuda R, Bong SH, Hall D, et al. J-edited DIffusional proton nuclear magnetic resonance spectroscopic measurement of glycoprotein and supramolecular phospholipid biomarkers of inflammation in human serum. *Anal Chem*. (2022) 94:1333–41. doi: 10.1021/acs.analchem.1c04576

18. Bylesjö M, Rantalainen M, Cloarec O, Nicholson JK, Holmes E, Trygg J. OPLS discriminant analysis: combining the strengths of PLS-DA and SIMCA classification. *J Chemom*. (2006) 20:341–51. doi: 10.1002/cem.1006

19. Jiménez B, Holmes E, Heude C, Tolson RF, Harvey N, Lodge SL, et al. Quantitative lipoprotein subclass and low molecular weight metabolite analysis in human serum and plasma by 1H NMR spectroscopy in a multilaboratory trial. *Anal Chem*. (2018) 90:11962–71. doi: 10.1021/acs.analchem.8b02412

20. Nicholson JK, Buckingham MJ, Sadler PJ. High resolution 1H n.m.r. studies of vertebrate blood and plasma. *Biochem J*. (1983) 211:605–15. doi: 10.1042/bj2110605

21. Holmes E, Lodge S, Hall D, Schaefer H, Spraul M, Embade N, et al. Diffusion and relaxation edited proton NMR spectroscopy of plasma reveals a high-fidelity supramolecular biomarker signature of SARS-CoV-2 infection. *Anal Chem*. (2021) 93:3976–86. doi: 10.1021/acs.analchem.0c04952

22. Cloarec O, Dumas ME, Craig A, Barton RH, Trygg J, Hudson J, et al. Statistical Total correlation spectroscopy: An exploratory approach for latent biomarker identification from metabolic 1H NMR data sets. *Anal Chem*. (2005) 77:1282–9. doi: 10.1021/ac048630x

23. Bell JD, Brown JCC, Nicholson JK, Sadler PJ. Assignment of resonances for 'acute-phase' glycoproteins in high resolution proton NMR spectra of human blood plasma. *FEBS Lett*. (1987) 215:311–5. doi: 10.1016/0014-5793(87)80168-0

24. Ballout RA, Remaley AT. GlycA: a new biomarker for systemic inflammation and cardiovascular disease (CVD) risk assessment. *J Lab Precis Med*. (2020) 5:17–7. doi: 10.21037/jlpm.2020.03.03

25. Cediel G, Teis A, Codina P, Julve J, Domingo M, Santiago-Vacas E, et al. GlycA and GlycB as inflammatory markers in chronic heart failure. *Am J Cardiol*. (2022) 181:79–86. doi: 10.1016/j.amjcard.2022.07.019

26. Llauradó G, Amigó N, Fuertes-Martín R, Romero A, Cano A, Albert L, et al. Measurement of serum N-Glycans in the assessment of early vascular aging (arterial stiffness) in adults with type 1 diabetes. *Diabetes Care*. (2022) 45:2430–8. doi: 10.2337/dc22-0331

27. Fuertes-Martín R, Taverner D, Vallvé JC, Paredes S, Masana L, Correig Blanchar X, et al. Characterization of 1H NMR plasma glycoproteins as a new strategy to identify inflammatory patterns in rheumatoid arthritis. *J Proteome Res*. (2018) 17:3730–9. doi: 10.1021/acs.jproteome.8b00411

28. Serés-Noriega T, Giménez M, Perea V, Blanco J, Vinagre I, Pané A, et al. Quantification of glycoproteins by nuclear magnetic resonance associated with preclinical carotid atherosclerosis in patients with type 1 diabetes. *Nutr Metab Cardiovasc Dis*. (2021) 31:2099–108. doi: 10.1016/j.numecd.2021.03.021

29. An L, Liu Q, Feng H, Bai X, Dang Y, Li C, et al. Increased glycoprotein acetylation is associated with high cardiac event rates: analysis using coronary computed tomography angiography. *Anatol J Cardiol*. (2018) 20:152–8. doi: 10.14744/AnatolJCardiol.2018.01058

30. Connelly MA, Shimizu C, Winegar DA, Shalaurova I, Pourfarzib R, Otvos JD, et al. Differences in GlycA and lipoprotein particle parameters may help distinguish acute Kawasaki disease from other febrile illnesses in children. *BMC Pediatr*. (2016) 16:151. doi: 10.1186/s12887-016-0688-5

31. Rydén M, Dicker A, van Harmelen V, Hauner H, Brunnberg M, Perbeck L, et al. Mapping of early signaling events in tumor necrosis factor-alpha -mediated lipolysis in human fat cells. *J Biol Chem*. (2002) 277:1085–91. doi: 10.1074/jbc.M109498200

32. Mecott GA, Al-Mousawi AM, Gauglitz GG, Herndon DN, Jeschke MG. The role of hyperglycemia in burned patients: evidence-based studies. *Shock*. (2010) 33:5–13. doi: 10.1097/SHK.0b013e3181af0494

33. Sierawska O, Małkowska P, Taskin C, Hrynkiewicz R, Mertowska P, Grywalska E, et al. Innate immune system response to Burn damage—focus on cytokine alteration. *Int J Mol Sci*. (2022) 23:716. doi: 10.3390/ijms23020716

34. Ivanova EA, Myasoedova VA, Melnichenko AA, Grechko AV, Orekhov AN. Small dense low-density lipoprotein as biomarker for atherosclerotic diseases. *Oxidative Med Cell Longev*. (2017) 2017:1–10. doi: 10.1155/2017/1273042

35. St-Pierre AC, Cantin B, Dagenais GR, Mauriège P, Bernard PM, Després JP, et al. Low-density lipoprotein subfractions and the Long-term risk of ischemic heart disease

in men. *Arterioscler Thromb Vasc Biol*. (2005) 25:553–9. doi: 10.1161/01.ATV.0000154144.73236.f4

36. Ip S, Lichtenstein AH, Chung M, Lau J, Balk EM. Systematic review: association of low-density lipoprotein subtractions with cardiovascular outcomes. *Ann Intern Med*. (2009) 150:474–84. doi: 10.7326/0003-4819-150-7-200904070-00007

37. Barrett LW, Fear VS, Waithman JC, Wood FM, Fear MW. Understanding acute burn injury as a chronic disease. *Burns Trauma*. (2019) 7:23. doi: 10.1186/s41038-019-0163-2

38. Coombes EJ, Shakespeare PG, Batstone GF. Lipoprotein changes after burn injury in man. *J Trauma*. (1980) 20:971–5. doi: 10.1097/00005373-198011000-00012

39. Mert S, Bulutoglu B, Chu C, Dylewski M, Lin FM, Yu YM, et al. Multiorgan metabolomics and Lipidomics provide new insights into fat infiltration in the liver, muscle wasting, and liver–muscle crosstalk following Burn injury. *J Burn Care Res*. (2021) 42:269–87. doi: 10.1093/jbcr/iraa145

40. Pratt VC, Tredget EE, Clandinin MT, Field CJ. Fatty acid content of plasma lipids and erythrocyte phospholipids are altered following burn injury. *Lipids*. (2001) 36:675–82. doi: 10.1007/s11745-001-0772-y

41. Willis MS, Carlson DL, Dimaio JM, White MD, White DJ, Adams GA, et al. Macrophage migration inhibitory factor mediates late cardiac dysfunction after burn injury. *Am J Physiol Heart Circ Physiol*. (2005) 288:H795–804. doi: 10.1152/ajpheart.00189.2004

42. Elnaggar RK, Osailan AM, Mahmoud WS, Alqahtani BA, Azab AR. Beyond the acute phase: understanding relationships among cardiorespiratory response to exercises, physical activity levels, and quality of life in children after Burn injuries. *J Burn Care Res*. (2022) 43:827–33. doi: 10.1093/jbcr/irab203

43. Badoiu SC, Miricescu D, Stanescu-Spinu II, Totan AR, Badoiu SE, Costagliola M, et al. Glucose metabolism in Burns–what happens? *Int J Mol Sci*. (2021) 22:5159. doi: 10.3390/ijms22105159

44. Hart DW, Wolf SE, Mlcak R, Chinkes DL, Ramzy PI, Obeng MK, et al. Persistence of muscle catabolism after severe burn. *Surgery*. (2000) 128:312–9. doi: 10.1067/msy.2000.108059

45. Carter EA, Burks D, Fischman AJ, White M, Tompkins RG. Insulin resistance in thermally-injured rats is associated with post-receptor alterations in skeletal muscle, liver and adipose tissue. *Int J Mol Med*. (2004) 14:653–8.

46. Jeschke MG, Kraft R, Emdad F, Kulp GA, Williams FN, Herndon DN. Glucose control in severely thermally injured pediatric patients: what glucose range should be the target? *Ann Surg*. (2010) 252:521–8. doi: 10.1097/SLA.0b013e3181f2774c

47. Gauglitz GG, Herndon DN, Kulp GA, Meyer WJ, Jeschke MG. Abnormal insulin sensitivity persists up to three years in pediatric patients post-burn. *J Clin Endocrinol Metab*. (2009) 94:1656–64. doi: 10.1210/jc.2008-1947

48. Zhang L, Zhang Y, Ma Z, Zhu Y, Chen Z. Altered amino acid metabolism between coronary heart disease patients with and without type 2 diabetes by quantitative 1H NMR based metabolomics. *J Pharm Biomed Anal*. (2021) 206:114381. doi: 10.1016/j.jpba.2021.114381

49. Krebs M, Krssak M, Bernroider E, Anderwald C, Brehm A, Meyerspeer M, et al. Mechanism of amino acid-induced skeletal muscle insulin resistance in humans. *Diabetes*. (2002) 51:599–605. doi: 10.2337/diabetes.51.3.599

50. Williams FN, Herndon DN, Suman OE, Lee JO, Norbury WB, Branski LK, et al. Changes in cardiac physiology AFTER severe BURN injury. *J Burn Care Res*. (2011) 32:269–74. doi: 10.1097/BCR.0b013e31820aafcf

51. Yoon MS. The emerging role of branched-chain amino acids in insulin resistance and metabolism. *Nutrients*. (2016) 8:405. doi: 10.3390/nu8070405

52. Duke JM, Randall SM, Fear MW, Boyd JH, Rea S, Wood FM. Diabetes mellitus after injury in burn and non-burned patients: a population based retrospective cohort study. *Burns*. (2018) 44:566–72. doi: 10.1016/j.burns.2017.10.019

53. Ren W, Xia Y, Chen S, Wu G, Bazer FW, Zhou B, et al. Glutamine metabolism in macrophages: a novel target for obesity/type 2 diabetes. *Adv Nutr*. (2019) 10:321–30. doi: 10.1093/advances/nmy084

54. Sikorski C, Azab S, de Souza RJ, Shanmuganathan M, Desai D, Teo K, et al. Serum metabolomic signatures of gestational diabetes in south Asian and white European women. *BMJ Open Diabetes Res Care*. (2022) 10:e002733. doi: 10.1136/bmjdrc-2021-002733

55. Elshorbagy AK, Turner C, Bastani N, Refsum H, Kwok T. The association of serum sulfur amino acids and related metabolites with incident diabetes: a prospective cohort study. *Eur J Nutr*. (2022) 61:3161–73. doi: 10.1007/s00394-022-02872-5

56. Holmes E, Wist J, Masuda R, Lodge S, Nitschke P, Kimhofer T, et al. Incomplete systemic recovery and metabolic Phenoreversion in post-acute-phase nonhospitalized COVID-19 patients: implications for assessment of post-acute COVID-19 syndrome. *J Proteome Res*. (2021) 20:3315–29. doi: 10.1021/acs.jproteome.1c00224

57. Ardawi MSM, Newsholme EA. Maximal activities of glutaminase and some enzymes of glycolysis and ketone body utilization and rates of utilization of glutamine, glucose and ketone bodies by intestinal mucosa after burn injury. *Burns*. (1987) 13:438–44. doi: 10.1016/0305-4179(87)90220-8

58. Armstrong MD, Stave U. A study of plasma free amino acid levels. II Normal values for children and adults. *Metabolism*. (1973) 22:561–9. doi: 10.1016/0026-0495(73)90069-3

59. Patsouris D, Qi P, Abdullahi A, Stanojcic M, Chen P, Parousis A, et al. Burn induces Browning of the subcutaneous White adipose tissue in mice and humans. *Cell Rep*. (2015) 13:1538–44. doi: 10.1016/j.celrep.2015.10.028

60. Aussel C, Cynober L, Lioret N, Coudray-Lucas C, Vaubourdolle M, Saizy R, et al. Plasma branched-chain keto acids in burn patients. *Am J Clin Nutr*. (1986) 44:825–31. doi: 10.1093/ajcn/44.6.825

61. Valbuena GN, Rizzardini M, Cimini S, Siskos AP, Bendotti C, Cantoni L, et al. Metabolomic analysis reveals increased aerobic glycolysis and amino acid deficit in a cellular model of amyotrophic lateral sclerosis. *Mol Neurobiol*. (2016) 53:2222–40. doi: 10.1007/s12035-015-9165-7

62. Wolfe RR, Herndon DN, Jahoor F, Miyoshi H, Wolfe M. Effect of severe Burn injury on substrate cycling by glucose and fatty acids. *N Engl J Med*. (2010) 317:403–8. doi: 10.1056/NEJM198708133170702

63. Karmen A, Wroblewski F, Ladue JS. Transaminase activity in human blood. *J Clin Invest*. (1955) 34:126–33. doi: 10.1172/JCI103055

64. Chiarelli A, Casadei A, Pornaro E, Siliprandi L, Mazzoleni F. Alanine and aspartate aminotransferase serum levels in burned patients: a long-term study. *J Trauma*. (1987) 27:790–4. doi: 10.1097/00005373-198707000-00017

65. Chang XJ, Yang CC, Hsu WS, Xu WZ, Shih TS. Serum and erythrocyte amino acid pattern: studies on major burn cases. *Burns*. (1983) 9:240–8. doi: 10.1016/0305-4179(83)90053-0

66. Stinnett JD, Alexander JW, Watanabe C, BG MM, Fischer JE, Morris MJ, et al. Plasma and skeletal muscle amino acids following severe burn injury in patients and experimental animals. *Ann Surg*. (1982) 195:75–89. doi: 10.1097/00000658-198201001-00012

67. Abbott WC, Birkhahn RH, Schiller WR, Long CL, Blakemore WS. The effect of major thermal injury on plasma ketone body levels. *J Parenter Enter Nutr*. (1985) 9:153–8. doi: 10.1177/0148607185009002153

68. Tschöp J, Martignoni A, Reid MD, Adediran SG, Gardner J, Noel GJ, et al. Differential immunological phenotypes are exhibited after scald and flame burns. *Shock*. (2009) 31:157–63. doi: 10.1097/SHK.0b013e31817fbf4d

69. Valvis SM, Waithman J, Wood FM, Fear MW, Fear VS. The immune response to skin trauma is dependent on the etiology of injury in a mouse model of Burn and excision. *J Invest Dermatol*. (2015) 135:2119–28. doi: 10.1038/jid.2015.123

70. Dona AC, Jiménez B, Schäfer H, Humpfer E, Spraul M, Lewis MR, et al. Precision high-throughput proton NMR spectroscopy of human urine, serum, and plasma for large-scale metabolic phenotyping. *Anal Chem*. (2014) 86:9887–94. doi: 10.1021/ac5025039

71. Nicholson JK, Foxall PJD, Spraul M, Farrant RD, Lindon JC. 750 MHz 1H and 1H-13C NMR spectroscopy of human blood plasma. *Anal Chem*. (1995) 67:793–811. doi: 10.1021/ac00101a004

72. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J R Stat Soc*. (1995) 57:289–300. doi: 10.1111/j.2517-6161.1995.tb02031.x

73. Langfelder P, Horvath S. WGCNA: An R package for weighted correlation network analysis. *BMC Bioinformatics*. (2008) 9:1–13. doi: 10.1186/1471-2105-9-559

74. Barrat A, Barthélemy M, Pastor-Satorras R, Vespignani A. The architecture of complex weighted networks. *Proc Natl Acad Sci U S A*. (2004) 101:3747–52. doi: 10.1073/pnas.0400087101

frontiers | Frontiers in Pediatrics

TYPE Case Report
PUBLISHED 08 June 2023
DOI 10.3389/fped.2023.1195222

OPEN ACCESS

EDITED BY
Zhen-Yu Zhang,
KU Leuven, Belgium

REVIEWED BY
Sofina Begum,
Harvard Medical School, United States
Maria Paola Lombardi,
University of Amsterdam, Netherlands

*CORRESPONDENCE
Hiroshi Kawamura
kawamuu1031@gmail.com

RECEIVED 28 March 2023
ACCEPTED 22 May 2023
PUBLISHED 08 June 2023

CITATION
Kawamura H, Ikawa M, Hirono K, Kimura J, Okuno T, Kawatani M, Inai K, Hata Y, Nishida N and Yoshida Y (2023) Low-frequency maternal novel MYH7 mosaicism mutation in recurrent fetal-onset severe left ventricular noncompaction: a case report.
Front. Pediatr. 11:1195222.
doi: 10.3389/fped.2023.1195222

Low-frequency maternal novel MYH7 mosaicism mutation in recurrent fetal-onset severe left ventricular noncompaction: a case report

Hiroshi Kawamura[1]*, Masamichi Ikawa[2], Keiichi Hirono[3], Junya Kimura[4], Takashi Okuno[5], Masao Kawatani[2,5], Kunihiro Inai[6], Yukiko Hata[7], Naoki Nishida[7] and Yoshio Yoshida[1]

[1]Department of Obstetrics and Gynecology, University of Fukui, Fukui, Japan, [2]Department of Medical Genetics, University of Fukui Hospital, Fukui, Japan, [3]Department of Pediatrics, University of Toyama, Toyama, Japan, [4]Division of Diagnostic Pathology, Surgical Pathology, University of Fukui Hospital, Fukui, Japan, [5]Department of Pediatrics, University of Fukui, Fukui, Japan, [6]Department of Molecular Pathology, University of Fukui, Fukui, Japan, [7]Department of Legal Medicine, Faculty of Medicine, University of Toyama, Toyama, Japan

Background: Left ventricular noncompaction (LVNC) is a rare inherited cardiomyopathy with a broad phenotypic spectrum. The genotype-phenotype correlations in fetal-onset LVNC have not yet been fully elucidated. In this report, we present the first case of severe fetal-onset LVNC caused by maternal low-frequency somatic mosaicism of the novel myosin heavy chain 7 (MYH7) mutation.

Case presentation: A 35-year-old pregnant Japanese woman, gravida 4, para 2, with no significant medical or family history of genetic disorders, presented to our hospital. In her previous pregnancy at 33 years of age, she delivered a male neonate at 30 weeks of gestation with cardiogenic hydrops fetalis. Fetal echocardiography confirmed LVNC prenatally. The neonate died shortly after birth. In the current pregnancy, she again delivered a male neonate with cardiogenic hydrops fetalis caused by LVNC at 32 weeks of gestation. The neonate died shortly after birth. Genetic screening of cardiac disorder-related genes by next-generation sequencing (NGS) was performed which revealed a novel heterozygous missense MYH7 variant, NM_000257.3: c.2729A > T, p.Lys910Ile. After targeted and deep sequencing by NGS, the same MYH7 variant (NM_000257.3: c.2729A > T, p.Lys910Ile) was detected in 6% of the variant allele fraction in the maternal sequence but not in the paternal sequence. The MYH7 variant was not detected by conventional direct sequencing (Sanger sequencing) in either parent.

Conclusions: This case demonstrates that maternal low-frequency somatic mosaicism of an MYH7 mutation can cause fetal-onset severe LVNC in the offspring. To differentiate hereditary MYH7 mutations from *de novo* MYH7 mutations, parental targeted and deep sequencing by NGS should be considered in addition to Sanger sequencing.

KEYWORDS

left ventricular noncompaction, myosin heavy chain 7, next-generation sequencing, mosaicism mutation, case report

1. Introduction

Left ventricular noncompaction (LVNC) is a rare inherited cardiomyopathy characterized morphologically by a severely thickened two-layered myocardium, excessive trabeculation of the left ventricle, and deep intertrabecular recesses leading to the left ventricular cavity (1). LVNC has a wide range of phenotypic expressions, ranging from severe prenatal manifestations to asymptomatic presentation in adulthood (2). The condition has been shown to have either a sporadic or familial genetic background, with hereditary causes accounting for approximately 30% of all LVNC cases (3). Recent studies using large cardiac disease gene panels have identified several genetic variants responsible for LVNC (4, 5). Of the genetic mutations causing LVNC, more than 50% are associated with sarcomeres, which are the smallest functional unit of the striated muscle tissue. The most common sarcomere-related gene associated with LVNC is that encoding for myosin heavy chain 7 (MYH7) (5).

With recent advances in genetic analysis technology, some genetic variants originally thought to be *de novo* mutations have been shown to be caused by parental somatic or gonadal mosaic mutations (6–8). Recent studies revealing parental mosaicism emphasize the importance of using more sensitive analysis techniques, such as digital polymerase chain reaction (dPCR), pyrosequencing, high-resolution melting analysis, and next-generation sequencing (NGS), rather than conventional direct sequencing (i.e., Sanger sequencing). The detection of parental mosaic MYH7 mutations associated with familial LVNC using sensitive methods has not yet been reported.

Herein, we report an extremely rare case of recurrent non-immune hydrops fetalis caused by fetal-onset severe LVNC associated with a mosaic mutation in the MYH7 gene.

2. Case presentation

A 35-year-old pregnant Japanese woman (spontaneously conceived), gravida 4, para 2, with no significant medical or family history, presented to our hospital. She had a spontaneous abortion during the first trimester of her first pregnancy. In the second pregnancy at 28 years of age, she delivered a healthy term female newborn with a birthweight of 2,908 grams. In the third pregnancy at 33 years of age, she was referred to our hospital at 23 + 5 weeks of gestation for perinatal management of hydrops fetalis. The fetus presented with remarkable systemic edema, ascites, and bilateral pleural effusion on transabdominal ultrasonography. Detailed fetal echocardiography revealed significant cardiomegaly (cardiothoracic area ratio, 56.7%) with severe tricuspid valve regurgitation (TR) and moderate mitral valve regurgitation (MR). Both ventricles were hypokinetic; the left and right myocardial performance indices were 0.92 and 0.85, respectively. Non-compacted layers in both ventricles and an extensive trabeculated layer with multiple deep intertrabecular recesses filled with blood directly from the left ventricular cavity were identified. Fetal echocardiography at 26 + 0 weeks of gestation is shown in **Figure 1A**. The fetus was diagnosed with cardiogenic hydrops fetalis caused by LVNC. At 30 + 6 weeks of gestation, regular uterine contractions with cervical dilation

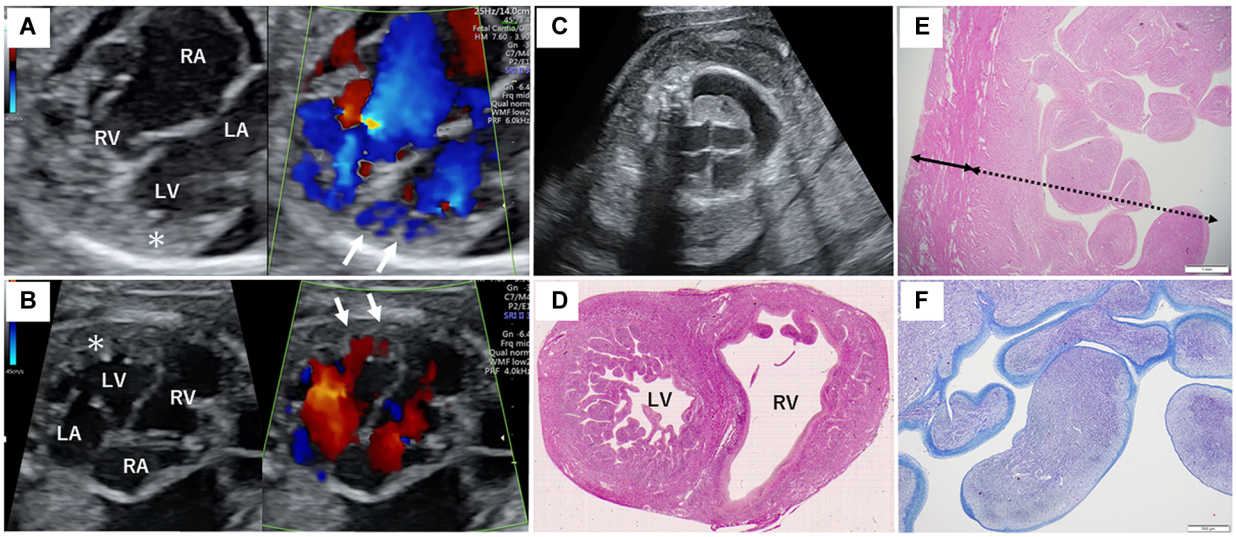


FIGURE 1
Fetal sonography and pathological findings of the proband's heart. (**A**) Fetal echocardiography at 26 + 0 weeks of gestation during the second pregnancy. (**B**) Fetal echocardiography at 25 + 4 weeks of gestation during the third pregnancy. The asterisk indicates the severely thickened myocardium, and the white arrows show the blood flow into the deep intertrabecular recesses of the left ventricle. (**C**) Fetal sonography showing marked subcutaneous edema and right pleural effusion in the proband. (**D**) Hematoxylin and eosin staining of the horizontal section of the middle level of the ventricular long axis of the autopsy. Remarkable trabeculation of the left ventricle is detected. (**E**) The solid bidirectional arrow shows the compacted layer, and the dotted bidirectional arrow shows the thickened non-compacted layer of the left ventricle. (**F**) Histological appearance with Azan staining reveals fibrosis of the endocardium of the left ventricle. The endocardium is stained blue more intensely. RA, right atrium; RV, right ventricle; LA, left atrium; LV, left ventricle.

occurred spontaneously, indicating the onset of labor. We discussed the mode of delivery with the parents and decided on vaginal delivery because of the fatal prognosis of the fetus. At 31 + 0 weeks of gestation, the mother delivered a male neonate with a birth weight of 2,440 grams; Apgar scores of 1 and 1 at 1 and 5 min, respectively; and umbilical arterial pH of 7.310. The newborn died soon after birth, despite neonatal resuscitation. We offered the parents a pathological autopsy and genetic testing of the newborn to obtain important information for future pregnancies; however, they declined these examinations.

In the current pregnancy, we monitored the fetus every 2–3 weeks after 13 weeks of gestation, especially for the fetal hydropic sign and contractile dysfunction of the fetal heart on ultrasound. The mother did not take any precautions or interventions because there was no effective prevention of recurrence of hydrops fetalis. At 21 + 1 weeks of gestation, abnormal findings were not detected. However, at 23 + 1 weeks of gestation, we detected noticeably decreased ventricular contraction with moderate TR and MR. In addition, echocardiographic findings observed in the fetal myocardium were consistent with LVNC and were almost similar to those in the previous fetus. At 25 + 4 weeks of gestation, hydropic signs including systemic skin edema, pleural effusion, and ascites were noted. Fetal echocardiography is shown in **Figure 1B**. The fetal course was very similar to that of the previous fetus; therefore, we strongly suspected familial LVNC. The hydropic signs worsened during the course of the pregnancy (**Figure 1C**). Based on the previous pregnancy, we discussed perinatal management (especially the timing and mode of delivery) with the parents and respecting the parents' wishes, decided to perform cesarean section to prevent fetal death. There were no maternal cardiac signs suggestive of Mirror syndrome. At 31 weeks of gestation, transabdominal sonography revealed an edematous and thickened placenta, and pulse-wave Doppler revealed continuous absent or reversed blood flow in the umbilical artery. To avoid fetal death, a cesarean section was performed at 32 + 0 weeks of gestation. A male newborn with breech presentation was delivered. His birth weight was 2,680 grams; Apgar scores at 1 and 5 min were 1 and 1, respectively; and umbilical arterial pH was 7.194. The newborn died shortly after birth, despite neonatal resuscitation. The placenta was grossly edematous, weighing 760 grams. The mother's postoperative course was favorable, and she was discharged without complications. In contrast to the previous pregnancy, the parents requested a pathological autopsy and genetic testing of the neonate. Gross anatomical findings at autopsy included systemic skin edema, bilateral pleural effusion, ascites, markedly dilated right ventricle, and hypertrophic left ventricle. Histological examination of the left ventricle revealed a two-layered structure composed of a prominent trabeculated and compacted layer (**Figures 1D**, **E**), and endocardial elastic fibrous proliferation throughout the left ventricle (**Figure 1F**). After obtaining informed consent from the parents, DNA was isolated from the neonatal whole blood. Genetic screening of 182 cardiac disorder-related genes associated with cardiomyopathies and channelopathies by NGS revealed a novel heterozygous missense MYH7 variant, NM_000257.3: c.2729A > T, p.Lys910Ile, which had not been reported in several genetic databases, including ClinVar, HGMD®, dbSNP, gnomAD, and Jmorp (Japanese Multi Omics Reference Panel) (**Figure 2A**). The GADD score and PolyPhen-2, which predicted the effect of a variant on protein function, showed that this novel MYH7 variant was pathogenic. The pedigree is shown in **Figure 2B**. After genetic counseling, parental genetic analyses were performed. By Sanger sequencing, the MYH7 variant was not detected in the father (Ⅰ-1), while in the mother (Ⅰ-2) a slight change (c.2729A > T) of unclear significance was detected in the chromatogram (**Figure 3**). Therefore, targeted and deep sequencing was performed on the whole blood of both parents by NGS. The same MYH7 variant (NM_000257.3: c.2729A > T, p.Lys910Ile) was detected in 6% (807/14,266 coverages) of the variant allele fraction (VAF) in the

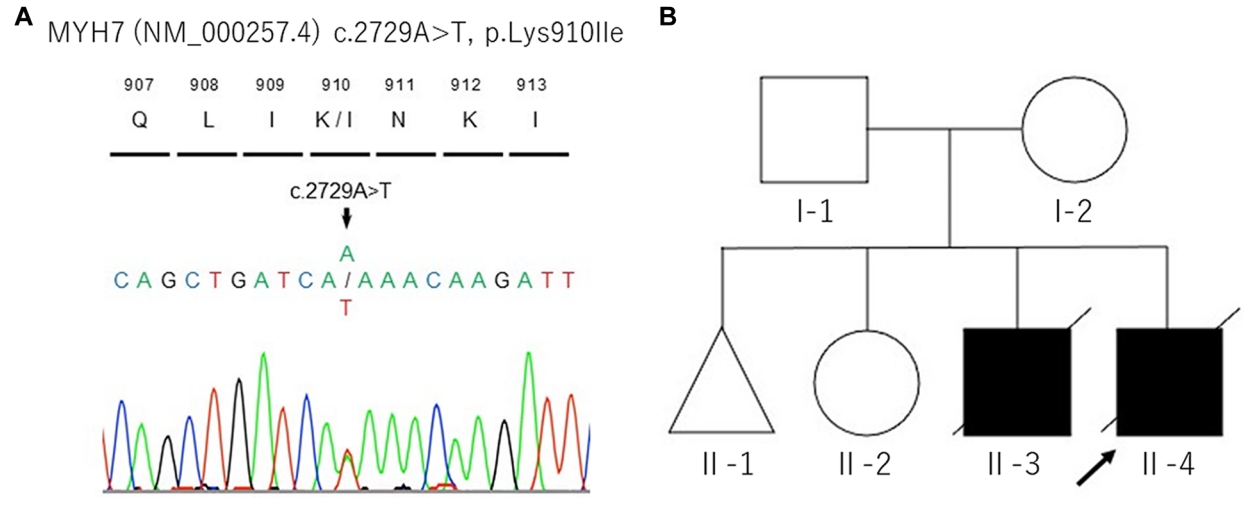


FIGURE 2
DNA sequencing analysis of proband's whole blood (A) and the pedigree of this family (B). The black arrow indicates the proband (II-4).

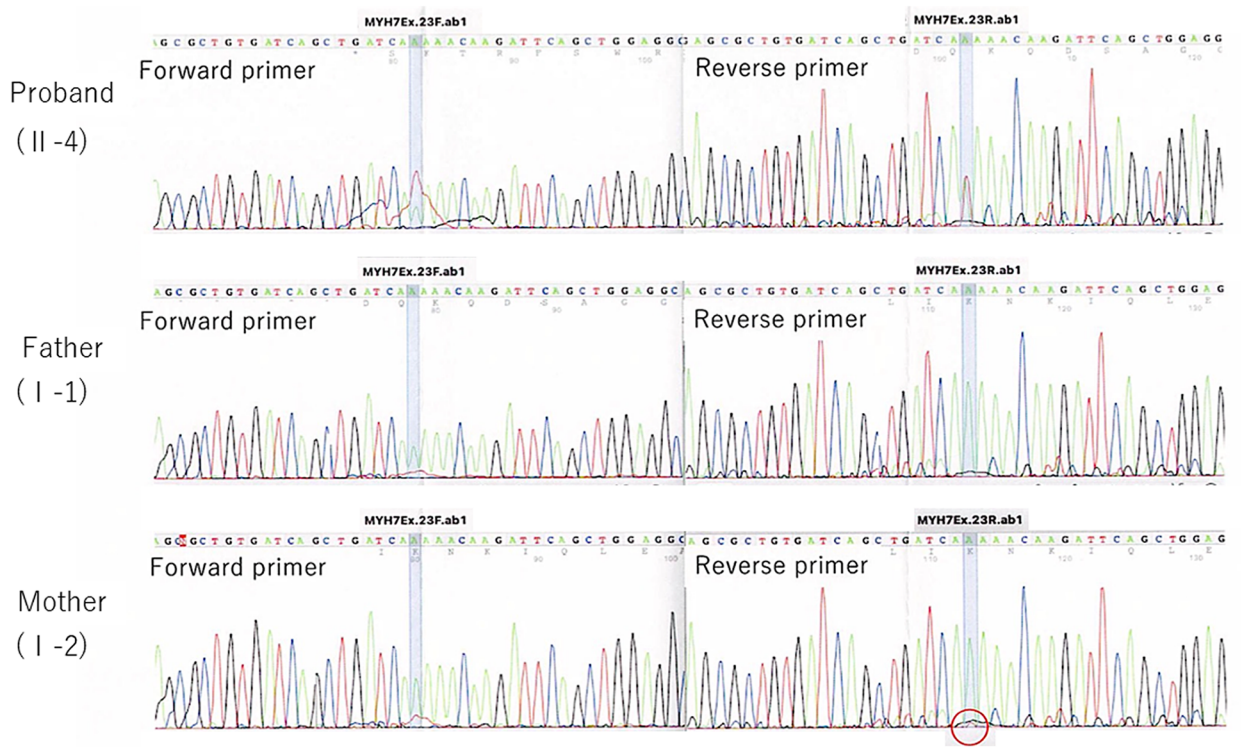


FIGURE 3
Direct sequencing trio analysis chromatograms. A red circle indicates a slight change (c.2729A > T) of unclear significance.

maternal sequence but not in the paternal sequence [0% (0/1,658 coverages) of VAF]. Echocardiography revealed no abnormal findings in the myocardia of the parents. The parents did not present with generalized muscle weakness. Furthermore, there was no increase in the maternal serum creatine kinase. Figure 4 illustrates the workflow from the delivery of the previous fetus (II-3) to parental sequencing.

3. Discussion and conclusions

To the best of our knowledge, this is the first report of fetal-onset severe LVNC caused by maternal low-frequency somatic mosaicism of the novel MYH7 mutation.

The MYH7 gene is composed of 40 exons of approximately 23 kilobases and is located on the long arm of chromosome 14

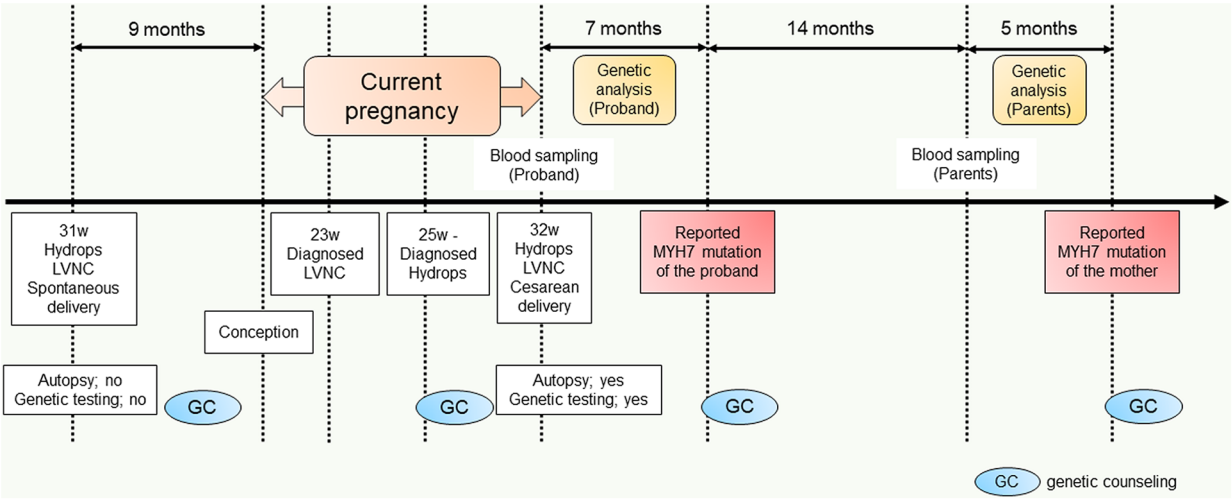


FIGURE 4
Diagram of the workflow from the delivery of the previous fetus (II-3) to parental sequencing.

(14q11.2-q13). It encodes myosin heavy chain (MHC)-β and slow MHC, which are expressed in the myocardium and type 1 skeletal muscle fibers, respectively (9). A pathogenic MYH7 mutation was first reported by Lowrance et al. in patients with familial hypertrophic cardiomyopathy (10). Currently [HGMD®, available at http://www.hgmd.org (accessed February 11, 2023)], more than 1,200 MYH7 variants have been classified as pathogenic gene mutations.

To date, there have been few reports of mosaic mutations in MYH7. Forissier et al. reported two siblings with familial hypertrophic cardiomyopathy that was probably caused by maternal germline MYH7 mosaicism (11). In another study, somatic MYH7 mosaicism was identified in the father of the proband who had distal myopathy. In that report, the mosaicism was evaluated in the paternal peripheral blood cells (12). However, these two reports did not describe the VAF of MYH7 variants. In the present case, the targeted and deep sequencing by NGS was effective in detecting the rather low frequency (6.0%) mosaicism of the maternal MYH7 mutation, which was unclear by Sanger sequencing. In a previous report, the detection limit of Sanger sequencing was reported to be 15%–20% of the VAF (13). Our case report shows that the detection of the rather low-frequency mosaicism, which was undetectable by the conventional analysis method, was attributed to obtaining more accurate information about parental mosaicism.

The heterozygous missense MYH7 variant detected in both the proband (II-4) and his mother (I-2) is a novel variant that has not been previously reported in the available genetic databases. We judged this variant to be the pathogenic mutation causing LVNC with hydrops fetalis in the proband (II-4), based on the GADD score and PolyPhen-2 results. The similarity in the phenotypes of the proband and those of the previous fetus (II-3), including fetal-onset of heart failure and echocardiographic findings characteristic of LVNC, suggested that the same variant was probably present in the two brothers.

A recent systematic review identified 66 genes responsible for LVNC, and found that sarcomere-related genes, including MYH7, accounted for 52% of LVNC causal genes (5). Interestingly, this review showed that the risk of major adverse cardiac events was relatively low in patients, especially adults, with sarcomere-related gene mutations. Furthermore, among the sarcomere-related genes, MYH7 was associated with the lowest risk of major adverse cardiac events. However, in the present report, the MYH7 mutation caused progressive heart failure in the neonatal proband.

MYH7 mutations play an important role in the development of severe heart failure in fetal-onset LVNC. Previous reports of MYH7-related fetal LVNC found heart failure at mid to late of 2nd trimester of pregnancy (14, 15). In the proband (II-4) of our case, a fetal echocardiography showed signs of LVNC at 23 weeks of gestation and hydropic sign at 25 weeks of gestation, which is consistent with the clinical characteristics of previous reports. A study of the genetic background of 33 cases of fetal-onset LVNC showed that the most frequent causative variants were detected in MYH7 (7 out of 15 variants) (16). The reported variants were widely distributed between exon 5 and exon 37 of MYH7, and the present case harbored a variant in exon 23 of MYH7. Moreover, MYH7 variants cause hypertrophic and dilated cardiomyopathy in addition to LVNC, suggesting that the location of the variants may not be associated with the LVNC phenotype. Few studies have demonstrated MYH7 variants in fetal-onset LVNC (16, 17); therefore, further investigations are needed to validate the genotype and phenotype correlations in fetal-onset LVNC in more detail.

A strength of this report is that it highlights the importance of distinguishing true *de novo* variants from inherited, low-mosaic mutations in the diagnosis of genetic diseases, which probably contributes to assessment of the recurrence risk. One of the limitations of this report is that in the present case, MYH7 mosaicism was evaluated only in the peripheral blood cells and not in the germline cells because it was impossible to obtain germline cells from the mother without an invasive procedure. Another limitation of this report is that the possibility that unknown genetic mutations which not included in the screening of 182 cardiac-disorder related genes in this study may be involved.

In conclusion, this case demonstrates that maternal low-frequency somatic mosaicism of an MYH7 mutation can cause fetal-onset severe LVNC in the offspring and that parental targeted and deep sequencing by NGS should be considered to differentiate hereditary mutations from *de novo* mutations. This important finding should contribute to the genetic counseling of parents who wish to elucidate the genetic causes of recurrent severe perinatal adverse outcomes in their offspring.

Data availability statement

The datasets presented in this study can be found in online repositories. https://www.ncbi.nlm.nih.gov/nuccore/LC765465. Further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by The Research Ethics Committee of the University of Toyama in Japan (I2014003). The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

HK and MI: collected clinical data and prepared the manuscript. KH: obtained the funding and revised the manuscript. JK, KI, YH, and NN: performed the data analysis. TO and MK: made the substantial contribution to clinical

management. YY: supervised the manuscript. All authors contributed to the article and approved the submitted version.

Funding

KH was supported by grants from The Ministry of Education, Culture, Sports, Science and Technology in Japan (Grant-in-Aid for Scientific Research No. 22K07932).

Acknowledgments

The authors are grateful to Prof. Atsushi Watanabe, Division of Clinical Genetics, University of Kanazawa Hospital, Ishikawa, Japan, for his expert suggestions on genetic testing.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Chin TK, Perloff JK, Williams RG, Jue K, Mohrmann R. Isolated noncompaction of left ventricular myocardium. A study of eight cases. *Circulation*. (1990) 82:507–13. doi: 10.1161/01.cir.82.2.507

2. van Waning JI, Caliskan K, Hoedemaekers YM, van Spaendonck-Zwarts KY, Baas AF, Boekholdt SM, et al. Genetics, clinical features, and long-term outcome of noncompaction cardiomyopathy. *J Am Coll Cardiol*. (2018) 71:711–22. doi: 10.1016/j.jacc.2017.12.019

3. Hirono K, Ichida F. Left ventricular noncompaction: a disorder with genotypic and phenotypic heterogeneity-a narrative review. *Cardiovasc Diagn Ther*. (2022) 12:495–515. doi: 10.21037/cdt-22-198

4. Richard P, Ader F, Roux M, Donal E, Eicher JC, Aoutil N, et al. Targeted panel sequencing in adult patients with left ventricular non-compaction reveals a large genetic heterogeneity. *Clin Genet*. (2019) 95:356–67. doi: 10.1111/cge.13484

5. van Waning JI, Moesker J, Heijsman D, Boersma E, Majoor-Krakauer D. Systematic review of genotype-phenotype correlations in noncompaction cardiomyopathy. *J Am Heart Assoc*. (2019) 8:e012993. doi: 10.1161/JAHA.119.012993

6. Chesneau B, Plancke A, Rolland G, Chassaing N, Coubes C, Brischoux-Boucher E, et al. Parental mosaicism in marfan and ehlers-danlos syndromes and related disorders. *Eur J Hum Genet*. (2021) 29:771–9. doi: 10.1038/s41431-020-00797-3

7. Yamamoto K, Kubota T, Takeyari S, Kitaoka T, Miyata K, Nakano Y, et al. Parental somatogonadal COL2A1 mosaicism contributes to intrafamilial recurrence in a family with type 2 collagenopathy. *Am J Med Genet A*. (2020) 182:454–60. doi: 10.1002/ajmg.a.61422

8. Nagaya S, Maruyama K, Watanabe A, Meguro-Horike M, Imai Y, Hiroshima Y, et al. First report of inherited protein S deficiency caused by paternal PROS1 mosaicism. *Haematologica*. (2022) 107:330–3. doi: 10.3324/haematol.2021.278527

9. Fiorillo C, Astrea G, Savarese M, Cassandrini D, Brisca G, Trucco F, et al. Italian network on congenital myopathies. MYH7-related myopathies: clinical, histopathological and imaging findings in a cohort of Italian patients. *Orphanet J Rare Dis*. (2016) 11:91. doi: 10.1186/s13023-016-0476-1

10. Tanigawa G, Jarcho JA, Kass S, Solomon SD, Vosberg HP, Seidman JG, et al. A molecular basis for familial hypertrophic cardiomyopathy: a beta cardiac myosin heavy chain gene missense mutation. *Cell*. (1990) 62:999–1006. doi: 10.1016/0092-8674(90)90273-h

11. Forissier JF, Richard P, Briault S, Ledeuil C, Dubourg O, Charbonnier B, et al. First description of germline mosaicism in familial hypertrophic cardiomyopathy. *J Med Genet*. (2000) 37:132–4. doi: 10.1136/jmg.37.2.132

12. Lamont PJ, Wallefeld W, Hilton-Jones D, Udd B, Argov Z, Barboi AC, et al. Novel mutations widen the phenotypic spectrum of slow skeletal/β-cardiac myosin (MYH7) distal myopathy. *Hum Mutat*. (2014) 35:868–79. doi: 10.1002/humu.22553

13. Tsiatis AC, Norris-Kirby A, Rich RG, Hafez MJ, Gocke CD, Eshleman JR, et al. Comparison of sanger sequencing, pyrosequencing, and melting curve analysis for the detection of KRAS mutations: diagnostic and clinical implications. *J Mol Diagn*. (2010) 12:425–32. doi: 10.2353/jmoldx.2010.090188

14. Hoedemaekers YM, Cohen-Overbeek TE, Frohn-Mulder IM, Dooijes D, Majoor-Krakauer DF. Prenatal ultrasound diagnosis of MYH7 non-compaction cardiomyopathy. *Ultrasound Obstet Gynecol*. (2013) 41:336–9. doi: 10.1002/uog.12279

15. Nomura Y, Momoi N, Hirono K, Hata Y, Takasaki A, Nishida N, et al. A novel MYH7 gene mutation in a fetu with left ventricular noncompaction. *Can J Cardiol*. (2015) 31:103.e1–3. doi: 10.1016/j.cjca.2014.11.012

16. Hirono K, Hata Y, Ozawa SW, Toda T, Momoi N, Fukuda Y, et al. A burden of sarcomere gene variants in fetal-onset patients with left ventricular noncompaction. *Int J Cardiol*. (2021) 328:122–9. doi: 10.1016/j.ijcard.2020.12.013

17. Stöllberger C, Wegner C, Finsterer J. Fetal ventricular hypertrabeculation/noncompaction: clinical presentation, genetics, associated cardiac and extracardiac abnormalities and outcome. *Pediatr Cardiol*. (2015) 36:1319–26. doi: 10.1007/s00246-015-1200-y

frontiers | Frontiers in Pediatrics

TYPE Original Research
PUBLISHED 23 June 2023
DOI 10.3389/fped.2023.1184320

OPEN ACCESS

EDITED BY
Zhen-Yu Zhang,
KU Leuven, Belgium

REVIEWED BY
Christopher Yilgwan,
University of Jos, Nigeria
Hamidreza Badeli,
Gilan University of Medical Sciences, Iran

*CORRESPONDENCE
Joseph Ezeogu
✉ jezeogu@yahoo.com

RECEIVED 11 March 2023
ACCEPTED 08 June 2023
PUBLISHED 23 June 2023

CITATION
Atoh I, Ezeogu J, Ekure E, Omokhodion SI and Njokanma FO (2023) Impact of the 2017 AAP clinical guideline on the prevalence of high blood pressure among adolescents in Lagos, Nigeria.
Front. Pediatr. 11:1184320.
doi: 10.3389/fped.2023.1184320

Impact of the 2017 AAP clinical guideline on the prevalence of high blood pressure among adolescents in Lagos, Nigeria

Ifeoma Atoh[1], Joseph Ezeogu[2]*, Ekanem Ekure[1], Samuel Ilenre Omokhodion[3] and Fidelis Olisamedua Njokanma[4]

[1]Department of Paediatrics, College of Medicine, University of Lagos, Lagos, Nigeria, [2]Department of Paediatrics, Federal University Teaching Hospital Owerri, Owerri, Nigeria, [3]Department of Paediatrics, College of Medicine, University of Ibadan, Ibadan, Nigeria, [4]Department of Paediatrics, College of Medicine, Lagos State University, Lagos, Nigeria

Introduction: Adolescent high blood pressure (HBP) can lead to several end-organ complications if it continues into adulthood. The 2017 AAP Guideline has lower blood pressure cut-off points and consequently leads to the identification of more people with high blood pressure. This study evaluated the impact of the 2017 American Academy of Pediatrics (AAP) Clinical Guideline on the prevalence of high blood pressure among adolescents when compared to the 2004 Fourth Report.

Methodology: A descriptive cross-sectional study was conducted from August 2020 to December 2020. The selection of 1,490 students, 10–19 years old, was by a two-stage sampling technique. Socio-demographic information and relevant clinical data were obtained using a structured questionnaire. Blood pressure was measured according to standard protocol. Categorical and numerical variables were summarized using frequency, percentages, mean, and standard deviation. The McNemar-Bowker test of symmetry was used to compare the blood pressure values in the 2004 Fourth Report and the 2017 AAP Clinical Guideline. The Kappa statistic was used to test for the degree of agreement between the 2004 Fourth Report and the 2017 AAP Clinical Guideline.

Results: The prevalence rates of high blood pressure, elevated blood pressure, and hypertension among adolescents were 26.7%, 13.8%, and 12.9%, respectively, using the 2017 AAP Clinical Guideline, and 14.5%, 6.1%, and 8.4%, respectively, using the 2004 Fourth Report. The degree of agreement between the 2004 and 2017 guidelines with respect to the classification of blood pressure was 84.8%. The Kappa statistic was 0.71 (CI: 0.67–0.75). The impact of this was a 12.2%, 7.7%, and 4.5% increase in the prevalence of high blood pressure, elevated blood pressure, and hypertension, respectively, using the 2017 AAP Clinical Guideline.

Conclusion: The 2017 AAP Clinical Guideline detects a greater proportion of high blood pressure among adolescents. The adoption of this new guideline in clinical practice and its use in the routine screening of high blood pressure among adolescents is recommended.

KEYWORDS

high blood pressure, elevated blood pressure, hypertension, adolescent, secondary school

Introduction

The global burden of high blood pressure (HPB) in adolescents is rising and constitutes a major public health challenge, affecting approximately one billion people worldwide and accounting for 9.4 million deaths each year (1). Song et al. (2) revealed a trend of the increasing prevalence of HPB in children and adolescents which was observed during the past two decades with approximately one in seven adolescents aged 12–19 years having elevated BP or hypertension (HTN) during 2013–2016 (3). Risk factors for HBP in adolescents include age, gender, obesity, physical inactivity, family history of HTN in first degree relatives, socioeconomic status, cigarette smoking, and alcohol intake (4). Other risk factors include birth weight, maturity during birth, heredity, renal abnormalities due to diet, coarctation of the aorta, medications, and neoplasm (5). Adolescents with these risk factors need to have their BP evaluated regularly.

However, the evaluation and detection of adolescent HBP can be cumbersome and complex with many challenges and discrepancies (6) given that BP in adolescents is subject to many variables including height, age, and gender which must all be accounted for when attempting to describe "normal" and "abnormal" BP. A solution for this was provided by the advent of evidence-based practice (EBP).

The advent of EBP led to the development of several guidelines which serve to aid physicians in identifying symptoms and signs while making the best clinical decisions based on the most recent available evidence. Amongst these guidelines are the 2004 Fourth Report and the 2017 American Academy of Pediatrics (AAP) Clinical Guideline.

The 2004 Fourth Report included normative data and an adaptation of this data to the childhood growth charts from the Centers for Disease Control and Prevention for the year 2000 (7). Furthermore, overweight or obese children were included in the formation of these tables; the inclusion of these children likely biased normative BP values upwards. However, the increasing prevalence of global childhood obesity (8) and metabolic syndrome (9) implies that the obesity and HTN dyad should not be overlooked. In recognizing this importance, the 2017 AAP Clinical Guideline (10) included an obesity risk assessment tool that aids clinicians in identifying children at risk for obesity, so that guidance on healthy eating and physical activity [at least daily 1 h of physical activity for children (moderate to vigorous)] can be provided early. The 2017 AAP Guideline used new normative BP tables that shifted the 95th percentile down by about 1–4 mmHg, ensuring that adolescent hypertensives are not missed, with easier-to-read tables that have height in inches/centimeters, with values for height and blood pressure percentile all in one.

Given the significant changes in the 2017 AAP Clinical Guideline and its projected impact on the evaluation and management of high blood pressure in adolescents, there was therefore a need for a more systematic evaluation of the impact of its use on the prevalence of HBP in Nigerian children. It is hoped that our findings will provide data for clinicians to implement appropriate changes in their practice to ensure early diagnosis, treatment, and prevention of end-organ damage among adolescents.

Methodology

Study design

This was a descriptive cross-sectional study conducted in the Mushin Local Government Area of Lagos State in southwestern Nigeria from August 2020 to December 2020. It is one of the 20 Local Government Areas in Lagos State. Mushin is a densely populated, urban area covering a land area of 14.05 square kilometers with an estimated population of 1,868,743 (11). It shares boundaries in the north with Oshodi-Isolo Local Government, to the east with Somolu and in the south with Surulere. It has one educational district called Educational District VI located in the Oshodi area of Lagos State. There are 129 secondary schools in the Mushin Local Government area comprising 113 private and 16 public secondary schools.

Study population

This study was conducted among adolescents aged 10–19 years, in 14 (12 private and 2 public) secondary schools in the Mushin Local Government Area of Lagos State. The total population of students in both public and private secondary schools, as obtained from the Educational District VI Oshodi, was 38,266 with 25,125 of them in public secondary schools and 13,141 students in private secondary schools. The ratio of students in public to private schools was approximately 2:1. Our work was done over a 5-month period, August through December 2020. Ethical approval was obtained from the Health Research Ethics Committee of the Lagos University Teaching Hospital numbered as NHREC/DCST/HERC/2659. Approval was also obtained from the Lagos State Ministry of Education with approval number LG/C530/VI/122.

The sample size was determined using the formula for prevalence studies (12).

$$n = Z^2 p/Qd^2$$

where:

n = minimum sample size when the study population is >10,000

z = Standard normal deviate corresponding to 95% confidence interval = 1.96

p = prevalence rate of HBP in adolescents from a previous study done in

Lagos, Nigeria, i.e., 16.5% (0.17) (13).

$q = (1 - p)$, i.e., 0.83

d = precision level was set at 2% (0.02)

Substituting these figures into the formula:

$n = 1.962 \times 0.17 \times 0.830.022 = 1{,}355$.

The minimum sample size was 1,355. An additional 10% (135 pupils) was added to make up for possible non-responses. This

brought the total calculated sample size for the study to 1,490. Thus 1,490 adolescents were recruited for the study.

A total of 1,355 students aged 10–19 years who attended private or public secondary school in Mushin Local Government Area of Lagos State whose parents/guardians gave consent; and adolescents aged 18 years or more who gave consent were consecutively enrolled. Adolescents who were known or suspected to have renal conditions, such as acute glomerulonephritis, reno-vascular, and renal parenchymal diseases, and those who were on antihypertensive medications were excluded.

A two-stage sampling technique was used. Based on the student population, a ratio of one public school to six private schools was selected by simple random sampling. Within selected schools, participants were recruited from each class determined by proportional allocation using the school's register. Students were stratified along gender lines (girls and boys) using the class register. Participants were selected from each stratum by simple random sampling (balloting). Before being enrolled in the study, the selected students and their parents gave written and oral consent/assent. Socio-demographic information and relevant clinical data were obtained using a structured questionnaire. Questions were asked to exclude participants based on the presence of symptoms of renal disease and a history of hypertension.

Procedure

Anthropometry and blood pressure measurements were taken according to standard protocol. Body mass index Z scores were determined using the WHO chart for children 5–19 years (14). Weight was measured to the nearest 0.1 kg with minimal clothing (school uniforms with bare feet) using a standardized weighing scale (SECA model 756). Height was measured with the participant standing straight on bare feet, with both heels placed together, and buttocks, shoulder blades, and head without headgear [in a Frankfort plane (15)] in contact with the measuring rule, and readings recorded to the nearest 0.5 cm using a stadiometer (SECA model 213). Blood pressure was measured using an Accoson sphygmomanometer after the participant had rested in a seated position for 5 min legs uncrossed and flat on the floor. The measurement was done as recommended in the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7) (16) The cuff covered approximately two-thirds of the arm with the lower border 2 cm above the cubital fossa. The manometer was at the level of the cuff. The radial pulse was palpated, thereafter, the cuff was inflated to record the systolic blood pressure (SBP) by palpation and later deflated. The brachial artery was palpated and its position was noted. The cuff was then inflated to a pressure of 30 mmHg above the level at which the radial pulse was no longer palpable. The stethoscope was placed over the brachial artery in the cubital fossa and the pressure in the cuff was deflated at 2 mmHg per s. The first audible sound (the first Korotkoff sound) was recorded as the SBP. The fifth Korotkoff sound, i.e., the point of disappearance of all sound, was recorded as the diastolic blood pressure (DBP). Blood pressure was measured three times at an interval of 2 min and the mean was recorded. The systolic and diastolic recording, as well as the age, gender, and height in centimeters (cm) of the participant, were used to obtain the blood pressure percentile based on the 2017 AAP Clinical Guideline using the MD CALC (17), a tool developed in partnership with the AAP. The tool is useful for adolescents aged less than 13 years, while the determination of HBP was done manually for adolescents aged 13 years and above. The MSD manual calculator was the tool used in calculating the blood pressure percentiles based on the 2004 Fourth Report (18).

Normal blood pressure (NBP) was defined as an SBP and DBP that are <the 90th percentile for gender, age, and height (19). Elevated BP was defined as an SBP and/or DBP that are either ≥the 90th percentile and <the 95th percentile or between 120/<80 and 129/<80 mmHg (whichever was lower) (10). Stage 1 HTN was defined as an SBP and/or DBP that are either ≥the 95th percentile and <95th percentile +12 mmHg or between 130/80 and 139/89 mmHg (whichever was lower) (10). Stage 2 HTN was defined as an SBP and/or DBP that are either ≥95th percentile +12 mmHg or ≥140/90 mmHg (whichever was lower) (10).

Social class was determined using the socioeconomic indices of the parents as described by Oyedeji (20).

Healthy weight was defined as a Body Mass Index (BMI) for age between the 5th and 85th percentiles, overweight was defined as a BMI for age between the 85th and 95th percentiles, and obesity as a BMI for age above the 95th percentile (21).

Data analysis

Data were analyzed using the Statistical Package for Social Sciences (SPSS) version 23. Descriptive statistics were used to describe the socio-demographic and anthropometric characteristics. The prevalence rates of HBP, elevated BP, and HTN based on the 2017 AAP Clinical Guideline and 2004 Fourth Report were summarized using frequency and percentages, while numerical variables were summarized using mean and standard deviation. The McNemar-Bowker test of symmetry was used to compare the difference in the prevalence of HBP values using the 2017 AAP Clinical Guideline and the 2004 Fourth Report. The Kappa statistic was used to test for the degree of agreement between the 2004 Fourth Report and the 2017 AAP Clinical Guideline.

Results

Characteristics of the study participants

Of the initial 1,500 adolescents invited into the study, 1490 completed responses, giving a response rate of 99.3%. There was approximately equal representation of boys and girls and the mean age of the participants was 14.39 ± 2.79 years. The highest proportion of participants (649: 43.6%) belonged to the upper socio-economic class. The majority of the participants (83.5%) had a healthy weight as assessed by

TABLE 1 Distribution of characteristics of study participants by age.

Variable	Frequency (n = 1,490)	Percentage
Age (years)		
10–13	590	39.6
14–16	504	33.8
17–19	396	26.6
Mean age ± SD	14.39 ± 2.79	
Sex		
Male	744	49.9
Female	746	50.1
Socioeconomic status		
Upper class (I and II)	649	43.6
Middle class (III)	545	36.6
Lower class (IV and V)	296	19.8
Body mass index (BMI Z score)		
Underweight (<−2SD)	88	5.9
Healthy weight (≥−2SD–≤+1SD)	1,245	83
Overweight (>+1 SD–≤+2 SD)	1 32	8.9
Obese (>+2 SD)	25	1.7

BMI, body mass index, SD, standard deviation.

BMI, while 88 (5.9%) were underweight. There were 132 (8.9%) overweight and 25 (1.7%) obese participants (Table 1).

Prevalence of HBP among participants based on the 2004 Fourth Report

The overall prevalence of HBP in the study population based on the 2004 Fourth Report was 14.5% (n = 216), while 1,274 (85.5%) had NBP.

Prevalence of HBP among participants based on the 2017 AAP clinical guideline

Based on the 2017 AAP Guideline, 398 participants had HBP with a prevalence rate of 26.7%.

Pattern of HBP among participants based on the 2004 Fourth Report

Table 2 shows the pattern of HBP when based on the 2004 Fourth Report. The prevalence rate of prehypertension was 6.1% while the prevalence rate of stage 1 HTN was 4.8% and the prevalence rate of stage 2 HTN was 3.6%. With respect to the 216 participants that had HBP, 42.6% had prehypertension, 32.9% had stage 1 HTN, and 24.5% had stage 2 HTN. The mean SBP and DBP increased steadily across the various blood pressure categories.

Pattern of HBP among participants based on the 2017 AAP clinical guideline

Table 3 shows the pattern of HBP. The prevalence rate of elevated BP was 13.8%, the prevalence rate of stage 1 HTN was 9.3%, and the prevalence rate of stage 2 HTN was 3.6%. Among the 398 participants who had HBP, slightly more than half (51.5%) had elevated BP. The mean SBP was 123.10 ± 3.62 for participants with elevated BP, 132.16 ± 3.27 for participants with stage 1 HTN, and 140.61 ± 8.81 for participants with stage 2 HTN. The mean DBP also showed a steady increase and was highest (93.98 ± 4.52) for participants with stage 2 HTN. The prevalence of HTN among the boys was higher than the girls based on the 2017 AAP Clinical Guideline at 28.5% (212). This same effect was seen both in prehypertension/elevated BP and stage 1 HTN but not stage 2 HTN. The same pattern was observed among the girls. This is shown in Table 3.

Comparison of prevalence and patterns of HBP based on the 2004 Fourth Report and the 2017 AAP clinical guideline

Overall, the prevalence of HBP was higher based on the 2017 AAP Clinical Guideline than on the 2004 Fourth report (26.7% vs. 14.5%) with an increase of 12.2% (p = 0.001). The increase was reflected in

TABLE 2 Pattern of high blood pressure among participants based on the 2004 Fourth Report.

Variable	Frequency	Percentage of the study population	Percentage of high blood pressure	SBP (mean ± SD)	DBP (mean ± SD)
Prehypertension	92	6.1	42.6	127.95 ± 4.34	72.82 ± 7.74
Stage 1 HTN	71	4.8	32.9	133.21 ± 3.22	81.03 ± 7.48
Stage 2 HTN	53	3.6	24.5	140.58 ± 8.89	94.00 ± 4.65
High BP	216	14.5	100	132.78 ± 7.45	81.99 ± 7.08

SBP, systolic blood pressure; DBP, diastolic blood pressure; HTN, hypertension; SD, standard deviation; CI, confidence interval.

TABLE 3 Pattern of high blood pressure among participants based on the 2017 AAP guideline.

Variable	Frequency	Percentage of the study population	Percentage of high blood pressure	SBP (mean ± SD)	DBP (mean ± SD)
Elevated	205	13.8	51.5	123.10 ± 3.62	68.45 ± 6.83
Stage 1 HTN	139	9.3	34.9	132.16 ± 3.27	80.98 ± 6.46
Stage 2 HTN	54	3.6	13.6	140.61 ± 8.81	93.98 ± 4.52
High BP	398	26.7	100	128.64 ± 7.78	76.29 ± 8.19

AAP, American academy of pediatrics; SBP, systolic blood pressure; DBP, diastolic blood pressure; HTN, hypertension; SD, standard deviation; CI, confidence interval.

the prehypertension and stage 1 HTN groups ($p = 0.001$ each) but not in the stage 2 HTN group ($p = 0.999$). This is shown in Table 4.

Comparison of BP patterns according to the age group of participants based on the 2004 Fourth Report and the 2017 AAP clinical guideline

Within each age group, the prevalence of HBP was significantly higher based on the 2017 AAP Clinical Guideline ($p = 0.001$). The higher prevalence affected prehypertension/elevated BP and stage 1 HTN but not stage 2 HTN. This is shown in Table 5.

Level of agreement between the 2004 Fourth Report and the 2017 AAP clinical guideline on the classification of blood pressure

The degree of agreement between the 2004 and the 2017 guidelines on the classification of the BP of participants was assessed. Figure 1 shows that in 1,264 (84.8%) cases the two sets of guidelines agreed on classifying the participants as normal or abnormal. In 226 (15.2%) cases there was no agreement between the 2004 and 2017 guidelines. The Kappa statistic was 0.71 (CI: 0.67–0.75).

Discussion

The current study demonstrates that there is a high burden of HBP amongst adolescents in Mushin, Lagos, Nigeria, a low-income country. Our study demonstrates that the 2017 AAP Clinical Guideline commonly identifies more adolescents as hypertensives than the 2004 Fourth Report.

It confirms that pre-hypertension and elevated BP are common using either the 2004 Fourth Report or the 2017 AAP Clinical Guideline. Within each age group, the prevalence of HBP was significantly higher when based on the 2017 AAP Clinical Guideline. This accentuates the sensitivity of the 2017 AAP Clinical Guideline in the detection of HBP amongst adolescents.

TABLE 4 Comparison of prevalence and pattern of high blood pressure using the 2004 fourth report and 2017 AAP clinical guideline.

Variable	2004 Fourth Report *n* (%)	2017 AAP guideline *n* (%)	Difference in prevalence % (95% CI)	*p*-Value
PreHTN/elevated	92 (6.2)	205 (13.8)	7.6 (5.7, 9.5	0.001*
Stage 1 HTN	71 (4.8)	139 (9.3)	4.5 (3.4, 5.7)	0.001*
Stage 2 HTN	53 (3.5)	54 (3.6)	0.1 (0.08, 013)	0.999
Overall high BP	216 (14.5)	398 (26.7)	12.2 (10.5, 13.9)	0.001*

All *p*-values were calculated using the McNemar-Bowker test of symmetry. HTN, hypertension; BP, blood pressure; CI, confidence interval.
*Significant.

TABLE 5 Comparison of blood pressure patterns according to the age groups of participants using the 2004 fourth report and 2017 AAP guideline.

Variable / Age group	Blood pressure	2004 Fourth Report *n* (%)	2017 AAP guideline *n* (%)	*p*-Value
10–13 ($n = 590$)				
	Normal BP	504 (85.4)	466 (79.0)	0.001*
	High BP	86 (14.6)	124 (21.0)	0.001*
	High BP			
	Pre HTN/elevated BP	27 (4.6)	42 (7.1)	0.035*
	Stage 1 HTN	30 (5.1)	52 (8.8)	0.001*
	Stage 2 HTN	29 (4.9)	30 (5.1)	0.999
14–16 ($n = 504$)				
	Normal BP	425 (84.3)	367 (72.8)	0.001*
	High BP	79 (15.7)	137 (27.2)	0.001*
	High BP			
	Pre HTN/elevated BP	38 (7.5)	82 (16.3)	0.001*
	Stage 1 HTN	27 (5.4)	41 (8.1)	0.001*
	Stage 2 HTN	14 (2.8)	14 (2.8)	1.000
17–19 ($n = 396$)				
	Normal BP	345 (87.1)	259 (65.4)	0.001*
	High BP	51 (12.9)	137 (34.6)	0.001*
	High BP			
	Pre HTN/elevated BP	27 (6.8)	81 (20.5)	0.001*
	Stage 1 HTN	14 (3.5)	46 (11.6)	0.001*
	Stage 2 HTN	10 (2.5)	10 (2.5)	0.999

All *p*-values were calculated using the McNemar-Bowker test of symmetry. BP, blood pressure; HT, hypertension.
*Significant.

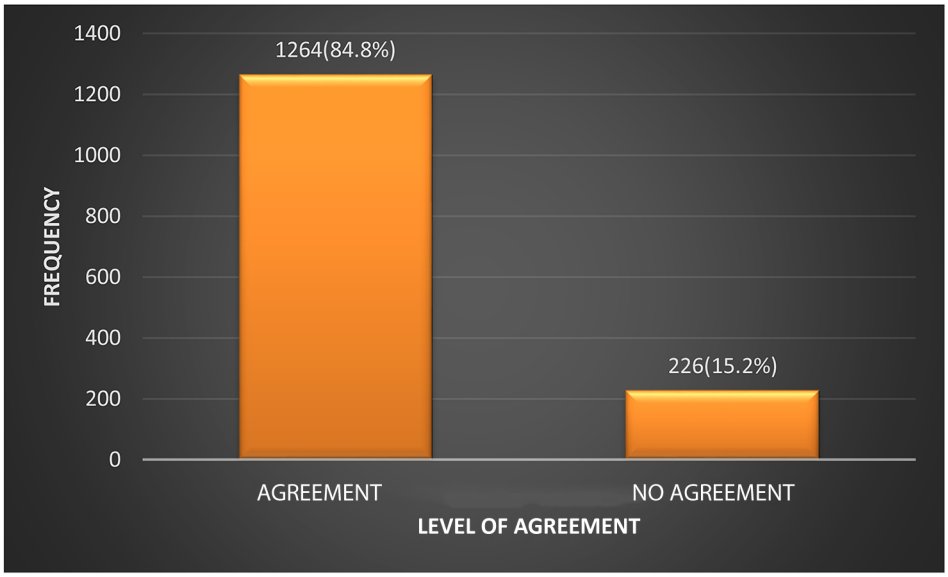


FIGURE 1
Level of agreement between the 2004 Fourth Report and the 2017 AAP clinical guideline on the classification of BP.

The first significant finding of this study is the establishment of the fact that the prevalence of HBP amongst adolescents in the current study was 14.5% using the 2004 Fourth Report and 26.7% with the 2017 AAP Clinical Guideline. Some previous studies had demonstrated a higher prevalence of HBP among adolescents of 27.5% (13) and 22. 5% (22) using the 2004 Fourth Report. This disparity may be attributable to the remarkably lower prevalence of overweight participants in the current study, 1.7%, compared to 9.6% and 12.6% in the previous Lagos and Enugu studies (13, 22). Using the 2017 AAP Guideline, the prevalence of HBP found in the current study was 26.7%. This difference in prevalence was significant and could be a result of the fact that the new reference tables in the 2017 AAP Clinical Guideline were produced excluding data from overweight and obese children. If this is so, the lower normative BP values in the 2017 AAP Clinical Guideline imply that there would be an increase in the prevalence of HBP in adolescents and a strong association between overweight/obesity and blood pressure. This exclusion resulted in 1–4 mm Hg drops in the elevated (≥90th percentile) and HTN (≥95th percentile) BP thresholds for children (23).

As anticipated, applying the 2017 AAP Clinical Guideline resulted in an increase in the prevalence rates of elevated BP (7.7%) and HTN (4.5%) over what they might have been using the 2004 Fourth Report. This is akin to the findings by Bell et al. (24), Sharma et al. (25), and Khoury et al. (26) in the US among children and adolescents. The implication of this is that the 2017 AAP Clinical Guideline is a more sensitive tool for the detection of HBP and fewer children with HBP will be missed. Missing HBP in any child exposes that child to adult HTN and hypertensive target organ damage including cerebrovascular accidents, retinopathy, coronary heart disease/myocardial infarction and heart failure, proteinuria and renal failure, and atherosclerotic changes (27).

Another striking finding with respect to age in the present study was that the prevalence of HBP increased progressively with the age group when the 2017 AAP Clinical Guideline was applied. This differed markedly from the pattern when using the 2004 Fourth Report in which the prevalence was lowest in the oldest age group and rates did not differ as much across age groups. This finding with the 2004 Fourth Report was unusual because BP is known to progressively increase with age.

The degree of agreement between the 2004 and 2017 guidelines with respect to the classification of BP was reasonably high at 84.8%, corroborating an earlier report of 84.8% by Sharma et al. (25) The corollary observation was that the 2004 and 2017 guidelines were at variance in the classification of 15.2% of participants. In all cases, as seen in the present study, affected participants were reclassified from normal to high blood pressure or from prehypertension to hypertension. There was no downward reclassification (23, 24, 28).

Strengths and limitations of the study

The current report is one of the earliest in Nigeria that used the 2017 AAP Clinical Guideline and the first to prospectively compare with the 2004 Fourth Report recommendation, with a fairly large sample of participants covering the full range of adolescent years. Evidence has been provided showing high prevalence rates of elevated BP and HTN among adolescents in secondary schools in Lagos. Due to limited resources, the study was done only in adolescents in secondary students to the exclusion of those who were not in school. It is plausible that social factors that influence BP may differ between the two subgroups of adolescents.

Conclusion

That more than a quarter of the adolescents in the present study had high blood pressure is indicative of a high prevalence, underscoring the need for routine blood pressure screening. Application of the 2017 AAP Clinical Guideline instead of the 2004 Fourth Report results in a substantial increase in the prevalence of high blood pressure among adolescents in secondary schools.

Data availability statement

The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by the Lagos University Teaching Hospital with number NHREC/DCST/HERC/2659. Approval with number LG/C530/VI/122 was also obtained from the Lagos State Ministry of Education. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

IA, SO, EE participated in the conceptualization, proposal-writing, data collection, data analysis. Later text amendments were carried out by JE, FN. All authors contributed to the article and approved the submitted version.

Funding

Funding for this study, was provided by the authors.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. World Health Organization. Global brief on hypertension: silent killer, global public health crisis. World health Day 2013. Available at: https://www.who.int/publications/i/item/a-global-brief-on-hypertension-silent-killer-global-public-health-crisis-world-health-day-2013 (Accessed December 20, 2020)

2. Song P, Zhang Y, Yu J, Zha M, Zhu Y, Rahimi K, et al. Global prevalence of hypertension in children: a systematic review and meta-analysis. *JAMA Pediatr*. (2019) 173(12):1154–63. doi: 10.1001/jamapediatrics.2019.3310

3. Jackson SL, Zhang Z, Wiltz JL, Loustalot F, Ritchey MD, Goodman AB, et al. Hypertension among youths—United States, 2001–2016. *MMWR Morb Mortal Wkly Rep*. (2018) 67(27):758–62. doi: 10.15585/mmwr.mm6727a2

4. Ewald DR, Haldeman LA. Risk factors in adolescent hypertension. *Glob Pediatr Heal*. (2016) 3(1):1–26; 7. doi: 10.1177/2333794X15625159

5. Hill KD, Li JS. Childhood hypertension: an underappreciated epidemic? *Pediatrics*. (2016) 138(6):e20162857. doi: 10.1542/peds.2016-2587

6. Hansen ML, Gunn PW, Kaelber DC. Underdiagnosis of hypertension in children and adolescents. *J Am Med Assoc*. (2007) 298(8):874–9. doi: 10.1001/jama.298.8.874

7. National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. *Paediatrics*. (2004) 114(2):555–76. doi: 10.1542/peds.114.2.S2.555

8. Bhadoria A, Sahoo K, Sahoo B, Choudhury A, Sufi N, Kumar R. Childhood obesity: causes and consequences. *J Fam Med Prim Care*. (2015) 4(2):187. doi: 10.4103/2249-4863.154628

9. Noubiap JJ, Nansseu JR, Lontchi-Yimagou E, Nkeck JR, Nyaga UF, Ngouo AT, et al. Global, regional, and country estimates of metabolic syndrome burden in children and adolescents in 2020: a systematic review and modelling analysis. *Lancet Child Adolesc Health*. (2022 Mar) 6(3):158–70. doi: 10.1016/S2352-4642(21)00374-6

10. Flynn JT, Kaelber DC, Baker-Smith CM, Blowey D, Carroll AE, Daniels SR, et al. Clinical practice guideline for screening and management of high blood pressure in children and adolescents. *Pediatrics*. (2017) 140(3):1–72. doi: 10.1542/peds.2017-1904

11. Lagos Bureau of Statistics. Digest of statistics (2017). Available at: http://lagosstate.gov.ng/Digest_of_Statistics_2017 (Accessed January 2, 2021).

12. Kirkwood BR. *Essential medical statistics*. 2nd ed. Malden, MA: Blackwell Science (2003). 420 p; p. 413.

13. Oduwole AA, Ladapo TA, Fajolu IB, Ekure EN, Adeniyi OF. Obesity and elevated blood pressure among adolescents in Lagos, Nigeria: a cross-sectional study. *BMC Public Health*. (2012) 12(1):616. doi: 10.1186/1471-2458-12-616

14. World Health Organization. Growth reference 5–19 years—BMI-for-age (5–19 years). Available at: https://www.who.int/tools/growth-reference-data-for-5to19-years/indicators/bmi-for-age (Accessed June 19, 2021).

15. Medical dictionary. Frankfort horizontal plane|definition of Frankfort horizontal plan. Available at: https://www.merriam-webster.com/medical/Frankfort (Accessed December 23, 2020)

16. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL, et al.. Seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure. *Hypertension*. (2003) 42(6):1206–52. doi: 10.1161/01.HYP.0000107251.49515.c2

17. AAP pediatric hypertension guidelines—MDCalc. Available at: www.mdcalc.com/aap-pediatric-hypertension-guidelines (Accessed December 23, 2020)

18. Calculators: weight unit conversions—MSD manual professional edition. https://www.msdmanuals.com/professional/multimedia/clinical-calculator/Weight Unit Conversions (Accessed December 21, 2020)

19. National High Blood Pressure Education Program. Working group on high blood pressure in children and adolescents: the fourth report on the diagnosis, evaluation and treatment of high blood pressure in children and adolescents. *Pediatrics*. (2004) 114(Suppl 2):555–76.

20. Oyedeji GA. Socioeconomic and cultural background of hospitalized children in Ilesha Nigeria. *Nig J Paediatr*. (1985) 12(4):111–7.

21. Must A, Dallal GE, Dietz WH. Reference data for obesity: 85th and 95th percentiles of body mass index (wt/ht^2)-a correction. *Am J Clin Nutr*. (1991) 53 (4):839–46. doi: 10.1093/ajcn/53.4.839

22. Ujunwa FA, Ikefuna AN, Nwokocha ARC, Chinawa JM. Hypertension and prehypertension among adolescents in secondary schools in Enugu, South East Nigeria. *Ital J Pediatr*. (2013) 39(1):70. doi: 10.1186/1824-7288-39-70

23. Dong Y, Song Y, Zou Z, Ma J, Dong B, Prochaska JJ. Updates to pediatric hypertension guidelines. *J Hypertens*. (2019) 37(2):297–306. doi: 10.1097/HJH.0000000000001903

24. Bell CS, Samuel JP, Samuels JA. Prevalence of hypertension in children. *Hypertension*. (2019) 73(1):148–52. doi: 10.1161/HYPERTENSIONAHA.118.11673

25. Sharma AK, Metzger DL, Rodd CJ. Prevalence and severity of high blood pressure among children based on the 2017 American academy of pediatrics guidelines. *JAMA Pediatr*. (2018) 172(6):557–65. doi: 10.1001/jamapediatrics.2018.0223

26. Khoury M, Khoury PR, Dolan LM, Kimball TR, Urbina EM. Clinical implications of the revised AAP pediatric hypertension guidelines. *Pediatrics*. (2018) 142(2):1–11. doi: 10.1542/peds.2018-0245

27. Schmieder RE. End organ damage in hypertension. *Dtsch Arztebl*. (2010) 107 (49):866–73. doi: 10.3238/arztebl.2010.0866

28. Yang L, Kelishadi R, Hong YM, Khadilkar A, Nawarycz T, Krzywińska-Wiewiorowska M, et al. Impact of the 2017 American academy of pediatrics guideline on hypertension prevalence compared with the fourth report in an international cohort. *Hypertension*. (2019) 74(6):1343–8. doi: 10.1161/HYPERTENSIONAHA.119.13807

frontiers | Frontiers in Cardiovascular Medicine

TYPE Review
PUBLISHED 27 June 2023
DOI 10.3389/fcvm.2023.1191119

OPEN ACCESS

EDITED BY
Zhen-Yu Zhang,
KU Leuven, Belgium

REVIEWED BY
Kate Denton,
Monash University, Australia
Vannina Gonzalez Marrachelli,
University of Valencia, Spain

*CORRESPONDENCE
Coziana Ciurtin
✉ c.ciurtin@ucl.ac.uk

RECEIVED 21 March 2023
ACCEPTED 14 June 2023
PUBLISHED 27 June 2023

CITATION
Allalou A, Peng J, Robinson GA, Marruganti C, D'Aiuto F, Butler G, Jury EC and Ciurtin C (2023) Impact of puberty, sex determinants and chronic inflammation on cardiovascular risk in young people.
Front. Cardiovasc. Med. 10:1191119.
doi: 10.3389/fcvm.2023.1191119

Impact of puberty, sex determinants and chronic inflammation on cardiovascular risk in young people

Amal Allalou[1], Junjie Peng[2,3], George A. Robinson[2,3], Crystal Marruganti[4], Francesco D'Aiuto[4], Gary Butler[5,6], Elizabeth C. Jury[3] and Coziana Ciurtin[2,3]*

[1]University College London Medical School, University College London, London, United Kingdom, [2]Centre for Adolescent Rheumatology Versus Arthritis, University College London, London, United Kingdom, [3]Centre for Rheumatology Research, Division of Medicine, University College London, London, United Kingdom, [4]Eastman Dental Hospital, University College London Hospital, London, United Kingdom, [5]Department of Paediatric Endocrinology, University College London Hospital, London, United Kingdom, [6]Institute of Child Health, University College London, London, United Kingdom

Worrying trends of increased cardiovascular disease (CVD) risk in children, adolescents and young people in the Modern Era have channelled research and public health strategies to tackle this growing epidemic. However, there are still controversies related to the dynamic of the impact of sex, age and puberty on this risk and on cardiovascular health outcomes later in life. In this comprehensive review of current literature, we examine the relationship between puberty, sex determinants and various traditional CVD-risk factors, as well as subclinical atherosclerosis in young people in general population. In addition, we evaluate the role of chronic inflammation, sex hormone therapy and health-risk behaviours on augmenting traditional CVD-risk factors and health outcomes, ultimately aiming to determine whether tailored management strategies for this age group are justified.

KEYWORDS

cardiovascular risk factors, children and young poeple, chronic inflammation, puberty, obesity, sex determinants

Introduction

Cardiovascular disease (CVD) is the most common cause of death worldwide (1). Atherosclerosis is one of the earliest signs of CVD. It is characterised by progressive accumulation of cholesterol-laden macrophages in the subendothelial layers of larger arteries which progress to more complex fibrous plaques. Acute plaque rupture or erosion can result in the formation of a thrombus, culminating in the clinical manifestation of myocardial infarction or ischaemic stroke (2). Although more prevalent with increased age, atherosclerotic vascular changes have been documented in young people in multiple post-mortem studies at the end of the past century (3–6). Most notably, asymptomatic microscopic lesions have been described in the coronary arteries of infants in the first 5 years of life, which are thought to precede the more invasive fatty streak lesions associated with atherosclerosis (4, 5). Future studies, built on these findings, established associations between the extent of arterial fatty streaks and fibrotic lesions in young people and traditional CVD-risk factors, such as increasing age and body mass index (BMI), hypertension (HP), dyslipidaemia, aberrant glucose tolerance and smoking, as well

as chronic inflammation (3, 7, 8). The presence of CVD-risk factors between the ages of 18–30 can strongly predict the development of subclinical atherosclerosis in later adulthood (9). Interestingly, the sexual dimorphism characterising the CVD prevalence in adulthood is also observed in the prevalence of subclinical atherosclerotic lesions in young people, which were detected in 2% vs. 0% of young men vs. women aged 15–19 years, respectively, and 20% vs. 8% in men vs. women aged 30–34 years, respectively (10). One of the main drivers of this sex difference in prevalence is the higher incidence of traditional CVD risk factors in young males compared to females (6). This is reflected in the sex-disaggregated rate of progression of carotid intima-media thickness (CIMT), which is used as a validated marker of subclinical atherosclerosis, where CIMT progression begins in boys around age 6, and in girls around age 9, and increases gradually with age (11).

Adolescence is a key period of profound physiological changes with significant impact for preservation or deterioration of cardiovascular health, often associated with abnormal cardiovascular health metrics, or significant behavioural changes which impact on diet and other health-related outcomes (12). In addition, sex hormones and genes present on sex chromosomes differentially influence the regulation of the immune system (13), which is also reflected in the sex-bias observed in the predisposition to various autoimmune disorders as well as differential risk for chronic inflammation, which subsequently increases the risk for CVD.

In this review, we aim to assess the impact of sex determinants and puberty in driving metabolic abnormalities leading to atherosclerosis progression in young people and CVD-risk later in life, as well as the impact of chronic inflammation and health-risk on augmenting this risk. Identifying CVD-risk factors earlier in life and tailoring management strategies for prevention of CVD is likely to have significant societal implications. We summarised in **Table 1** and **Figure 1**, the main factors contributing to CVD-risk in young people as well as the main effects of puberty and sex determinants which will be discussed in detail in this review.

Sex-biased trends in cardiovascular risk factors in young people in general population

Various traditional CVD-risk factors have been studied in young people and have been included in clinical scores/tools aiming at assessing an individual's risk and tailor public health interventions to minimise the risk for CVD over time. We will focus on the main traditional CVD-risk factors from the perspective of the impact of sex-determinants and puberty on their prevalence, features and trends over time.

Obesity

Between 1975 and 2016, the global prevalence of obesity has nearly tripled (14). As of 2021, WHO estimates an annual mortality of 2.8 million people across all age groups as a direct result of the ongoing obesity epidemic. Targeting excessive weight during childhood and adolescence has been identified as the key intervention in reducing obesity-associated CVD- risk later in life. A higher BMI percentile and central adiposity correlate to a higher risk of obesity and metabolic syndrome in adolescence and adulthood (15, 16). The association between obesity in youth and later life was found to increase with age and is stronger in females (17).

The mechanism by which obesity causes increased CVD- risk is multifactorial. Obesity is associated with chronic mild inflammation, largely mediated by the secretion of inflammatory adipokines by excessive adipose tissue. Higher adiposity throughout puberty was associated with a more atherogenic metabolic profile and greater aortic stiffness (independent of metabolic factors), while reverting to a healthy weight during adolescence prevents this association and results in no difference in arterial stiffness compared to a normal weight control cohort (18). Not all obese individuals are at increased CVD-risk. A high body fat percentage in both adults and children (without additional features of metabolic syndrome—i.e., high blood glucose, insulin resistance, dyslipidaemia) is considered a metabolically healthy obese (MHO) state, and is not associated with increased CVD-risk (19, 20). However, children with prepubertal obesity are at a greater risk of metabolic syndrome, and the pronounced changes to their metabolic parameters during puberty often cause the shift to a metabolically unhealthy status (21, 22).

We summarise below the main effects of obesity on CVD-risk in young populations by sex, including its timing and its bidirectional relationship with puberty.

Obesity in childhood increases the risk of obesity in adulthood and CVD-risk factors in a sex biased way (15). A higher BMI percentile during childhood and adolescence correlates with a high risk of being overweight or obese in adulthood, and the association becomes stronger as age increases. The link observed is stronger in females than in males (17). During all stages of puberty, there is a positive link between trunk fat and systolic and diastolic blood pressure (BP). This association is seen in males only (23).

Obesity is associated with a pro-inflammatory state from an early age. Obesity associated with chronic mild inflammation led to elevated inflammatory markers, including C-reactive protein (CRP), Tumour Necrosis Factor-α (TNF-α), interleukin (IL)-6, IL-18, haptoglobin, macrophage inhibitory factor (MIF) and plasminogen activator inhibitor-1 (24). White adipose tissue has been noted to play an endocrine role, secreting leptin and adiponectin (25, 26). Obesity (particularly visceral fat) in childhood and adolescence increased the risk of metabolic syndrome in adulthood and adolescence, independent of baseline insulin level (16), suggesting that lifestyle factors may contribute more to the development of metabolic syndrome in young people than hereditary factors (27).

Obesity affects the timing of puberty. Obesity causes early and shorter puberty in girls (28–30), which can be explained by the "weight hypothesis", which suggests that adipokines increase

TABLE 1 Main effects of puberty and sex determinants on traditional CVD-risk factors and subclinical atherosclerosis in young populations.

Risk factors	Impact of puberty	Sex differences
Traditional CVD-risk factors		
Obesity	Increases with puberty.	Both sexes, but stronger effect in girls
	Causes early and shorter puberty.	Stronger effect in girls
	Early puberty is associated with increased obesity risk.	Both sexes, but stronger effect in girls
	In all puberty stages, obesity correlates with increased BP.	Stronger effect in boys
	Increased subcutaneous fat post-menarche.	In girls
	Visceral fat distribution post-puberty.	Stronger effect in boys
	Obesity related biomarkers:	
	IL-6 decreased during puberty.	Both sexes
	Adiponectin decreased during puberty.	Stronger effect in boys
	Leptin increased during puberty	Stronger effect in girls
Metabolic syndrome	Puberty is associated with instability in metabolic syndrome parameters.	In both sexes
	Puberty and adolescents are associated with increased metabolic risk.	Stronger effect in boys
	Adulthood is associated with increased metabolic risk.	Stronger effect in women
Insulin resistance/diabetes	Tanner stages 1–3 increase the risk	Independent of sex or obesity
	Risk increases at the onset of puberty, peaking at Tanner stage 3, but returns to pre-pubertal levels by the end of puberty.	Stronger effect in girls
	Early menarche is associated with increased insulin levels and increased risk of type 2 diabetes mellitus.	In girls
	Obesity increases the risk of insulin resistance post-puberty.	Stronger effect in boys
Dyslipidaemia	Prepuberty, no correlations with atherosclerosis.	In both sexes
	Puberty onset altered lipid profiles	In both sexes
	Post-puberty, there is an increase in pro-atherogenic lipid profile	In young men
	Post-puberty, there is an increase in athero-protective lipid profile	In young women
	After puberty blockers, cross-sex hormone therapy with testosterone drove a pro-atherogenic lipid profile	In young trans-men
Hypertension	Systolic BP increases in children entering puberty.	In both sexes
	BP reaches adult values at the end of puberty	In both sexes
	Puberty timing associated with transitory changes in the BP trajectories.	In both sexes
	In young adulthood, significant increased prevalence of systolic HP which started prepuberty.	In boys and young men
	Endogenous oestrogen exposure starting from puberty decreases the risk	In girls/women
	Risk increases with age, from post-puberty into early adulthood	In boys and young men
Subclinical atherosclerosis		
Carotid artery subclinical atherosclerosis	Puberty increases the prevalence of subclinical atherosclerosis.	In both sexes
Coronary artery atherosclerotic lesions	From age 6–30 (including puberty)	More prevalent in boys/young men
Increased progression of atherosclerosis	Associated with low testosterone and positively correlated with serum oestrogen levels (post-puberty/early adulthood)	In men

androgen conversion to oestrogen, therefore influencing the timing of puberty. Earlier puberty in obese children is determined by an interplay between molecular factors such as leptin, insulin and oestrogen. There is evidence that serum leptin levels are inversely correlated with age at menarche in girls (31, 32), while there was a close positive correlation between body fat and serum leptin levels in girls throughout puberty (31–35). Children with obesity have lower sex hormone-binding globulin than normal weight children (36), while obese adolescent boys have lower serum testosterone and higher oestradiol than normal weight adolescent males (36, 37). Overweight girls have reduced sleep-associated luteinising hormone (LH) synthesis, the first hormonal change observed at the onset of puberty (38).*Puberty timing affects the obesity risk.*. Early puberty in girls may be related to obesity due to the effect of oestradiol in increasing the body fat, while early menarche was associated with increased CVD-risk and mortality (39, 40). Early menarche was also related to reduced sex hormone binding globulin and higher oestrogen levels throughout adolescence and into adulthood (41–43), as well as increased risk of metabolic syndrome in adulthood, independent of BMI (44–50). Early puberty is associated with higher accumulation of subcutaneous fat on lower trunk in both males and females (49). The large AVENA study (50) assessed more than 500 children and adolescents and found that the waist circumference and BMI increased in girls as puberty continued, while in boys there were no correlations with the pubertal stage. An increase in total body fat was observed in both females and males throughout puberty, and BMI increased through the 8–18 years interval of observation (51). This was largely driven by the increase in the lean component of BMI, particularly in boys (52). Pubertal stage also affects the adipokine profile (53), and inflammation caused by obesity was somewhat affected by pubertal changes in sex hormones (54).

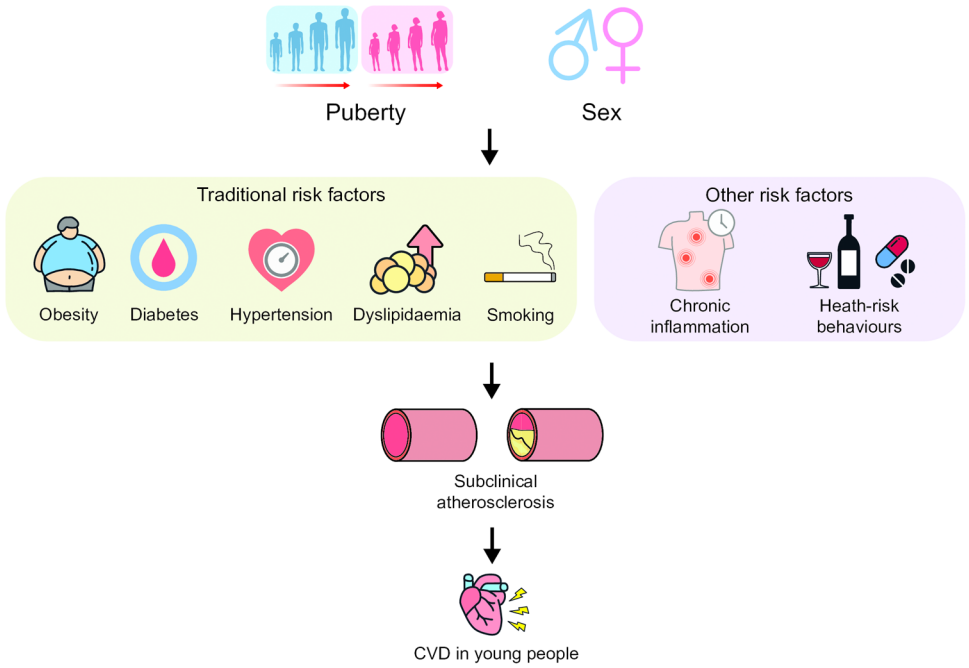


FIGURE 1
CVD-risk factors yin young populations. Legend: CVD—cardiovascular disease.

Obesity related biomarkers are also influenced by puberty and sex hormones. Although no significant difference between prepubertal and pubertal levels of leptin were found independent of body fat content (35), circulating IL-6 levels correlated positively with testosterone and oestradiol levels, and leptin: receptor ratio correlated positively with BMI in both sexes. In addition, IL-6 decreased throughout puberty in both boys and girls but was only found to be correlated to oestradiol and not testosterone. Adiponectin decreases in males from mid-puberty to levels below the ones found in females (53) and levels of circulating androgens were found to decrease plasma adiponectin and may be the cause for increased risk of insulin resistance and atherosclerosis in men (55). Higher serum leptin levels were observed in girls than males pre-, during and post-puberty, even after correcting for increased female adiposity. It is proposed that this may be due to oestradiol stimulating leptin synthesis and testosterone suppressing it (56). At the onset of puberty, leptin increases in girls and decreases in boys, potentially reflecting the increase in fat mass in girls (34), in addition to the potential role of testosterone in suppressing the leptin production (57). By the age of 15, there is an increase in IL-6, IL-8, IL-10 serum concentrations in obese and overweight girls compared to normal weight females even after adjustment for pubertal status, but no significant difference was observed in boys (58).

However, the relationship between early and shorter puberty on CVD-risk later in life is less certain. Data from the Avon Longitudinal Study of Parents and Children (ALSPAC) which recruited children born between April 1, 1991, and December 31, 1992 who were followed-up for 25 years, concluded that earlier puberty was unlikely to have a major impact on pre-clinical CVD-risk in early adulthood, appreciated using a variety of CVD validated outcome measures (59).

There are significant sex differences in adipose tissue distribution around puberty. Over the course of puberty, the prevalence of obesity or excess weight status (measured by BMI) doubles in girls (60). Post menarche, girls have greater subcutaneous fat deposits than pre-menarcheal girls, particularly in the gluteo-femoral region, therefore the sexual dimorphism in fat distribution begins in or is triggered by early puberty (61, 62). Higher oestrogen correlated with gynoid fat distribution in pubertal females (63). Age at menarche negatively correlated to hip and thigh circumference and negatively correlated to waist circumference (61), while early menarche associated with increased adiposity in childhood and increased risk for metabolic syndrome in adulthood (64). In boys, higher serum testosterone was associated with increase in subcutaneous abdominal fat deposition during puberty (63).

Sexual dimorphism in storage of adipose tissue (fat distribution) may underlie the increased CVD-risk in men. Visceral fat and fat deposition around abdomen are favoured in men (central android fat distribution), while subcutaneous fatty deposition in women is largely observed around hips, thighs, and buttocks (gynoid/ gluteal-femoral fat distribution) until menopause, after which there is a shift towards increased deposition of visceral fat (65, 66). Lipoprotein lipase is one of the key enzymes that facilitates the accumulation of adipose tissue. Testosterone inhibits lipoprotein lipase activity in subcutaneous fat in men (67). Lipoprotein activity in women is greater in gluteal subcutaneous fat than in abdominal visceral fat, and higher in abdominal fat in men (68). Distribution of receptors that

modulate lipolysis in subcutaneous and intraabdominal fat depots account in part for the sexual dimorphism in body fat deposition. Oestradiol upregulates expression of anti-lipolytic α2-adrenergic receptors in subcutaneous adipocytes but not in abdominal depots (69). The ratio of α2 receptors to lipolytic β1–2 adrenergic receptors is higher in subcutaneous adipose tissue in young women than in men, promoting lower rates of lipolysis in these depots and a reduced lipolytic response to adrenaline and noradrenaline (70).

Increased visceral fat is associated with decreased insulin resistance, increased risk of glucose intolerance and metabolic syndrome (71, 72). Visceral fats have a higher lipolytic rate (65). Higher rate of lipolysis of visceral fat, as observed in males, releases more free fatty acids into the circulation, which in turn causes increased gluconeogenesis and hyperinsulinaemia (73). Subcutaneous fat on the other hand is associated with a lower CVD-risk and do not have the same diabetes-associated risk (74).

Despite good evidence that puberty and sex determinants influence obesity in young people, there is evidence of obesity risks that precede puberty. Children with one obese parent are more than twice as likely to be obese (75), and increased maternal pre-pregnancy weight and gestational weight gain increases the child's adverse CVD-risk. Children of mothers with higher gestation weight gain had higher BMI, waist circumference, fat mass, leptin, CRP and IL6 levels, as well as high density lipoprotein (HDL)-cholesterol and Apolipoprotein (Apo) A1) (76).

In conclusion, obesity in childhood is associated with increased traditional CVD-risk factors overall, as well as increased risk of obesity in adulthood. Obesity triggers early and shorter puberty, while early puberty also predisposes to obesity. There is also evidence of sex dimorphism in fat distribution and obesity-related biomarkers underpinning sex-differencs in CVD-risk from adolescence and young adulthood.

Metabolic syndrome

Metabolic syndrome is defined as a combination of risk factors for CVD, such as diabetes, HP, dyslipidaemia and obesity. The diagnosis of metabolic syndrome in children and adolescents is slightly controversial as only 50% of adolescents diagnosed with metabolic syndrome maintained a stable diagnosis over 3 years (77) and only 30% of obese children and adolescents diagnosed with metabolic syndrome at baseline were found to still maintain the required characteristics at a 60-day follow up (78). This instability may be a result of the dynamic changes observed throughout puberty. Metabolic syndrome in adolescence is higher in males than females by ~10% (79), but this trend reverses with age as it becomes more prevalent in adult women (80). There is no correlation between any circulating metabolites and measures of atherosclerosis in children, but an inverse correlation between HDL-cholesterol levels and measures of atherosclerosis independent of BMI and BP are present in adulthood (81). However, CVD-risk is nine times higher in children with metabolic syndrome (82). Children with one parent with metabolic syndrome were also at greater risk of obesity and insulin resistance (75). In conclusion, puberty may promote metabolic instability, with a reversal of the sex-bias from male to female from adolescence into adulthood.

Insulin resistance is measured as impaired fasting glucose or impaired glucose tolerance. Hyperglycaemia measured indirectly through levels of glycohemoglobin in post-mortem studies was found to be associated with increases fatty streaks and raised coronary atherosclerotic lesions in young people who died in road traffic accidents from the age of 25, and aortic lesions from the age of 30 (83). In adolescence, obese males have a higher risk for insulin resistance and impaired fasting glucose than obese females (84). Insulin resistance increases at the onset of puberty, peaking at Tanner stage 3, but returns to baseline pre-pubertal levels by the end of puberty (85) and girls are more insulin resistant than boys at all pubertal stages. Serum insulin is highest at Tanner stage 2 in both sexes, independent of body mass and retains a consistent level throughout puberty (86). Between Tanner stages 1–3, there is an increase in fasting glucose, insulin and acute insulin response and an associated reduction in insulin sensitivity independent of sex or obesity status. The reduction in insulin sensitivity was not associated with androgen, oestradiol, visceral fat, or IGF-1 (87) and high levels of insulin in childhood were associated with early menarche (64).

Earlier menarche associated with increased risk of type 2 diabetes mellitus (T2DM) in adulthood independent of BMI at 18 years of age (45). This implies a potential role for sex hormones in the pathophysiology of T2DM (46). Hyperandrogenic profiles in women (e.g., polycystic ovary syndrome) are associated with insulin resistance and glucose intolerance (47, 48), while high oestradiol, high testosterone and low sex hormone binding globulin associated with increased risk of T2DM in women, independent of BMI (46, 88, 89).

In conclusion, puberty onset and early timing of puberty, as well as hyperandrogenic profiles in women increase the insulin resistance and diabetes risk, while early phases of puberty are associated with increased risk in both sexes, independent of obesity.

Dyslipidaemia

Prevalence of dyslipidaemia in children and adolescents across the world is increasing, being four-times more common in children and adolescents with obesity (90). The relationship between lipid abnormalities and atherosclerosis or vascular dysfunction in young people is currently debated (81) as no correlation between lipids and CIMT or pulse wave velocity has been found in children aged 11–12, independent of their BMI or BP. However, associations between these vascular markers and HDL-cholesterol and glucose levels were found in adulthood, suggesting that perhaps these associations arise during/post- puberty. Changes in lipid profiles that occur in puberty however are relevant, as they predispose to increased CVD-risk in adulthood (91). Overall, higher concentrations of triglycerides, low density lipoproteins (LDL) and very low-density lipoproteins (VLDL) cholesterol and ApoB were found in men, with corresponding higher

concentrations of HDL-cholesterol, ApoA1, polyunsaturated fatty acids (PUFA) and docosahexaenoic acid (DHA) in women (92, 93). Interestingly, cross-sex hormone therapy in young trans-sexual individuals undergoing gender-reassigning treatment partially reversed the sex bias observed post-puberty in healthy controls (93).

Sex differences in dyslipidaemia

Although no sex difference has been observed in the mean total cholesterol concentration in the Framingham Offspring Study (92), there were sex differences in HDL, LDL and VLDL particles size, which are potentially influenced by sex hormones. Oestrogens have a role in promoting an atheroprotective lipid profile. High serum oestrogen promoted VLDL and LDL clearance as well as increased synthesis of HDL in mouse models through mediation of the hepatic oestrogen receptor α (Erα), the actions of which have been proposed to be modulated by an interaction with Liver X receptor α (LXRα) (94). Contrastingly, cellular study analysing HDL efflux in macrophages in trans-gender women undergoing hormone therapy found reduction in HDL efflux, with a specific decrease in ATP-binding cassette transporter A1 mediated HDL efflux (95).

No sex difference between total HDL concentrations have been reported in the large Framingham Offspring Study either (92). However, young men had a greater concentration of small and intermediate HDL particle subclasses, while women had almost double the concentration of large HDL particles (92). Although women have larger HDL particles than men, this difference is less prominent with increasing age (92). There is some evidence for a stronger inverse correlation between CVD-risk and HDL-cholesterol levels in women than men (96), and this could be attributable to the size of HDL particles (92). This trend seems to be related to the presence of female sex hormones as increased oestradiol serum concentrations correlated with increased HDL-cholesterol in young trans women too (93). ApoA1 is a metabolite for HDL cholesterol which is also affected by sex bias. Women have higher HDL-associated ApoA1 than men while ApoA1 levels were positively corelated with the length of oestradiol therapy and oestradiol serum concentrations in young trans women on cross-sex hormone therapy. However, there was no correlation with testosterone levels in young trans men (93).

Men have a greater total LDL-cholesterol serum concentration than women (92) and smaller LDL particles than women (92, 97–99). This is likely due to a greater concentration of small and intermediate LDL particle subclasses in men, and a greater concentration of large LDL subclasses in women (92). It has been suggested that the sex difference in total LDL particle concentration may be responsible for the sex bias observed in CVD-risk, as the sex difference in LDL concentrations also decreases with age, similar to the trend in CVD risk. There is an increase in small LDL in men before 50 that might underlie the increased CVD risk in middle aged men compared to younger men (92).

Men also have a higher VLDL-cholesterol serum concentration (92), and in particular this affects the larger and intermediate VLDL subclasses as men overall have larger mean VLDL particle sizes (92).

Puberty affects the lipid profiles

Although, no significant difference in lipid profiles were detected between prepubertal girls and boys (93), the onset of puberty altered lipid profiles (100), although these changes normalised post-puberty, raising awareness that changes observed during this puberty should be considered in clinical guidelines for CVD-risk-assessment in adolescents and young people (101).

In conclusion, post-puberty, there is evidence for a trend towards a pro-atherogenic lipid profile in young men or trans-men undergoing cross-sex hormone gender re-assignment therapy with testosterone, while young women have higher concentrations of athero-protective HDL-associated ApoA1.

Hypertension (HP)

It is widely recognised that arterial BP increases with age (102), although has been also gradually increasing in prevalence in younger populations in the recent years Primary HP has been found to be more prevalent in children over age of 6, with associated increased BMI and positive family history (103). The most common causes for secondary HP in children and adolescents are congenital malformations, renal diseases, medications (such as corticosteroids, albuterol and pseudoephedrine), and endocrine causes, while in adolescents, additional factors are related to substance abuse and teen pregnancy (104).

Impact of puberty on HP

Despite less research available overall in younger populations compared to adults, there is evidence that the hormonal and metabolic changes associated with puberty impact BP. The overall prevalence of confirmed HP in children is 2%–5%, with many more being diagnosed with pre-hypertensive states (15.3%) (105). While initial research identified low birth weight as a risk factor for HP in childhood (106, 107), more recent studies found evidence that infants born with appropriate for gestational age or excessive birth weight are both at higher risk for primary HP compared to children with small weight for gestational age (odds ratio = 1.31 and 1.19 respectively) (107). Systolic BP increases in children entering puberty, reaching adult values at the end of puberty, process considered to be significantly influenced by the increased production of sex hormones, growth hormone, insulin-like growth factor-1 and insulin during puberty (108).

Puberty timing also influences the risk of HP. In a large prospective cohort study, which evaluated more than 4,000 children over time, males had significantly increased prevalence of systolic HP compared with females in early adulthood, but this was accrued before puberty, while puberty timing was associated only with small transient differences in systolic BP trajectories post-puberty in both sexes, suggesting that interventions targeting puberty timing are unlikely to influence systolic BP in early adulthood (109–114).

Sex differences in HP are underpinned by various mechanisms

The inhibition of the renin-angiotensin-aldosterone system (RAAS) is a recognised therapeutic option for HP; however, there is evidence that suggests responses to treatment is different in men and in women (115). Endogenous oestrogen is associated with a lower BP in women (116), while there is no consensus from literature data on the effect of exogenous oestrogen, which has been found to decrease (117–119), increase (120–122) or not affect BP measurements (123, 124). These differences may have arisen due to the administration of different oestrogenic compounds at different doses through different routes of administration, and different methods used to measure BP (125). The protective effect of female sex hormones could be explained by the role of oestrogen in promoting vasodilation and exerting cardioprotective effects on the RAAS system. In animal models, oestrogen has been found to upregulate synthesis of angiotensinogen and downregulate synthesis of renin and angiotensin enzyme (ACE) (124, 126, 127), leading protective effects. In rats, oestrogen has been found to reduce calcium efflux in vascular, renal and cardiac cells (128) as well as reduce BP by inhibiting synthesis of angiotensin II (AT II), endothelin 1 (ET1) and catecholamines that all have vasoconstrictive effects (124, 129, 130). One of the mechanisms of oestrogen's effect on BP is mediated through its modulation of expression of ET1, which is a potent vasoconstrictor and its receptors (131). The administration of exogenous 17β-oestradiol to ovariectomised rats decreased the circulating ET1 levels (132, 133) and reduced the expression and activity of endothelin-converting enzyme (133, 134). In vitro studies also find that 17β-oestradiol inhibits ET1 synthesis by increasing nitric oxide synthase (135) +/- decreasing AT II synthesis (136, 137).

Testosterone is pro-hypertensive, through potential modulation of the plasma ET1 levels, resulting in ET1 levels that are 40% higher in men and 90% higher in trans men treated with testosterone therapy than in premenopausal women (138, 139). Testosterone also promotes vasoconstriction and renal sodium reabsorption through the stimulation of AT1 receptor (AT1R) (140–142). In animal studies, it has been noted that males have a higher vascular AT1R:AT2R ratio than females (127, 143, 144).

Sex differences in Hp prevalence in adolescents and young adults

Sex differences in HP in adulthood are well-recognised, with males being more at risk; however, sex differences are particularly pronounced in early adulthood, with one study reporting both sex and ethnic differences in HP among 18- to 29-year-old adults (1.5% in White women vs. 5% White men and 4% and 10% for Black women and men, respectively) (145).

In a large American study of a large representative sample of adolescents followed up to age 24–34, young women were far less likely to be hypertensive compared to men (12% vs. 27%), and there were also sex differences in HP awareness among young people (32% and 25% of hypertensive women and men, respectively were aware of their status) (146).

In conclusion, the prevalence of HP is increased overall from the onset of puberty in both sexes, reaching adult values at the end of puberty, and is significantly influenced by molecular mechanisms subjected to sex hormones and metabolic factors regulation driving the overall increased risk in young males.

Subclinical atherosclerosis in young people in general population

As a consequence of various CVD-risk factors encountered in young population, there is also evidence of presence of subclinical atherosclerosis, usually evaluated on vascular scans or post-mortem studies. Subclinical atherosclerosis is one of the best predictors of CVD later in life. Coronary artery atherosclerotic lesions measured post-mortem in individuals aged 6–30 were more prevalent in men than women (6) All the traditional CVD-risk factors influence the prevalence of subclinical atherosclerosis. Puberty was associated with increased subclinical atherosclerosis in children with a benign obesity phenotype (147). In young people, HP contributes to atherosclerosis by accelerating development of raised lesions rather than fatty streaks. A post-mortem study in people aged 15–34 found that HP, causing increased intimal thickness of small renal arteries, was associated with more extensive raised atherosclerotic lesions in the abdominal aorta and in the right coronary artery (148). A post-mortem histological study of coronary arteries from American young people aged 15–34 found a higher prevalence of advanced atherosclerotic lesions in young men compared to young women (10). Positive correlation between serum oestrogen and progression of carotid atherosclerosis was found in men with intact oestradiol synthesis independent of BMI and other risk factors (149), while low testosterone in men associated with increased progression of atherosclerosis (measured by CIMT) (149).

In conclusion, there is a significant male sex bias in prevalence of subclinical atherosclerosis from early childhood into adulthood.

Effect of chronic inflammation on the cardiovascular risk of young people

Chronic inflammation is one of the known drivers of CVD-risk in patients of all ages. In addition to inflammation, some of the treatments that are used in young people with chronic inflammatory conditions (in particular, corticosteroids or small molecule immunosuppressants, such as Janus Kinase inhibitors and biologic treatments, such as IL6 blockers, etc) have significant metabolic effects (150), which indirectly impact the CVD-risk of a certain individual. Assessment of disease activity in young people with chronic inflammation usually pertain to composite scores aiming to combine objective and subjective assessment of disease manifestations, as well as laboratory parameters which are relevant for systemic inflammation or immune system abnormalities contributing to chronic inflammation (151–153). Despite improvement in quantifying inflammation and improved guidelines to ensure tighter control of disease activity in young people with chronic inflammatory and autoimmune conditions (154–156), there is still evidence of increased CVD-risk in children and young people which is not adequately captured by

the CVD-risk assessment tools routinely used for primary care prevention strategies in general population(157, 158).

Long-term inflammation as well as glucocorticoid treatment used in the treatment of many childhood onset diseases, such as juvenile idiopathic arthritis (JIA), juvenile systemic lupus erythematosus (JSLE), juvenile dermatomyositis (JDM), inflammatory bowel disease (IBD), etc, influence the body composition by increasing body fat mass and reducing skeletal muscle mass (159). Obesity is more common in patients with JIA than in the healthy population (160, 161) and is associated with insulin resistance, HP, higher serum triglycerides and early atherosclerosis (162). Obesity and excess weight in JIA population is caused, in part, by glucocorticoid treatment, and functional limitation that causes a less active lifestyle (163) Children with systemic JIA and enthesitis-related arthritis (ERA) had the highest rates of overweight and obesity compared to other JIA subtypes (163). Several studies explored the association between obesity and disease activity or number of active and reported both no association (164, 165), and a positive correlation between obesity and disease activity (particularly on lower limb joints), number of affected joints and higher levels of CRP and ESR compared to the healthy population (166). Children with JIA and a BMI lower than 23 kg/m^2 had lower serum leptin than healthy subjects, while children who were overweight or obese had higher prevalence of insulin resistance, lower insulin sensitivity and higher insulin secretion than age matched overweight or obese healthy children. In lean children with systemic JIA, insulin sensitivity was not different to lean age-matched controls (167).

In JDM, a condition associated with muscle and skin inflammation, a unique adipokine profile was found, characterised by higher serum adiponectin and resistin, and lower leptin levels in young women (168). A study of 17 patients with severe JDM, found a very high prevalence of obesity and excess weight, as well as insulin resistance and hypertriglyceridaemia (169). The increased CVD-risk observed in JDM is very likely multifactorial, largely accounted for by chronic inflammation, steroid treatment and poor functional levels leading to increased weight in some patients (170).

No significant difference in the prevalence of obesity in children and adolescents with JSLE compared to healthy controls has been reported (171), although there was a positive correlation between obesity (BMI) in JSLE patients and higher serum levels of TNF-α than in healthy controls. TNF-α is a pro-inflammatory adipokine, associated with a decreased activity of lipoprotein lipase in adipose tissue. It also has a role in the early inflammatory response that contributes to atherosclerosis. Furthermore, it is associated with hyperglycaemia, insulin resistance and dyslipidaemia, mediated by inhibition of insulin receptor autophosphorylation and signal transduction (172, 173). In a small study, it has been found that the prevalence of metabolic syndrome in patients with JSLE was higher than in the healthy population (174).

Children and adolescents with T1DM also had more severe periodontal inflammation (175), which was also associated with increased BMI in young people (176). Periodontal disease is also associated with atherosclerosis risk, potentially from early in life (177). In addition, chronic conditions, such as type II DM (T2DM), RA and SLE which are recognised risk factors for CVD are also associated with periodontal disease, although the majority of studies are derived from adult populations, characterised by a higher prevalence of gum disease (178–180).

Higher prevalence of dyslipidaemia was also observed in young people with T1DM characterised by increased triglycerides and LDL-cholesterol levels, with female adolescents having lower levels of HDL-cholesterol than healthy controls (181). Children with T1DM have higher triglyceride levels, independent of pubertal stage (unlike in healthy controls where TC decreased throughout puberty) which also correlated strongly with ApoB levels (182).

Impact of sex determinants on chronic inflammation and other cardiovascular risk factors relevant to young people's health

There is a recognised female sex bias in autoimmune rheumatic diseases associated with chronic inflammation, although this is less pronounced in diseases with paediatric onset (183). This sex-bias is due to a combination of genetic and epigenetic mechanisms (184), as well as due to impact of sex determinants at the time of puberty on the disease mechanisms and risk overall (185, 186). Many of the autoimmune conditions in young people are rare diseases overall. Therefore, it is not always easy to tease apart sex differences in CVD-risk due to chronic inflammation as many cohort studies are underpowered to detect this. Although, this sex bias is less evident in T1DM (187) and has inverse trends in IBD, where there is evidence of females have a lower risk of Crohn's disease compared with males until puberty, at which point there is a reversal, with females developing higher risk over time (188), the long-term impact of increased CVD-risk in patients with chronic inflammation is less defined by sex differences, suggesting that chronic inflammation is the main driver of this risk (189). However, there is evidence that younger age is an independent factor from increased CVD-risk in patients with RA, which is one of the most prevalent and better studied inflammatory rheumatic conditions (190), suggesting that chronic inflammation rather than increase in prevalence of traditional CVD-risk factor are likely to impact cardiovascular health overall.

No post-pubertal sex differences in serum lipid levels were found between adult men and women with JSLE (93), although in female adolescents with JSLE, dyslipidaemia was more than two times more prevalent than in healthy controls, and these differences were characterised by a lower serum HDL and a higher homocysteine in JSLE cohort (191). Dyslipidaemia in JSLE was also associated with decreased smaller HDL particle subsets than in healthy controls. Active disease accentuated this difference and was further associated with higher VLDL particles when compared to JSLE patients with lower disease activity, and it was related to B- and T-cell lipid rafts, inflammation, and disturbed liver function (192). JSLE patients with active disease also had increase in ApoB:ApoA1 ratio which is a pro-atherosclerotic biomarker (192). In addition, JSLE patients with a high ApoB:ApoA1 ratio (baseline levels correlated positively to

SLE disease activity index) had increased cardiometabolic risk conferred by greater number of CD8+ T-lymphocytes and CD8+ T-lymphocyte transcriptomic profile which expressed a higher number of genes associated with interferon signalling and other processes that contribute to atherosclerosis (193).

In conclusion, while chronic inflammatory conditions in adolescents and young people are associated with an increased CVD-risk overall, this is likely driven by both traditional and non-traditional CVD-risk factors, and it is less influenced by puberty or other sex-determinants as the effect of underlying chronic inflammatory disease and treatment seem to override their impact.

Other cardiovascular risk factors relevant for young people

Role of (cross-) sex hormones, hormonal contraception, and hormone replacement therapy (HRT) on cardiovascular risk

The role of sex hormones in the development of atherosclerosis has been a point of contention. It has been suggested that sex-hormones have differential effects in either sex, although there are less published data in young people (194).

Low endogenous testosterone has been linked to increased CVD and mortality in men, suggesting an atheroprotective role in men, albeit through an unclear mechanism (195). It has also been argued however, that causation is uncertain, and low testosterone may be reflective of reduced general health status in men and thus indicative of other factors that may be directly linked to CVD-risk rather than the causative factor itself (196).

There is evidence of increased CVD-risk with oestrogen-combined oral contraceptives in women of reproductive age, in particularly the risk of venous thrombosis (2–7-fold), as well as arterial thrombosis and HP (197, 198). As a consequence, despite benefits in preventing unwanted pregnancies, as well as addressing other medical conditions common in adolescent and young females, such as menstrual irregularities, heavy menstrual bleeding, menstrual discomfort, or required to treat endometriosis, polycystic ovary syndrome, acne and ovarian cysts, combined oral contraceptives are not recommended (WHO-MEC 3) or even contraindicated (WHO-MEC4) in women with cardiac disease, increased thrombotic risk, either venous or arterial, ischaemic heart disease or HP (199).

Emergency contraception (Levonogestrel) has a small effect on blood clotting parameters and increases fibrinogen at 24 and 48 h post-dose, while being associated with a reduction in anti-thrombin III lasting from 2 to 12 h post treatment (200). However, despite these changes in laboratory parameters, there was no evidence of an increased risk of thrombosis in users of emergency contraception (201).

Large-scale studies thus far have been unable to establish a benefit of HRT for cardioprotective purposes. There is however some evidence for a benefit if treatment started immediately post-menopause, leading to the "timing hypothesis", which suggests that the type of oestrogen used and the time between the start of menopause and initiation of HRT can lead to differential cardiovascular outcomes (202). However, no data are available in younger populations as this as sex hormone therapy is very rarely warranted. The impact of cross-sex hormone therapy in young trans-sex populations is insufficiently studied (203) as there are unmet needs to involve gender-diverse people in research in medicine overall (204).

In conclusion, while associated with a small CVD-risk overall, sex hormone therapies containing oestrogen have to be used cautiously in young female populations at risk, especially as alternatives are available (progesterone only contraceptive preparations or intrauterine devices and barrier protection).

Sex differences in health-risk behaviours contributing to cardiovascular risk in young people

According to the WHO, 10% of mortality due to CVD can be attributed to cigarette smoking (205) Smoking was associated with more extensive fatty streaks and raised atherosclerotic lesions in the abdominal aorta of young people in post-mortem study (206). Inhalation of cigarette smoke, both passively and actively, increases CVD-risk, as 10% of smoking-related mortality can be attributed to passive cigarette smoking (207). Smoking increases the risk of myocardial infarction and stroke (208) and exposure to cigarette smoke affects the regulation of mechanisms responsible for the formation of intravascular thrombi, inducing a hypercoagulable state and contributing to increased risked of acute thrombotic events (208). There is a higher mortality rate in female smokers than male smokers, with female smokers being 25% more likely to develop coronary heart disease (209).

A study conducted on healthy young men and women found that CVD-risk factors occur earlier in young female smokers than male cigarette smokers (210). In women only, exposure to cigarette smoke increased monocyte and lymphocyte counts, whereas in men, neutrophils and eosinophils were significantly increased. Global DNA methylation was reduced more in women than men who smoked, while smoking increased the number of platelets in women, and decreased the number of platelets in men. Smoking also seemed to affect endothelial function in women more than in men by causing a significant increase in asymmetric dimethyl arginine (ADMA), an endogenous inhibitor of nitric oxide synthesis, and L-arginine, a precursor of nitric oxide synthesis in women only. These are both surrogate measures of endothelial dysfunction. The trans-sulphuration pathway involves interconversion of cysteine and homocysteine. The forward reaction in this pathway produces homocysteine, a recognised marker of CVD-risk (211). In the non-smoking control group, homocysteine was found to be lower in females than in males, while exposure to cigarette smoke increased homocysteine levels in women only. Smoking also eradicated the sexual dimorphism in TNF-α release from human monocyte-derived macrophages (hMDMs) as even if in non-smokers, there is a higher basal TNF-α release from hMDMs in men than in

women, the smoking increased TNF-α release in women only. Early onset of puberty associated with increased risk of smoking throughout adolescence (212).

Cigarette smoking intensity (acute smoking measured as number of cigarettes smoked per day) has been associated with increased serum concentration of biomarkers of CVD, particularly, markers of systemic inflammation, with hsCRP, being the most sensitive (213).

A large meta-analysis found a dose-dependent relationship between the number of cigarettes smoked per day, with pooled relative risk for coronary heart disease in men of 1.48 for smoking one cigarette per day and 2.04 for 20 cigarettes, while in women, the risk was 1.57 and 2.84, respectively (214).

Long-term exposure (chronic cigarette smoking), commonly assessed using smoking duration (years), or cumulative exposure (pack-years) was also associated with measures of either inflammation or subclinical atherosclerosis (215), which is relevant to adolescents, especially as cigarette smoking initiation rates during early adolescence (11–15 years) showed a marked increase after 1990 especially in West Europe, while smoking initiation during late adolescence (16–20 years) declined, with the exception of South Europe (216).

Recent research has been directed towards understanding the cardiovascular health effects of electronic vaping cigarettes (EVC) and heat-not-burn cigarettes, which are popular alternatives to traditional combustion cigarettes. An analysis of 7 systematic reviews found that acute EVC use was associated with several toxic effects, including detrimental impact on BP management, tachycardia, worsened arterial stiffness, as well as increased prevalence of atrial fibrillation and myocardial infarction, even if the causal link is still debated (217).

Adolescence is also associated with increased use of illicit substances (218), with potential devastating impact on cardiovascular health (219). Many studies investigated sex and gender differences as well as contextual factors and relationships associated with substance use and academic and health-related outcomes (220–224), highlighting the complexity of this phenomenon which cannot be simply disaggregated by sex. Significant atherosclerosis has been particularly linked to cocaine use compared to opioid use and other poor-health related factors (225). Illicit substance use is one of the main drivers of CVD in young people overall (226).

Is there any need for tailored CVD-risk strategies in young people?

There is ample evidence in the literature that puberty and adolescence are very dynamic periods in the life of young people associated with various metabolic changes and CVD-risk trends, some of which are reversable. Correct phenotyping of an individual, as well as assessment of risk over time are important strategies for managing the potential health consequences of having increased CVD-risk or subclinical atherosclerosis later in life. We would argue that certain groups of young people, especially in the context of genetic predisposition, concomitant chronic inflammatory conditions or at the time of intense vulnerability driven by physiological, socio-economic or psychological factors would benefit from tailored management strategies, irrespective of being aimed at addressing chronic inflammation, improving physical exercise or diet, or tackling health-risk associated behaviours. In addition, early identification of increased CVD-risk through improved detection strategies as well as dynamic assessment of this risk over time are likely to lead to improved outcomes. Although, there is evidence of a male bias in increased CVD-risk in young people, especially post-puberty, future research is needed to establish whether this can be addressed by sex-biased therapeutic and management strategies from early life.

Conclusions

There is an unmet need for better CVD-risk assessment and management strategies in young people overall, as although the traditional risk factors are clearly linked to subclinical atherosclerosis, there are other contributing determinants, related to pubertal changes, chronic inflammation and treatment addressing inflammation, as well as health-risk behaviours that are particularly relevant in this population. There are well documented sex differences in CVD-risk and subclinical atherosclerosis which maintain the male-biased predominance observed in the older populations; however, in the context of chronic inflammatory conditions, the upregulation of the pro-inflammatory pathways or the use of various treatments associated with metabolic effects with role in CVD-risk modulation seem to override the sex and puberty driven differences observed in the general population. Further research is needed to capture the long-term outcomes of young people with chronic inflammatory diseases and contrast them with the impact of traditional CVD-risk factors in the general population, disaggregated by sex, to give us the possibility to properly investigate whether sex and gender-tailored CVD-risk management strategies are warranted.

Author contributions

Conceptualization, CC and AA; methodology, CC and AA; investigation, AA and CC; data curation, AA and CC; writing—original draft preparation, AA and CC; writing—review and editing, all authors.; visualization, JP and CC; supervision, CC; project administration, CC and AA; funding acquisition, GR, EJ and CC. All authors contributed to the article and approved the submitted version.

Funding

This work was performed within the Centre for Adolescent Rheumatology Versus Arthritis at UCL, UCLH and GOSH supported by grants from Versus Arthritis (21593, 22856 and 20164) and NIHR UCLH Biomedical Research Centre grant BRC773/III/CC/101350. The views expressed are those of the

authors and not necessarily those of the NHS, the NIHR or the Department of Health.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. WHO. Fact Sheet: Noncommunicable diseases. (cited 2023 Jan 23). Available at: https://www.who.int/en/news-room/fact-sheets/detail/noncommunicable-diseases (2015).

2. Lusis AJ. Atherosclerosis. *Nature*. (2000) 407(6801):233. doi: 10.1038/35025203

3. Berenson GS, Srinivasan SR, Bao W, Newman WP, Tracy RE, Wattigney WA. Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults. The Bogalusa Heart Study. *N Engl J Med*. (1998) 338 (23):1650–6. doi: 10.1056/NEJM199806043382302

4. Stary HC, Chandler AB, Glagov S, Guyton JR, Insull W, Rosenfeld ME, et al. A definition of initial, fatty streak, and intermediate lesions of atherosclerosis. A report from the committee on vascular lesions of the council on arteriosclerosis, American heart association. *Circulation*. (1994) 89(5):2462–78. doi: 10.1161/01.CIR.89.5.2462

5. Stary HC. Macrophages, macrophage foam cells, and eccentric intimal thickening in the coronary arteries of young children. *Atherosclerosis*. (1987) 64(2–3):91–108. doi: 10.1016/0021-9150(87)90234-6

6. Berenson GS, Wattigney WA, Tracy RE, Newman WP, Srinivasan SR, Webber LS, et al. Atherosclerosis of the aorta and coronary arteries and cardiovascular risk factors in persons aged 6 to 30 years and studied at necropsy (the bogalusa heart study). *Am J Cardiol*. (1992) 70(9):851–8. doi: 10.1016/0002-9149(92)90726-F

7. McGill J, McMahan CA, Herderick EE, Malcom GT, Tracy RE, Jack P. Origin of atherosclerosis in childhood and adolescence. *Am J Clin Nutr*. (2000) 72(5 Suppl):1307S–15S. doi: 10.1093/ajcn/72.5.1307s

8. Del Rincón I, Polak JF, O'Leary DH, Battafarano DF, Erikson JM, Restrepo JF, et al. Systemic inflammation and cardiovascular risk factors predict rapid progression of atherosclerosis in rheumatoid arthritis. *Ann Rheum Dis*. (2015) 74 (6):1118–23. doi: 10.1136/annrheumdis-2013-205058

9. Gidding SS, Rana JS, Prendergast C, McGill H, Carr JJ, Liu K, et al. Pathobiological determinants of atherosclerosis in youth (PDAY) risk score in young adults predicts coronary artery and abdominal aorta calcium in middle age. *Circulation*. (2016) 133(2):139–46. doi: 10.1161/CIRCULATIONAHA.115.018042

10. McGill HC, McMahan CA, Zieske AW, Tracy RE, Malcom GT, Herderick EE, et al. Association of coronary heart disease risk factors with microscopic qualities of coronary atherosclerosis in youth. *Circulation*. (2000) 102(4):374–9. doi: 10.1161/01.CIR.102.4.374

11. Juonala M, Magnussen CG, Venn A, Dwyer T, Burns TL, Davis PH, et al. Influence of age on associations between childhood risk factors and carotid intima-media thickness in adulthood: the cardiovascular risk in young Finns study, the childhood determinants of adult health study, the bogalusa heart study, and the muscatine study for the international childhood cardiovascular cohort (i3C) consortium. *Circulation*. (2010) 122(24):2514–20. doi: 10.1161/CIRCULATIONAHA.110.966465

12. Henriksson P, Henriksson H, Labayen I, Huybrechts I, Gracia-Marco L, Ortega FB, et al. Correlates of ideal cardiovascular health in European adolescents: the HELENA study. *Nutr Metab Cardiovasc Dis*. (2018) 28(2):187–94. doi: 10.1016/j.numecd.2017.10.018

13. Klein SL, Flanagan KL. Sex differences in immune responses. *Nat Rev Immunol*. (2016) 16(10):626–38. doi: 10.1038/nri.2016.90

14. Obesity and Overweight Fact Sheet (2021).

15. Han JC, Lawlor DA, Kimm SY. Childhood obesity. *Lancet*. (2010) 375 (9727):1737–48. doi: 10.1016/S0140-6736(10)60171-7

16. Srinivasan SR, Myers L, Berenson GS. Predictability of childhood adiposity and insulin for developing insulin resistance syndrome (syndrome X) in young adulthood: the Bogalusa Heart Study. *Diabetes*. (2002) 51(1):204–9. doi: 10.2337/diabetes.51.1.204

17. Guo SS, Wu W, Chumlea WC, Roche AF. Predicting overweight and obesity in adulthood from body mass index values in childhood and adolescence. *Am J Clin Nutr*. (2002) 76(3):653–8. doi: 10.1093/ajcn/76.3.653

18. Dangardt F, Charakida M, Georgiopoulos G, Chiesa ST, Rapala A, Wade KH, et al. Association between fat mass through adolescence and arterial stiffness: a population-based study from the avon longitudinal study of parents and children. *Lancet Child Adolesc Health*. (2019) 3(7):474–81. doi: 10.1016/S2352-4642(19)30105-1

19. Prince RL, Kuk JL, Ambler KA, Dhaliwal J, Ball GDC. Predictors of metabolically healthy obesity in children. *Diabetes Care*. (2014) 37(5):1462–8. doi: 10.2337/dc13-1697

20. Reinehr T, Wolters B, Knop C, Lass N, Holl RW. Strong effect of pubertal Status on metabolic health in obese children: a longitudinal study. *J Clin Endocrinol Metab*. (2015) 100(1):301–8. doi: 10.1210/jc.2014-2674

21. Tobisch B, Blatniczky L, Barkai L. Cardiometabolic risk factors and insulin resistance in obese children and adolescents: relation to puberty. *Pediatr Obes*. (2015) 10(1):37–44. doi: 10.1111/j.2047-6310.2013.00202.x

22. Pilia S, Casini MR, Foschini ML, Minerba L, Musiu MC, Marras V, et al. The effect of puberty on insulin resistance in obese children. *J Endocrinol Invest*. (2009) 32(5):401–5. doi: 10.1007/BF03346475

23. He Q, Horlick M, Fedun B, Wang J, Pierson RN, Heshka S, et al. Trunk fat and blood pressure in children through puberty. *Circulation*. (2002) 105(9):1093–8. doi: 10.1161/hc0902.104706

24. Hauner H. Secretory factors from human adipose tissue and their functional role. *Proc Nutr Soc*. (2005) 64(2):163–9. doi: 10.1079/PNS2005428

25. Trayhurn P, Wood IS. Adipokines: inflammation and the pleiotropic role of white adipose tissue (2004).

26. Trayhurn P, Beattie JH. Physiological role of adipose tissue: white adipose tissue as an endocrine and secretory organ. *Proc Nutr Soc*. (2001) 60:329–39. doi: 10.1079/PNS200194

27. Despres JP. Abdominal obesity as important component of insulin-resistance syndrome. *Nutrition*. (1993) 9(5):452–9.

28. Aksglaede L, Juul A, Olsen LW, Sørensen TIA. Age at puberty and the emerging obesity epidemic. *PLoS One*. (2009) 4(12):e8450. doi: 10.1371/journal.pone.0008450

29. De Leonibus C, Marcovecchio ML, Chiavaroli V, De Giorgis T, Chiarelli F, Mohn A. Timing of puberty and physical growth in obese children: a longitudinal study in boys and girls. *Pediatr Obes*. (2014) 9(4):292–9. doi: 10.1111/j.2047-6310.2013.00176.x

30. Rosenfield RL, Lipton RB, Drum ML. Thelarche, pubarche, and menarche attainment in children with normal and elevated body mass index. *Pediatrics*. (2009) 123(1):84–8. doi: 10.1542/peds.2008-0146

31. Bandini LG, Must A, Naumova EN, Anderson SE, Caprio S, Spadano-Gasbarro JL, et al. Change in leptin, body composition and other hormones around menarche—a visual representation. *Acta Paediatr*. (2008) 97(10):1454–9. doi: 10.1111/j.1651-2227.2008.00948.x

32. Matkovic V, Ilich JZ, Skugor M, Badenhop NE, Goel P, Clairmont A, et al. Leptin is inversely related to age at menarche in human females. *J Clin Endocrinol Metab*. (1997) 82(10):3239–45.

33. Ellis KJ, Nicolson M. Leptin levels and body fatness in children: effects of gender, ethnicity, and sexual development. *Pediatr Res*. (1997) 42(4):484–8. doi: 10.1203/00006450-199710000-00010

34. Ahmed ML, Ong KKL, Morrell DJ, Cox L, Drayer N, Perry L, et al. Longitudinal study of leptin concentrations during puberty: sex differences and relationship to changes in body composition. *J Clin Endocrinol Metab*. (1999) 84(3):899–905.

35. Arslanian S, Suprasongsin C, Kalhan SC, Drash AL, Brna R, Janosky JE. Plasma leptin in children: relationship to puberty, gender, body composition, insulin sensitivity, and energy expenditure. *Metab Clin Exp*. (1998) 47(3):309–12. doi: 10.1016/S0026-0495(98)90262-1

36. Nokoff N, Thurston J, Hilkin A, Pyle L, Zeitler PS, Nadeau KJ, et al. Sex differences in effects of obesity on reproductive hormones and glucose metabolism

in early puberty. *J Clin Endocrinol Metab*. (2019) 104:4390–7. doi: 10.1210/jc.2018-02747

37. Moriarty-Kelsey M, Harwood JEF, Travers SH, Zeitler PS, Nadeau KJ. Testosterone, obesity and insulin resistance in young males: evidence for an association between gonadal dysfunction and insulin resistance during puberty. *J Pediatr Endocrinol Metab*. (2010) 23(12):1281–7. doi: 10.1515/jpem.2010.202

38. Rosenfield RL, Bordini B. Evidence that obesity and androgens have independent and opposing effects on gonadotropin production from puberty to maturity. *Brain Res*. (2010) 1364:186–97. doi: 10.1016/j.brainres.2010.08.088

39. Lakshman R, Forouhi NG, Sharp SJ, Luben R, Bingham SA, Khaw KT, et al. Early age at menarche associated with cardiovascular disease and mortality. *J Clin Endocrinol Metab*. (2009) 94(12):4953–60. doi: 10.1210/jc.2009-1789

40. Jacobsen BK, Oda K, Knutsen SF, Fraser GE. Age at menarche, total mortality and mortality from ischaemic heart disease and stroke: the adventist health study, 1976-88. *Int J Epidemiol*. (2009) 38(1):245–52. doi: 10.1093/ije/dyn251

41. Vihko R, Apter D. Endocrine characteristics of adolescent menstrual cycles: impact of early menarche. *J Steroid Biochem*. (1984) 20(1):231–6. doi: 10.1016/0022-4731(84)90209-7

42. Apter D, Reinilä M, Vihko R. Some endocrine characteristics of early menarche, a risk factor for breast cancer, are preserved into adulthood. *Int J Cancer*. (1989) 44 (5):783–7. doi: 10.1002/ijc.2910440506

43. Apter D, Bolton NJ, Hammond GL, Vihko R. Serum sex hormone-binding globulin during puberty in girls and in different types of adolescent menstrual cycles. *Acta Endocrinol (Copenh)*. (1984) 107(3):413–9.

44. Kim Y, Je Y. Early menarche and risk of metabolic syndrome: a systematic review and meta-analysis. *J Womens Health*. (2019) 28(1):77–86. doi: 10.1089/jwh.2018.6998

45. He C, Zhang C, Hunter DJ, Hankinson SE, Buck Louis GM, Hediger ML, et al. Age at menarche and risk of type 2 diabetes: results from 2 large prospective cohort studies. *Am J Epidemiol*. (2009) 171(3):334–44. doi: 10.1093/aje/kwp372

46. Ding EL, Song Y, Malik VS, Liu S. Sex differences of endogenous sex hormones and risk of type 2 diabetes: a systematic review and meta-analysis. *JAMA*. (2006) 295 (11):1288–99. doi: 10.1001/jama.295.11.1288

47. Toprak S, Yönem A, Çakir B, Güler S, Azal Ö, Özata M, et al. Insulin resistance in nonobese patients with polycystic ovary syndrome. *Horm Res*. (2001) 55(2):65–70.

48. Oh JY, Barrett-Connor E, Wedick NM, Wingard DL. Endogenous sex hormones and the development of type 2 diabetes in older men and women: the rancho bernardo study. *Diabetes Care*. (2002) 25(1):55–60. doi: 10.2337/diacare.25.1.55

49. Kozieł S, Malina RM. Variation in relative fat distribution associated with maturational timing: the wrocław growth study. *Ann Hum Biol*. (2009) 32(6):691–701. http://dx.doi.org/101080/03014460500268531

50. Ruiz JR, Ortega FB, Tresaco B, Wärnberg J, Mesa JL, González-Gross M, et al. Serum lipids, body mass index and waist circumference during pubertal development in spanish adolescents: the AVENA study. *Horm Metab Res*. (2006) 38(12):832–7. doi: 10.1055/s-2006-956503

51. Asghari G, Mirmiran P, Rezaeemanesh A, Mahdavi M, Azizi F, Hadaegh F. Changes in ideal cardiovascular health among Iranian adolescents: 2007-2008 to 2015-2017. *BMC Pediatr*. (2022) 22(1):450. doi: 10.1186/s12887-022-03504-x

52. Siervogel RM, Maynard LM, Wisemandle WA, Roche AF, Guo SS, Chumlea WC, et al. Annual changes in total body fat and fat-free mass in children from 8 to 18 years in relation to changes in body mass Index: the fels longitudinal study. *Ann N Y Acad Sci*. (2000) 904(1):420–3. doi: 10.1111/j.1749-6632.2000.tb06494.x

53. Martos-Moreno GÁ, Barrios V, Argente J. Normative data for adiponectin, resistin, interleukin 6, and leptin/receptor ratio in a healthy spanish pediatric population: relationship with sex steroids. *Eur J Endocrinol*. (2006) 155(3):429–34. doi: 10.1530/eje.1.02227

54. Tam CS, Garnett SP, Cowell CT, Heilbronn LK, Lee JW, Wong M, et al. IL-6, IL-8 and IL-10 levels in healthy weight and overweight children. *Horm Res Paediatr*. (2010) 73(2):128–34. doi: 10.1159/000277632

55. Nishizawa H, Shimomura L, Kishida K, Maeda N, Kuriyama H, Nagaretani H, et al. Androgens decrease plasma adiponectin, an insulin-sensitizing adipocyte-derived protein. *Diabetes*. (2002) 51(9):2734–41. doi: 10.2337/diabetes.51.9.2734

56. Demerath EW, Towne B, Wisemandle W, Blangero J, Chumlea WC, Siervogel RM. Serum leptin concentration, body composition, and gonadal hormones during puberty. *Int J Obes Relat Metab Disord*. (1999) 23(7):678–85. doi: 10.1038/sj.ijo.0800902

57. Jockenhövel F, Blum WF, Vogel E, Englaro P, Müller-Wieland D, Reinwein D, et al. Testosterone substitution normalizes elevated serum leptin levels in hypogonadal men. *J Clin Endocrinol Metab*. (1997) 82(8):2510–3. doi: 10.1210/jcem.82.8.4174

58. Saputri NKD, Sidiartha IGLS, Utama IMGDL Correlation between interleukin-6 serum and hepcidin serum in obese children. *Am J Pediatr*. (2020) 6(1):27–30. doi: 10.11648/j.ajp.20200601.14

59. Maher GM, Ryan L, McCarthy FP, Hughes A, Park C, Fraser A, et al. Puberty timing and markers of cardiovascular structure and function at 25 years: a prospective cohort study. *BMC Med*. (2021) 19(1):78. doi: 10.1186/s12916-021-01949-y

60. Kimm SYS, Barton BA, Obarzanek E, McMahon RP, Kronsberg SS, Waclawiw MA, et al. Obesity development during adolescence in a biracial cohort: the NHLBI growth and health study. *Pediatrics*. (2002 Nov 1) 110(5):e54–e54. doi: 10.1542/peds.110.5.e54

61. Lassek WD, Gaulin SJC. Brief communication: menarche is related to fat distribution. *Am J Phys Anthropol*. (2007) 133(4):1147–51. doi: 10.1002/ajpa.20644

62. Bhadra M, Mukhopadhyay A, Chakraborty R, Bose K, Koziel S, Ulijaszek S. Relative fat distribution in relation to menarcheal status among bengalee hindu girls of West Bengal, India. *J Nat Sci Biol Med*. (2013) 4(2):369–73. doi: 10.4103/0976-9668.116997

63. Roemmich JN, Rogol AD. Hormonal changes during puberty and their relationship to fat distribution. *J Hum Biol*. (1999) 11:209–24. doi: 10.1002/(SICI)1520-6300(1999)11:2<209::AID-AJHB9>3.0.CO;2-G

64. Frontini MG, Srinivasan SR, Berenson GS. Longitudinal changes in risk variables underlying metabolic syndrome X from childhood to young adulthood in female subjects with a history of early menarche: the bogalusa heart study. *Int J Obes Relat Metab Disord*. (2003) 27(11):1398–404. doi: 10.1038/sj.ijo.0802422

65. Palmer BF, Clegg DJ. The sexual dimorphism of obesity. *Mol Cell Endocrinol*. (2015) 402:113–9. doi: 10.1016/j.mce.2014.11.029

66. Lovejoy JC, Champagne CM, De Jonge L, Xie H, Smith SR. Increased visceral fat and decreased energy expenditure during the menopausal transition. *Int J Obes*. (2008) 32:949–58. doi: 10.1038/ijo.2008.25

67. Ramirez ME, McMurry MP, Wiebke GA, Felten KJ, Ren K, Meikle AW, et al. Evidence for sex steroid inhibition of lipoprotein lipase in men: comparison of abdominal and femoral adipose tissue. *Metab Clin Exp*. (1997) 46(2):179–85. doi: 10.1016/S0026-0495(97)90299-7

68. Arner P, Lithell H, Wahrenberg H, Bronnegard M. Expression of lipoprotein lipase in different human subcutaneous adipose tissue regions. *J Lipid Res*. (1991) 32(3):423–9. doi: 10.1016/S0022-2275(20)42065-6

69. Pedersen SB, Kristensen K, Hermann PA, Katzenellenbogen JA, Richelsen B. Estrogen controls lipolysis by up-regulating α2A-adrenergic receptors directly in human adipose tissue through the estrogen receptor α. Implications for the female fat distribution. *J Clin Endocrinol Metab*. (2004) 89(4):1869–78. doi: 10.1210/jc.2003-031327

70. Gavin KM, Cooper EE, Raymer DK, Hickner RC. Estradiol effects on subcutaneous adipose tissue lipolysis in premenopausal women are adipose tissue depot specific and treatment dependent. *Am J Physiol Endocrinol Metab*. (2013) 304 (11):1167–74. doi: 10.1152/ajpendo.00023.2013

71. Caprio S, Perry R, Kursawe R. Adolescent obesity and insulin resistance: roles of ectopic fat accumulation and adipose inflammation. *Gastroenterology*. (2017) 152(7): P1638–46. doi: 10.1053/j.gastro.2016.12.051

72. Raji A, Seely EW, Arky RA, Simonson DC. Body fat distribution and insulin resistance in healthy Asian Indians and caucasians. *J Clin Endocrinol Metab*. (2001) 86(11):5366–71. doi: 10.1210/jcem.86.11.7992

73. Shulman GI. Ectopic fat in insulin resistance, dyslipidemia, and cardiometabolic disease. *N Engl J Med*. (2014) 12(18):1131–72. doi: 10.1056/NEJMra1011035

74. Van Pelt RE, Evans EM, Schechtman KB, Ehsani AA, Kohrt WM. Contributions of total and regional fat mass to risk for cardiovascular disease in older women. *Am J Physiol - Endocrinol Metab*. (2002) 282(5):45–5. doi: https://doi.org/101152/ajpendo004672001

75. Meigs JB, Tracy RP. Invited commentary: insulin resistance syndrome? Syndrome X? Multiple metabolic syndrome? A syndrome at all? Factor analysis reveals patterns in the fabric of correlated metabolic risk factors. *Am J Epidemiol*. (2000) 152(10):908–12. doi: 10.1093/aje/152.10.908

76. Fraser A, Tilling K, Macdonald-Wallis C, Sattar N, Brion MJ, Benfield L, et al. Epidemiology and Prevention Association of Maternal Weight Gain in Pregnancy With Offspring Obesity and Metabolic and Vascular Traits in Childhood (2010).

77. Goodman E, Daniels SR, Meigs JB, Dolan LM. Instability in the diagnosis of metabolic syndrome in adolescents. *Circulation*. (2007) 115(17):2316–22. doi: 10.1161/CIRCULATIONAHA.106.669994

78. Gustafson JK, Yanoff LB, Easter BD, Brady SM, Keil MF, Roberts MD, et al. The stability of metabolic syndrome in children and adolescents. *J Clin Endocrinol Metab*. (2009) 94(12):4828–34. doi: 10.1210/jc.2008-2665

79. Miller JM, Kaylor MB, Johannsson M, Bay C, Churilla JR. Prevalence of metabolic syndrome and individual criterion in US adolescents: 2001–2010 national health and nutrition examination survey. *Metab Syndr Relat Disord*. (2014) 12 (10):527–32. https://home.liebertpub.com/met. doi: 10.1089/met.2014.0055

80. Rochlani Y, Pothineni NV, Mehta JL. Metabolic syndrome: does it differ between women and men? *Cardiovasc Drugs Ther*. (2015) 29(4):329–38. doi: 10.1007/s10557-015-6593-6

81. Juonala M, Ellul S, Lawlor DA, Santos Ferreira DL, Carlin JB, Cheung M, et al. A cross-cohort study examining the associations of metabolomic profile and subclinical atherosclerosis in children and their parents: the child health CheckPoint study and avon longitudinal study of parents and children. *J Am Heart Assoc*. (2019) 8(14): e011852–e011852. doi: 10.1161/JAHA.118.011852

82. Cook S, Weitzman M, Auinger P, Nguyen M, Dietz WH. Prevalence of a metabolic syndrome phenotype in adolescents: findings from the third national health and nutrition examination survey, 1988-1994. *Arch Pediatr Adolesc Med*. (2003) 157(8):821–7. doi: 10.1001/archpedi.157.8.821

83. McGill HC, McMahan CA, Malcom GT, Oalmann MC, Strong JP. Relation of glycohemoglobin and adiposity to atherosclerosis in youth. Pathobiological determinants of atherosclerosis in youth (PDAY) research group. *Arterioscler Thromb Vasc Biol*. (1995) 15(4):431–40. doi: 10.1161/01.ATV.15.4.431

84. Aldhoon-Hainerová I, Zamrazilová H, Dušátková L, Sedláčková B, Hlavatý P, Hill M, et al. Glucose homeostasis and insulin resistance: prevalence, gender differences and predictors in adolescents. *Diabetol Metab Syndr*. (2014) 6(1):100. doi: 10.1186/1758-5996-6-100

85. Moran A, Jacobs DR, Steinberger J, Hong CP, Prineas R, Luepker R, et al. Insulin resistance during puberty: results from clamp studies in 357 children. *Diabetes*. (1999) 48(10):2039–44. doi: 10.2337/diabetes.48.10.2039

86. Potau N, Ibañez L, Riqué S, Carrascosa A. Pubertal changes in insulin secretion and peripheral insulin sensitivity. *Horm Res*. (1997) 48(5):219–26. doi: 10.1159/000185519

87. Goran MI, Gower BA. Longitudinal study on pubertal insulin resistance. *Diabetes*. (2001) 50(11):2444–50. doi: 10.2337/diabetes.50.11.2444

88. Tsai EC, Matsumoto AM, Fujimoto WY, Boyko EJ. Association of bioavailable, free, and total testosterone with insulin resistance: influence of sex hormone-binding globulin and body fat. *Diabetes Care*. (2004) 27(4):861–8. doi: 10.2337/diacare.27.4.861

89. Ding EL, Song Y, Manson JE, Rifai N, Buring JE, Liu S. Plasma sex steroid hormones and risk of developing type 2 diabetes in women: a prospective study. *Diabetologia*. (2007) 50(10):2076–84. doi: 10.1007/s00125-007-0785-y

90. Burlutskaya AV, Tril VE, Polischuk LV, Pokrovskii VM. Dyslipidemia in pediatrician's practice. *Rev Cardiovasc Med*. (2021) 22(3):817–34. doi: 10.31083/j.rcm2203088

91. Zimmet P, Alberti G, Kaufman F, Tajima N, Silink M, Arslanian S, et al. The metabolic syndrome in children and adolescents. *Lancet*. (2007) 369(9579):2059–61. doi: 10.1016/S0140-6736(07)60958-1

92. Freedman DS, Otvos JD, Jeyarajah EJ, Shalaurova I, Cupples A, Parise H, et al. Sex and age differences in lipoprotein subclasses measured by nuclear magnetic resonance spectroscopy: the framingham study. *Clin Chem*. (2004) 50(7):1189–200. doi: 10.1373/clinchem.2004.032763

93. Robinson GA, Peng J, Peckham H, Pineda-Torra I, Jury EC. Sex hormones drive changes in lipoprotein metabolism (2021).

94. Della Torre S, Mitro N, Fontana R, Gomaraschi M, Favari E, Recordati C, et al. An essential role for liver ERα in coupling hepatic metabolism to the reproductive cycle. *Cell Rep*. (2016) 15(2):360–71. doi: 10.1016/j.celrep.2016.03.019

95. van Velzen DM, Adorni MP, Zimetti F, Strazzella A, Simsek S, Sirtori CR, et al. The effect of transgender hormonal treatment on high density lipoprotein cholesterol efflux capacity. *Atherosclerosis*. (2021) 323:44–53. doi: 10.1016/j.atherosclerosis.2021.03.008

96. Roeters Van Lennep JE, Westerveld HT, Erkelens DW, Van Der Wall EE. Risk factors for coronary heart disease: implications of gender. *Cardiovasc Res*. (2002) 53(3):538–49. doi: 10.1016/S0008-6363(01)00388-1

97. Tan CE, Forster L, Caslake MJ, Bedford D, Watson TDG, McConnell M, et al. Relations between plasma lipids and postheparin plasma lipases and VLDL and LDL subfraction patterns in normolipemic men and women. *Arterioscler Thromb Vasc Biol*. (1995) 15(11):1839–48. doi: 10.1161/01.ATV.15.11.1839

98. Campos H, Blijlevens E, McNamara JR, Ordovas JM, Posner BM, Wilson PWF, et al. LDL Particle size distribution. Results from the framingham offspring study. *Arterioscler Thromb*. (1992) 12(12):1410–9. doi: 10.1161/01.ATV.12.12.1410

99. McNamara JR, Campos H, Ordovas JM, Peterson J, Wilson PW, Schaefer EJ. Effect of gender, age, and lipid status on low density lipoprotein subfraction distribution. Results from the framingham offspring study. *Arteriosclerosis*. (1987) 7(5):483–90. doi: 10.1161/01.ATV.7.5.483

100. Freedman DS, Bowman BA, Srinivasan SR, Berenson GS, Otvos JD. Distribution and correlates of high-density lipoprotein subclasses among children and adolescents. *Metab Clin Exp*. (2001) 50(3):370–6. doi: 10.1053/meta.2001.21027

101. Eissa MA, Mihalopoulos NL, Holubkov R, Dai S, Labarthe DR. Changes in fasting lipids during puberty. *J Pediatr*. (2016) 170:199–205. doi: 10.1016/j.jpeds.2015.11.018

102. Hilliard LM, Sampson AK, Brown RD, Denton KM. The "his and hers" of the renin-angiotensin system. *Curr Hypertens Rep*. (2013) 15(1):71–9. doi: 10.1007/s11906-012-0319-y

103. Flynn J, Zhang Y, Solar-Yohay S, Shi V. Clinical and demographic characteristics of children with hypertension. *Hypertension*. (2012) 60(4):1047–54. doi: 10.1161/HYPERTENSIONAHA.112.197525

104. Ashraf M, Irshad M, Parry NA. Pediatric hypertension: an updated review. *Clin Hypertens*. (2020) 26(1):22. doi: 10.1186/s40885-020-00156-w

105. Bell CS, Samuel JP, Samuels JA. Prevalence of hypertension in children. *Hypertension*. (2019) 73(1):148–52. doi: 10.1161/HYPERTENSIONAHA.118.11673

106. Edvardsson VO, Steinthorsdottir SD, Eliasdottir SB, Indridason OS, Palsson R. Birth weight and childhood blood pressure. *Curr Hypertens Rep*. (2012) 14(6):596–602. doi: 10.1007/s11906-012-0311-6

107. Weres A, Baran J, Czenczek-Lewandowska E, Leszczak J, Mazur A. Impact of birth weight and length on primary hypertension in children. *Int J Environ Res Public Health*. (2019) 16(23):4649. doi: 10.3390/ijerph16234649

108. Wojcik M, Starzyk JB, Drozdz M, Drozdz D. Effects of puberty on blood pressure trajectories—underlying processes. *Curr Hypertens Rep*. (2023) 25(7):117–25. doi: 10.1007/s11906-023-01241-9

109. O'Neill KN, Bell JA, Davey Smith G, Tilling K, Kearney PM, O'Keeffe LM. Puberty timing and sex-specific trajectories of systolic blood pressure: a prospective cohort study. *Hypertension*. (2022) 79(8):1755–64. doi: 10.1161/HYPERTENSIONAHA.121.18531

110. Colafella KMM, Denton KM. Sex-specific differences in hypertension and associated cardiovascular disease. *Nat Rev Nephrol*. (2018) 14(3):185–201. doi: 10.1038/nrneph.2017.189

111. Pilote L, Dasgupta K, Guru V, Humphries KH, McGrath J, Norris C, et al. A comprehensive view of sex-specific issues related to cardiovascular disease. *CMAJ*. (2007) 176(6):S1–44. doi: 10.1503/cmaj.051455

112. Kent AL, Kecskes Z, Shadbolt B, Falk MC. Normative blood pressure data in the early neonatal period. *Pediatr Nephrol*. (2007) 22(9):1335–41. doi: 10.1007/s00467-007-0480-8

113. Flynn JT, Daniels SR, Hayman LL, Maahs DM, McCrindle BW, Mitsnefes M, et al. Update: ambulatory blood pressure monitoring in children and adolescents: a scientific statement from the American heart association. *Hypertension*. (2014) 63(5):1116–35. doi: 10.1161/HYP.0000000000000007

114. Shen W, Zhang T, Li S, Zhang H, Xi B, Shen H, et al. Race and sex differences of long-term blood pressure profiles from childhood and adult hypertension: the bogalusa heart study. *Hypertension*. (2017) 70(1):66–74. doi: 10.1161/HYPERTENSIONAHA.117.09537

115. Cadeddu C, Franconi F, Cassisa L, Campesi I, Pepe A, Cugusi L, et al. Arterial hypertension in the female world: pathophysiology and therapy. *J Cardiovasc Med*. (2016) 17(4):229–36. doi: 10.2459/JCM.0000000000000315

116. Dubey RK, Oparil S, Imthurn B, Jackson EK. Sex hormones and hypertension. *Cardiovasc Res*. (2002) 53(3):688–708. doi: 10.1016/S0008-6363(01)00527-2

117. Butkevich A, Abraham C, Phillips RA. Hormone replacement therapy and 24-hour blood pressure profile of postmenopausal women. *Am J Hypertens*. (2000) 13(9):1039–41. doi: 10.1016/S0895-7061(00)00284-3

118. Cacciatore B, Paakkari I, Hasselblatt R, Nieminen MS, Toivonen J, Tikkanen MI, et al. Randomized comparison between orally and transdermally administered hormone replacement therapy regimens of long-term effects on 24-hour ambulatory blood pressure in postmenopausal women. *Am J Obstet Gynecol*. (2001) 184(5):904–9. doi: 10.1067/mob.2001.111246

119. Szekacs B, Vajo Z, Acs N, Hada P, Csuzi L, Bezeredi J, et al. Hormone replacement therapy reduces mean 24-hour blood pressure and its variability in postmenopausal women with treated hypertension. *Menopause*. (2000) 7(1):31–5. doi: 10.1097/00042192-200007010-00006

120. Crane MG, Harris JJ, Winsor W. Hypertension, oral contraceptive agents, and conjugated estrogens. *Ann Intern Med*. (1971) 74(1):13–21. doi: 10.7326/0003-4819-74-1-13

121. Notelovitz M. Effect of Natural Oestrogens on Blood Pressure and Weight in Postmenopausal Women.

122. Utian WH. Effect of postmenopausal estrogen therapy on diastolic blood pressure and bodyweight. *Maturitas*. (1978) 1(1):3–8. doi: 10.1016/0378-5122(78)90003-8

123. Karalis I, Beevers DG, Beevers M, Lip GYH. Hormone replacement therapy and arterial blood pressure in postmenopausal women with hypertension. *Blood Press*. (2005) 14(1):38–44. doi: 10.1080/08037050510008788

124. Schunkert H, Jan Danser AH, Hense HW, Derkx FHM, Kürzinger S, Riegger GAJ. Effects of estrogen replacement therapy on the renin-angiotensin system in postmenopausal women. *Circulation*. (1997) 95(1):39–45. doi: 10.1161/01.CIR.95.1.39

125. Ashraf MS, Vongpatanasin W. Estrogen and hypertension. *Curr Hypertens Rep*. (2006) 8(5):368–76. doi: 10.1007/s11906-006-0080-1

126. Klett C, Ganten D, Hellmann W, Kaling M, Ryffel GU, Weimar-Ehl T, et al. Regulation of hepatic angiotensinogen synthesis and secretion by steroid hormones. *Endocrinology*. (1992) 130(6):3660–8. doi: 10.1210/endo.130.6.1597163

127. Brosnihan KB, Hodgin JB, Smithies O, Maeda N, Gallagher P. Tissue-specific regulation of ACE/ACE2 and AT1/AT2 receptor gene expression by oestrogen in apolipoprotein E/oestrogen receptor-α knock-out mice. *Exp Physiol*. (2008) 93(5):658–64. doi: 10.1113/expphysiol.2007.041806

128. Mendelsohn ME, Karas RH. The protective effects of estrogen on the cardiovascular system. *NEMJ*. (1999) 340(23):1801–11. doi: https://doi.org/101056/NEJM199906103402306

129. Pasqualini C, Leviel V, Guibert B, Faucon-Biguet N, Kerdelhué B. Inhibitory actions of acute estradiol treatment on the activity and quantity of tyrosine hydroxylase in the median eminence of ovariectomized rats. *J Neuroendocrinol*. (1991) 3(5):575–80. doi: 10.1111/j.1365-2826.1991.tb00319.x

130. Ylikorkala O, Orpana A, Puolakka J, Pyörälä T, Viinikka L. Postmenopausal hormonal replacement decreases plasma levels of endothelin-1. *J Clin Endocrinol Metab*. (1995) 80(11):3384–7.

131. Yanagisawa M, Kurihara H, Kimura S, Tomobe Y, Kobayashi M, Mitsui Y, et al. A novel potent vasoconstrictor peptide produced by vascular endothelial cells. *Nature*. (1988) 332(6163):411–5. doi: 10.1038/332411a0

132. Akishita M, Ouchi Y, Miyoshi H, Orimo A, Kozaki K, Eto M, et al. Estrogen inhibits endothelin-1 production and c-fos gene expression in rat aorta. *Atherosclerosis*. (1996) 125(1):27–38. doi: 10.1016/0021-9150(96)05836-4

133. Tan Z, Wang TH, Yang D, Fu XD, Pan JY. Mechanisms of 17β-estradiol on the production of ET-1 in ovariectomized rats. *Life Sci*. (2003) 73(21):2665–74. doi: 10.1016/S0024-3205(03)00605-2

134. Rodrigo MC, Martin DS, Eyster KM. Vascular ECE-1 mRNA expression decreases in response to estrogens. *Life Sci*. (2003) 73(23):2973–83. doi: 10.1016/j.lfs.2003.05.001

135. Akishita M, Kozaki K, Eto M, Yoshizumi M, Ishikawa M, Toba K, et al. Estrogen attenuates endothelin-1 production by bovine endothelial cells via estrogen receptor. *Biochem Biophys Res Commun*. (1998) 251(1):17–21. doi: 10.1006/bbrc.1998.9409

136. Hong HJ, Liu JC, Chan P, Juan SH, Loh SH, Lin JG, et al. 17beta-estradiol Downregulates angiotensin-II-induced endothelin-1 gene expression in rat aortic smooth muscle cells. *J Biomed Sci*. (2004) 11(1):27–36.

137. Chao HH, Chen JJ, Chen CH, Lin H, Cheng CF, Lian WS, et al. Inhibition of angiotensin II induced endothelin-1 gene expression by 17-β-oestradiol in rat cardiac fibroblasts. *Heart*. (2005) 91(5):664–9. doi: 10.1136/hrt.2003.031898

138. Polderman KH, Stehouwer CDA, Van Kamp GJ, Dekker GA, Verheugt FWA, Gooren LJG. Influence of sex hormones on plasma endothelin levels. *Ann Intern Med*. (1993) 118(6):429–32. doi: 10.7326/0003-4819-118-6-199303150-00006

139. Van Kesteren PJM, Kooistra T, Lansink M, Van Kamp GJ, Asscheman H, Gooren LJG, et al. The effects of sex steroids on plasma levels of marker proteins of endothelial cell functioning. *Thromb Haemost*. (1998) 79(5):1029–33. doi: 10.1055/s-0037-1615115

140. Sampson AK, Jennings GLR, Chin-Dusting JPF. Y are males so difficult to understand?: a case where "x" does not mark the spot. *Hypertension*. (2012) 59(3):525–31. doi: 10.1161/HYPERTENSIONAHA.111.187880

141. Sullivan JC. Sex and the renin-angiotensin system: inequality between the sexes in response to RAS stimulation and inhibition. *Am J Physiol Regul Integr Comp Physiol*. (2008) 294(4):1220–6. doi: https://doi.org/101152/ajpregu008642007

142. Ely D, Liu B. Testosterone increases: sodium reabsorption, blood pressure, and renal pathology in female spontaneously hypertensive rats on a high sodium diet. *Adv Pharmacol Sci*. (2011) 2011:817835. doi: 10.1155/2011/817835

143. Sampson AK, Moritz KM, Denton KM. Postnatal ontogeny of angiotensin receptors and ACE2 in male and female rats. *Gend Med*. (2012) 9(1):21–32. doi: 10.1016/j.genm.2011.12.003

144. Silva-Antonialli MM, Tostes RCA, Fernandes L, Fior-Chadi DR, Akamine EH, Carvalho MHC, et al. A lower ratio of AT1/AT2 receptors of angiotensin II is found in female than in male spontaneously hypertensive rats. *Cardiovasc Res*. (2004) 62(3):587–93. doi: 10.1016/j.cardiores.2004.01.020

145. Cutler JA, Sorlie PD, Wolz M, Thom T, Fields LE, Roccella EJ. Trends in hypertension prevalence, awareness, treatment, and control rates in United States adults between 1988 and 1994 and 1999-2004. *Hypertension*. (2008) 52(5):818–27. doi: 10.1161/HYPERTENSIONAHA.108.113357

146. Everett B, Zajacova A. Gender differences in hypertension and hypertension awareness among young adults. *Biodemography Soc Biol*. (2015) 61(1):1–17. doi: 10.1080/19485565.2014.929488

147. Gilardini L, Pasqualinotto L, Di Matteo S, Caffetto K, Croci M, Girola A, et al. Factors associated with early atherosclerosis and arterial calcifications in young subjects with a benign phenotype of obesity. *Obesity*. (2011) 19(8):1684–9. doi: 10.1038/oby.2010.342

148. McGill HC, Alex McMahan C, Tracy RE, Oalmann MC, Frederick Cornhill J, Herderick EE, et al. Relation of a postmortem renal Index of hypertension to atherosclerosis and coronary artery size in young men and women. *Arterioscler Thromb Vasc Biol*. (1998) 18(7):1108–18. doi: 10.1161/01.ATV.18.7.1108

149. Muller M, Van Den Beld AW, Bots ML, Grobbee DE, Lamberts SWJ, Van Der Schouw YT. Endogenous sex hormones and progression of carotid atherosclerosis in elderly men. *Circulation*. (2004) 109(17):2074–9. doi: 10.1161/01.CIR.0000125854.51637.06

150. Robinson G, Pineda-Torra I, Ciurtin C, Jury EC. Lipid metabolism in autoimmune rheumatic disease: implications for modern and conventional therapies. *J Clin Invest*. (2022) 132(2):e148552. doi: 10.1172/JCI148552

151. Jones A, Cotton A, Guinto J, Wilton J, Ciurtin C. Outcome measures of disease activity for rare autoimmune rheumatic diseases. *Br J Hosp Med*. (2018) 79(7):396–401. doi: 10.12968/hmed.2018.79.7.396

152. Brown GA, Cotton A, Guinto J, Sharma A, Ciurtin C. Outcome measures of disease activity in inflammatory arthritis. *Br J Hosp Med*. (2017) 78(8):432–7. doi: 10.12968/hmed.2017.78.8.432

153. Van Andel EM, Koopmann BDM, Crouwel F, Noomen CG, de Boer NKH, van Asseldonk DP, et al. Systematic review of development and content validity of patient-reported outcome measures in inflammatory bowel disease: do we measure what we measure? *J Crohn's Colitis*. (2020) 14(9):1299–315. doi: 10.1093/ecco-jcc/jjaa057

154. Smith EMD, Aggarwal A, Ainsworth J, Al-Abadi E, Avcin T, Bortey L, et al. Towards development of treat to target (T2T) in childhood-onset systemic lupus erythematosus: pReS-endorsed overarching principles and points-to-consider from an international task force. *Ann Rheum Dis*. (2023) 82(6):788–98. doi: 10.1136/ard-2022-223328

155. Collison J. Treat-to-target possible for JIA. *Nat Rev Rheumatol*. (2018) 14(12):684. doi: 10.1038/s41584-018-0119-0

156. Nimri R, Lebenthal Y, Shalitin S, Benzaquen H, Demol S, Phillip M. Metabolic control by insulin detemir in basal-bolus therapy: treat-to-target study in children and adolescents with type 1 diabetes. *Pediatr Diabetes*. (2013) 14(3):196–202. doi: 10.1111/pedi.12012

157. Ciurtin C, Robinson GA, Pineda-Torra I, Jury EC. Challenges in implementing cardiovascular risk scores for assessment of young people with childhood-onset autoimmune rheumatic conditions. *Front Med (Lausanne)*. (2022) 9:814905. doi: 10.3389/fmed.2022.814905

158. Ciurtin C, Robinson GA, Pineda-Torra I, Jury EC. Comorbidity in young patients with juvenile systemic lupus erythematosus: how can we improve management? *Clin Rheumatol*. (2022) 41(4):961–4. doi: 10.1007/s10067-022-06093-3

159. Zonana-Nacach A, Barr SG, Magder LS, Petri M. Damage in systemic lupus erythematosus and its association with corticosteroids. *Arthritis Rheumatol*. (2000) 43(8):1801–8. doi: 10.1002/1529-0131(200008)43:8<1801::AID-ANR16>3.0.CO;2-O

160. Głowińska-Olszewska B, Bossowski A, Dobreńko E, Hryniewicz A, Konstantynowicz J, Milewski R, et al. Subclinical cardiovascular system changes in obese patients with juvenile idiopathic arthritis. *Mediators Inflamm*. (2013) 2013:436702. doi: 10.1155/2013/436702

161. Amine B, Ibn Yacoub Y, Rostom S, Hajjaj-Hassouni N. Prevalence of overweight among Moroccan children and adolescents with juvenile idiopathic arthritis. *Joint Bone Spine*. (2011) 78(6):584–6. doi: 10.1016/j.jbspin.2011.02.001

162. Głowińska-Olszewska B, Dobreńko E, Hryniewicz A, Tołwińska J, Żelazowska-Rutkowska B, Wojciuk M, et al. Influence of obesity on the early atherosclerosis in children with juvenile idiopathic arthritis. *Reumatologia/Rheumatology*. (2011) 49(4):231–8.

163. Schenck S, Niewerth M, Sengler C, Trauzeddel R, Thon A, Minden K, et al. Prevalence of overweight in children and adolescents with juvenile idiopathic arthritis. *Scand J Rheumatol*. (2015) 44(4):288–95. doi: 10.3109/03009742.2014.999351

164. Pelajo CF, Lopez-Benitez JM, Miller LC. Obesity and disease activity in juvenile idiopathic arthritis. *Pediatr Rheumatol Online J*. (2012) 10:3. doi: 10.1186/1546-0096-10-3

165. Souza L, Machado SH, Bredemeier M, Brenol JCT, Xavier RM. Effect of inflammatory activity and glucocorticoid [corrected] use on nutritional variables in patients with juvenile idiopathic arthritis. *J Rheumatol*. (2006) 33(3):601–8.

166. Giani T, De Masi S, Maccora I, Tirelli F, Simonini G, Falconi M, et al. The influence of overweight and obesity on treatment response in juvenile idiopathic arthritis. *Front Pharmacol*. (2019) 10:637. doi: 10.3389/fphar.2019.00637

167. Suppasit P, Vilaiyuk S, Poomthavorn P, Pongratanakul S, Khlairit P, Mahachoklertwattana P. Glucose metabolism in systemic juvenile idiopathic arthritis. *Pediatric Rheumatology*. (2022) 20(1):1–8. doi: 10.1186/s12969-022-00714-6

168. Silva MG, Borba EF, de Mello SBV, Shinjo SK. Serum adipocytokine profile and metabolic syndrome in young adult female dermatomyositis patients. *Clinics*. (2016) 71(12):709–14. doi: 10.6061/clinics/2016(12)06

169. Coyle K, Rother KI, Weise M, Ahmed A, Miller FW, Rider LG. Metabolic abnormalities and cardiovascular risk factors in children with myositis. *J Pediatr*. (2009) 155(6):882–7. doi: 10.1016/j.jpeds.2009.06.009

170. Held M, Sestan M, Jelusic M. Obesity as a comorbidity in children and adolescents with autoimmune rheumatic diseases. *Rheumatol Int*. (2022) 1:1–11. doi: 10.1007/s00296-022-05238-6

171. Sinicato NA, Postal M, Peres FA, Peliçari KDO, Marini R, Dos Santos ADO, et al. Obesity and cytokines in childhood-onset systemic lupus erythematosus. *J Immunol Res*. (2014) 2014:162047. doi: 10.1155/2014/162047

172. Mackay AG, Oliver JD, Perenna Rogers M. Regulation of lipoprotein lipase activity and mRNA content in rat epididymal adipose tissue in vitro by recombinant tumour necrosis factor. *Biochem J*. (1990) 269:123–6. doi: 10.1042/bj2690123

173. Pittas AG, Joseph NA, Greenberg AS. Adipocytokines and insulin resistance. *J Clin Endocrinol Metab*. (2004) 89(2):447–52. doi: 10.1210/jc.2003-031005

174. Sinicato NA, Postal M, de Oliveira Peliçari K, Rittner L, Marini R, Appenzeller S. Prevalence and features of metabolic syndrome in childhood-onset systemic lupus erythematosus. *Clin Rheumatol*. (2017) 36(7):1527–35. doi: 10.1007/s10067-017-3602-0

175. Lalla E, Cheng B, Lal S, Tucker S, Greenberg E, Goland R, et al. Periodontal changes in children and adolescents with diabetes: a case-control study. *Diabetes Care*. (2006) 29(2):295–9. doi: 10.2337/diacare.29.02.06.dc05-1355

176. Vaziri F, Bahrololoomi Z, Savabieh Z, Sezavar K. The relationship between children's body mass index and periodontal status. *J Indian Soc Periodontol*. (2022) 26(1):64–8. doi: 10.4103/jisp.jisp_899_20.

177. Karami S, Ghobadi N, Pakravan A, Dabirian M, Sobouti F. Periodontal diseases and possible future cardiovascular events, are they related? An overview. *J Pediatr Rev*. (2017) 6(1):44–8. doi: 10.5812/jpr.11144

178. D'Aiuto F, Gkranias N, Bhowruth D, Khan T, Orlandi M, Suvan J, et al. Systemic effects of periodontitis treatment in patients with type 2 diabetes: a 12 month, single-centre, investigator-masked, randomised trial. *Lancet Diabetes Endocrinol*. (2018) 6(12):954–65. doi: 10.1016/S2213-8587(18)30038-X

179. Hussain SB, Leira Y, Zehra SA, Botelho J, Machado V, Ciurtin C, et al. Periodontitis and systemic lupus erythematosus: a systematic review and meta-analysis. *J Periodontal Res*. (2022) 57(1):1–10. doi: 10.1111/jre.12936

180. Hussain SB, Botelho J, Machado V, Zehra SA, Mendes JJ, Ciurtin C, et al. Is there a bidirectional association between rheumatoid arthritis and periodontitis? A systematic review and meta-analysis. *Semin Arthritis Rheum*. (2020) 50. doi: 10.1016/j.semarthrit.2020.01.009

181. Homma TK, Endo CM, Saruhashi T, Mori API, de Noronha RM, Monte O, et al. Dyslipidemia in young patients with type 1 diabetes mellitus. *Arch Endocrinol Metab*. (2015) 59(3):215–9. doi: 10.1590/2359-3997000000040

182. Polak M, Souchon PF, Benali K, Tubiana-Rufi N, Czernichow P. Type 1 diabetic children have abnormal lipid profiles during pubertal years. *Pediatr Diabetes*. (2000) 1(2):74–81. doi: 10.1034/j.1399-5448.2000.010204.x

183. Cattalini M, Soliani M, Caparello MC, Cimaz R. Sex differences in pediatric rheumatology. *Clin Rev Allergy Immunol*. (2019) 56(3):293–307. doi: 10.1007/s12016-017-8642-3

184. Lambert NC. Nonendocrine mechanisms of sex bias in rheumatic diseases. *Nat Rev Rheumatol*. (2019) 15(11):673–86. doi: 10.1038/s41584-019-0307-6

185. de Gruijter NM, Naja M, Peckham H, Radziszewska A, Kinsella M, Glenister J, et al. A systematic review exploring the bidirectional relationship between puberty and autoimmune rheumatic diseases. *Pediatr Rheumatol Online J*. (2021) 19(1):47. doi: 10.1186/s12969-021-00528-y

186. Webb K, Peckham H, Radziszewska A, Menon M, Oliveri P, Simpson F, et al. Sex and pubertal differences in the type 1 interferon pathway associate with both X chromosome number and serum sex hormone concentration. *Front Immunol*. (2019) 9:3167. doi: 10.3389/fimmu.2018.03167

187. Gale EAM, Gillespie KM. Autoimmune diabetes and sex. *Diabetologia*. (2001) 48:2195–9.

188. Rustgi SD, Kayal M, Shah SC. Sex-based differences in inflammatory bowel diseases: a review. *Therap Adv Gastroenterol*. (2020) 13:1756284820915043. doi: 10.1177/1756284820915043

189. Wolfe F, Freundlich B, Straus WL. Increase in cardiovascular and cerebrovascular disease prevalence in rheumatoid arthritis. *J Rheumatol*. (2003) 30 (1):36–40.

190. Fransen J, Kazemi-Bajestani SMR, Bredie SJH, Popa CD. Rheumatoid arthritis disadvantages younger patients for cardiovascular diseases: a meta-analysis. *PLoS One*. (2016) 11(6):e0157360. doi: 10.1371/journal.pone.0157360

191. Ortiz TT, Terreri MT, Caetano M, Souza FS, D'Almeida V, Sarni ROS, et al. Dyslipidemia in pediatric systemic lupus erythematosus: the relationship with disease activity and plasma homocysteine and cysteine concentrations. *Ann Nutr Metab*. (2013) 63(1–2):77–82. doi: 10.1159/000351076

192. Robinson GA, Peng J, Pineda-Torra I, Ciurtin C, Jury EC. Metabolomics defines complex patterns of dyslipidaemia in juvenile-sle patients associated with inflammation and potential cardiovascular disease risk. *Metabolites*. (2022) 12(1):3. doi: 10.3390/metabo12010003

193. Robinson GA, Waddington KE, Coelewij L, Peng J, Naja M, Wincup C, et al. Increased apolipoprotein-B:a1 ratio predicts cardiometabolic risk in patients with juvenile onset SLE. *EBioMedicine*. (2021) 65:103243. doi: 10.1016/j.ebiom.2021.103243

194. Rosano GMC. Androgens and coronary artery disease. A sex-specific effect of sex hormones? *Eur Heart J*. (2000) 21(11):868–71. doi: 10.1053/euhj.1999.2050

195. Kelly DM, Jones TH. Testosterone: a vascular hormone in health and disease. *Article J Endocrinol*. (2013) 217(3):R47–71.

196. Araujo AB, Dixon JM, Suarez EA, Murad MH, Guey LT, Wittert GA. Clinical review: endogenous testosterone and mortality in men: a systematic review and meta-analysis. *J Clin Endocrinol Metab*. (2011) 96(10):3007–19. doi: 10.1210/jc.2011-1137

197. Lidegaard Ø, Løkkegaard E, Svendsen AL, Agger C. Hormonal contraception and risk of venous thromboembolism: national follow-up study. *Br Med J*. (2009) 339:7720. doi: 10.1136/bmj.b2890

198. Lidegaard Ø, Løkkegaard E, Jensen A, Skovlund CW, Keiding N. Thrombotic stroke and myocardial infarction with hormonal contraception. *Obstet Gynecol Surv*. (2012) 366:2257–66. doi: 10.1056/NEJMoa1111840

199. Roos-Hesselink JW, Cornette J, Sliwa K, Pieper PG, Veldtman GR, Johnson MR. Contraception and cardiovascular disease. *Eur Heart J*. (2015) 36.

200. Van Rooijen M, Bremme K, Rosing J, Silveira A, Thomassen S. 69 Rapid activation of haemostasis after hormonal emergency contraception. *Thromb Res*. (2007) 119. doi: 10.1016/S0049-3848(07)70114-7

201. Shen J, Che Y, Showell E, Chen K, Cheng L. Interventions for emergency contraception. *Cochrane Database Syst Rev*. (2019) 2019. doi: 10.1002/14651858.CD001324.pub

202. Dubey RK, Imthurn B, Barton M, Jackson EK. Vascular consequences of menopause and hormone therapy: importance of timing of treatment and type of estrogen. *Cardiovasc Res*. (2005) 66(2):295–306. doi: 10.1016/j.cardiores.2004.12.012

203. Peckham H, Webb K, Rosser EC, Butler G, Ciurtin C. Gender-Diverse inclusion in immunological research: benefits to science and health. *Front Med (Lausanne)*. (2022) 9:909789. doi: 10.3389/fmed.2022.909789

204. Henrickson M, Giwa S, Hafford-Letchfield T, Cocker C, Mulé NJ, Schaub J, et al. Research ethics with gender and sexually diverse persons. *Int J Environ Res Public Health*. (2022) 17(18):6615. doi: 10.3390/ijerph17186615

205. Morris J. WHO global report: mortality attributable to tobacco (2012).

206. McGill HC, Alex McMahan C, Malcom GT, Oalmann MC, Strong JP. Effects of Serum lipoproteins and smoking on atherosclerosis in young men and women. *Arterioscler Thromb Vasc Biol*. (1997) 17(1):95–106. doi: 10.1161/01.ATV.17.1.95

207. Gallucci G, Tartarone A, Lerose R, Lalinga AV, Capobianco AM. Cardiovascular risk of smoking and benefits of smoking cessation. *J Thorac Dis*. (2020) 12(7):3866. doi: 10.21037/jtd.2020.02.47

208. Barua RS, Ambrose JA. Mechanisms of coronary thrombosis in cigarette smoke exposure. *Arterioscler Thromb Vasc Biol*. (2013) 33(7):1460–7. doi: 10.1161/ATVBAHA.112.300154

209. Huxley RR, Woodward M. Cigarette smoking as a risk factor for coronary heart disease in women compared with men: a systematic review and meta-analysis of prospective cohort studies. *Lancet*. (2011) 378(9799):1297–305. doi: 10.1016/S0140-6736(11)60781-2

210. Campesi I, Carru C, Zinellu A, Occhioni S, Sanna M, Palermo M, et al. Regular cigarette smoking influences the transsulfuration pathway, endothelial function, and inflammation biomarkers in a sex-gender specific manner in healthy young humans. *Am J Transl Res*. (2013) 5(5):497.

211. Wierzbicki AS. Homocysteine and cardiovascular disease: a review of the evidence. *Diab Vasc Dis Res*. (2007) 4(2):143–9. doi: 10.3132/dvdr.2007.033

212. Van Jaarsveld CHM, Fidler JA, Simon AE, Wardle J. Persistent impact of pubertal timing on trends in smoking, food choice, activity, and stress in adolescence. *Psychosom Med*. (2007) 69(8):798–806. doi: 10.1097/PSY.0b013e3181576106

213. Al Rifai M, DeFillippis AP, McEvoy JW, Hall ME, Acien AN, Jones MR, et al. The relationship between smoking intensity and subclinical cardiovascular injury: the multi-ethnic study of atherosclerosis (MESA). *Atherosclerosis*. (2017) 258:119–30. doi: 10.1016/j.atherosclerosis.2017.01.021

214. Hackshaw A, Morris JK, Boniface S, Tang JL, Milenkovi D. Low cigarette consumption and risk of coronary heart disease and stroke: meta-analysis of 141 cohort studies in 55 study reports. *Br Med J*. (2018) 360:j5855. doi: 10.1136/bmj.j5855

215. McEvoy JW, Nasir K, Defilippis AP, Lima JAC, Bluemke DA, Hundley WG, et al. Relationship of cigarette smoking with inflammation and subclinical vascular disease: the multi-ethnic study of atherosclerosis. *Arterioscler Thromb Vasc Biol*. (2015) 35:1002–10. doi: 10.1161/ATVBAHA.114.304960

216. Marcon A, Pesce G, Calciano L, Bellisario V, Dharmage SC, Garcia-Aymerich J, et al. Trends in smoking initiation in Europe over 40 years: a retrospective cohort study. *PLoS One*. (2018) 13(8). doi: 10.1371/journal.pone.0201881

217. Peruzzi M, Biondi-Zoccai G, Carnevale R, Cavarretta E, Frati G, Versaci F. Vaping cardiovascular health risks: an updated Umbrella review. *Curr Emerg Hosp Med Rep*. (2020) 8(3):103–9. doi: 10.1007/s40138-020-00219-0

218. Wong WC, Ford KA, Pagels NE, McCutcheon JE, Marinelli M. Adolescents are more vulnerable to cocaine addiction: behavioral and electrophysiological evidence. *J Neurosci*. (2013) 33(11):4913–22. doi: 10.1523/JNEUROSCI.1371-12.2013

219. Morentin B, Ballesteros J, Callado LF, Meana JJ. Recent cocaine use is a significant risk factor for sudden cardiovascular death in 15-49-year-old subjects: a forensic case-control study. *Addiction*. (2014) 109(12). doi: 10.1111/add.12691

220. World Health Organization. Interpersonal violence and illicit drugs. *Addiction*. (2014) 37(1).

221. Velázquez JAV, Gamiño MNB, Ito DAF, Bautista CF, de López MLG, Buenabad NGA, et al. Contextual factors associated with marijuana use in school population. *Salud Mental*. (2017) 40(3).

222. Lac A, Unger JB, Basáñez T, Ritt-Olson A, Soto DW, Baezconde-Garbanati L. Marijuana use among latino adolescents: gender differences in protective familial factors. *Subst Use Misuse*. (2011) 46(5):644–55. doi: 10.3109/10826084.2010.528121

223. Rusby JC, Light JM, Crowley R, Westling E. Influence of parent-youth relationship, parental monitoring, and parent substance use on adolescent substance use onset. *J Fam Psychol*. (2018) 32(3):310–20. doi: 10.1037/fam0000350

224. Henry KL, Smith EA, Caldwell LL. Deterioration of academic achievement and marijuana use onset among rural adolescents. *Health Educ Res*. (2007) 22(3):372–84. doi: 10.1093/her/cyl083

225. Darke S, Kaye S, Duflou J. Comparative cardiac pathology among deaths due to cocaine toxicity, opioid toxicity and non-drug-related causes. *Addiction*. (2006) 101 (12):1771–7. doi: 10.1111/j.1360-0443.2006.01601.x

226. Andersson C, Vasan RS. Epidemiology of cardiovascular disease in young individuals. *Nat Rev Cardiol*. (2018) 15(4):230–40. doi: 10.1038/nrcardio.2017.154

frontiers | Frontiers in Public Health

TYPE Original Research
PUBLISHED 04 August 2023
DOI 10.3389/fpubh.2023.1198924

OPEN ACCESS

EDITED BY
Shikai Yu,
Tongji University, China

REVIEWED BY
Maria Piane,
Sapienza University of Rome, Italy
Shohreh Naderimagham,
Tehran University of Medical Sciences, Iran

*CORRESPONDENCE
Cuifen Zhao
✉ zhaocuifen@sdu.edu.cn
Xiaorong Yang
✉ yangxiaorong@sdu.edu.cn

RECEIVED 02 April 2023
ACCEPTED 24 July 2023
PUBLISHED 04 August 2023

CITATION
Kong Q, Li M, Wang M, Zhao H, Yang X and Zhao C (2023) Analysis of the disease burden of cardiomyopathy in children aged 0–14 years in China from 1990 to 2019.
Front. Public Health 11:1198924.
doi: 10.3389/fpubh.2023.1198924

Analysis of the disease burden of cardiomyopathy in children aged 0–14 years in China from 1990 to 2019

Qingyu Kong[1], Meng Li[1], Minmin Wang[1], Haizhao Zhao[1], Xiaorong Yang[2,3]* and Cuifen Zhao[1]*

[1]Department of Pediatric Cardiology, Qilu Hospital of Shandong University, Jinan, Shandong, China, [2]Clinical Epidemiology Unit, Qilu Hospital of Shandong University, Jinan, Shandong, China, [3]Clinical Research Center of Shandong University, Qilu Hospital, Cheeloo College of Medicine, Shandong University, Jinan, Shandong, China

Objectives: To assess the disease burden and changing trend of cardiomyopathy in children aged 0–14 years in China from 1990 to 2019.

Methods: This study was based on the Global Burden of Disease Study 2019; the age-specific prevalence rate, mortality rate and disability-adjusted life year (DALY) rate were used for analysis. Estimated annual percentage change (EAPC) in burden rate and its 95% confidence interval were calculated. The data of China were compared with the global average level.

Results: In 2019, the numbers of prevalence, deaths, and DALYs of cardiomyopathy in children aged 0–14 years in China were 4,493 [95% uncertainty interval (*UI*): 2687 ~ 6,838], 434 (95%*UI*: 337 ~ 565) and 37,522 (95%*UI*: 29,321 ~ 48,891), with declining amplitudes of 16.32, 70.56, and 70.74%, compared with 1990, respectively. In 2019, the prevalence rate of cardiomyopathy in Chinese children aged 0–14 years was 2.00/100,000 (95%*UI*: 1.2/100,000 ~ 3.04/100,000), higher than 1990 [1.66/100,000 (95%*UI*:1.00/100,000 ~ 2.53/100,000)]; mortality rate was 0.19/100,000 (95%*UI*: 0.15/100,000 ~ 0.25/100,000), significantly lower than 1990 [0.46/100,000 (95%*UI*: 0.25/100,000 ~ 0.95/100,000)]; DALY rate was 16.69/100,000 (95%*UI*: 13.04/100,000 ~ 21.75/100,000), also significantly lower than 1990 [39.71/100,000 (95%*UI*: 22.06/100,000 ~ 82.8/100,000)]. All burden rates of cardiomyopathy in Chinese children aged 0–14 years old were all lower than the global averages of 2019; the burden rates of male children were higher than female children. In all calendar years from 1990 to 2019, the mortality and DALY rates of children younger than 1-year-old were significantly higher than in the other age groups of 0–14 years old. From 1990 to 2019, the prevalence rate of cardiomyopathy aged 0–14 years old gradually increased, with EAPC of 0.82 (95%*CI*: 0.71–0.93); mortality rate and DALY rate decreased [EAPC = −2.32 (95%*CI*: −2.59 to −2.05)].

Conclusion: From 1990 to 2019, the disease burden of cardiomyopathy in children of China aged 0–14 years was heterogeneous; the burden of male children was higher than females; and the burden of cardiomyopathy in children younger than 1 year old needs more attention.

KEYWORDS

cardiomyopathy, prevalence, mortality, disability-adjusted life years, children, China

Introduction

Cardiomyopathy is a kind of cardiovascular disease which can seriously affect the physical and mental health of children (1). It has the characteristics of high disability and mortality, with extremely poor prognosis and a huge disease burden (2, 3). Genetic variations and systemic diseases account for the main etiologies of pediatric cardiomyopathy which are complex and heterogeneous (4, 5). In pediatric cardiomyopathy, dilated cardiomyopathy is the most common, followed by hyper-trophic cardiomyopathy; restrictive cardiomyopathy and left ventricular myocardial insufficiency are relatively rare (6). Structural cardiac disease, infections causes, autoimmune diseases, drug reactions, metabolic disorders, hypersensitive reactions, and other exposures can also lead to cardiomyopathy (7, 8). Nearly 40% of cardiomyopathy patients developed sudden death or require heart transplantation in childhood or adolescence (8). The risk factors including pathogenesis, clinical manifestations, structural abnormalities, genetic phenotype are the leading reasons for poor prognosis in pediatric cardiomyopathy. According to population-based studies in the United States, Finland and Australia, the annual incidence of primary cardiomyopathy in children was about 1 in 100,000, but there were some differences among ages, genders and races (9–11). The incidence of cardiomyopathy was high in infancy, eight times higher than in older children (9).

The epidemiological characterization of pediatric cardiomyopathy in specific populations can help guide the formulation of public health policies, and further researches on prevention, diagnosis and treatment strategies. Published clinical studies related to cardiomyopathy in children are very rare, and no epidemiological studies have been published on cardiomyopathy in the population of children aged 0–14 years. The Global Burden of Disease (GBD) is currently the most influential study of disease burden in the world, and its database was updated in 2019 (12, 13). Based on GBD 2019, this study analyzed the disease burden and changing trend of cardiomyopathy in children aged 0–14 years in China from 1990 to 2019, and compared with global data, which aimed to provide a reference for guiding the research of pediatric cardiomyopathy and formulation of prevention strategies.

Methods

Data source

This study was based on the data of GBD 2019 from Global Health Data Exchange. The GBD 2019 has collected global disease burden data from primary research studies and various databases, and performed subsequent data analysis to provide systematical estimations on 369 diseases (12), which gives a unique opportunity to understand the latest state of cardiomyopathy in children of China. Following the methodology framework and analytical strategies used in the GBD 2019 study, this present study aimed to summarize the prevalence, deaths, and disability-adjusted life years (DALYs), and the corresponding secular trends of cardiomyopathy in children aged 0–14 years in China and worldwide from 1990 to 2019. DALY is one of the most important comprehensive indicators describing the burden of disease. And, it refers to the total healthy life years lost from morbidity to death, including the loss of healthy life caused by disease and disability (14). The Guidelines for Accurate and Transparent Health Estimates Reporting (GATHER) statement were obeyed to analyze the GBD database in every step (Report Checklist). The database was classified according to gender, age groups and years, and the burden of pediatric cardiomyopathy was analyzed using the standard model after modification. The International Classification of Disease (ICD) codes were adopted to identify cardiomyopathy in children aged 0–14 years old. The disease codes include 425.0–425.3, 425.7–425.8, 429.0 in ICD 9; I42.1–I42.5, I42.7–I42.8, I43–I43.9 in ICD 10. Statistical analysis code is freely available from the following website: http://ghdx.healthdata.org/gbd-2019/code.

Analytical indicators

Age-specific prevalence rate (ASPR), age-specific mortality rate (ASMR), and age-specific DALY rate (ASDR) were used to assess the burden of pediatric cardiomyopathy. The estimated annual percentage change (EAPC) and its 95% confidence interval (CI) were calculated (15, 16). In this study, the burden of Chinese children aged 0–14 years from 1990 to 2019 was analyzed by gender, age groups, and calendar years, and was compared with the global data. Age grouping adopted the inherent age grouping mode of GBD 2019, including less than 1 year old, 1–4 years old, 5–9 years old, and 10–14 years old.

Statistical analysis

Based on GBD 2019, the burden of cardiomyopathy of Chinese children aged 0–14 years from 1990 to 2019 was modeled by the Cause of Death Ensemble tool, DisMod-MR, and spatiotemporal Gaussian regression. Previous studies have described the primary data explanations and analytic approaches of the GBD 2019 study in detail (12, 13, 17). In this study, we conducted a descriptive analysis of the numbers of prevalence, deaths, and DALYs in China and the world in 1990 and 2019, and calculated the annual trends of age-specific rates (ASRs) from 1990 to 2019. EAPC was used to assess the annual trend in ASR to characterize the long-term change in the burden of pediatric cardiomyopathy. The upward trend is defined as the minimum value of EAPC and its 95% CI being positive; instead, a decreasing trend was recognized when EAPCs and the maximum of the 95% CI were negative; and the ASR trend is stable when neither meets (18, 19). Statistical analysis was completed using the R language version 4.2.1.

Abbreviations: ASDR, Age-specific DALY rate; ASMR, Age-specific mortality rate; ASPR, Age-specific prevalence rate; ASR, Age-specific rate; CI, Confidence interval; DALY, Disability-adjusted life year; EAPC, Estimated annual percentage change; GATHER, Guidelines for Accurate and Transparent Health Estimates Reporting; GBD, Global Burden of Disease; ICD, International Classification of Disease; UI, Uncertainty interval.

TABLE 1 Prevalence and age-specific prevalence rate per 100,000 people of cardiomyopathy in children aged 0–14 years old in 1990 and 2019, and its estimated annual percentage change from 1990 to 2019.

Characteristics	1990		2019		EAPC of ASPR (95%CI) from 1990 to 2019
	Prevalence (95%UI)	ASPR/100,000 (95%UI)	Prevalence (95%UI)	ASPR/100,000 (95%UI)	
China					
Both	5,369 (3,221~8,164)	1.66 (1.00~2.53)	4,493 (2,687~6,838)	2.00 (1.2~3.04)	0.82 (0.71~0.93)
Male	3,167 (1,889~4,818)	1.88 (1.12~2.86)	2,711 (1,613~4,109)	2.23 (1.33~3.38)	0.74 (0.64~0.83)
Female	2,201 (1,331~3,344)	1.43 (0.86~2.16)	1,782 (1,080~2,732)	1.72 (1.04~2.64)	0.90 (0.78~1.02)
Age groups					
<1	178 (97~301)	0.76 (0.41~1.28)	134 (73~227)	0.89 (0.49~1.51)	0.73 (0.62~0.84)
1~4	1,910 (955~3,140)	1.86 (0.93~3.05)	1,535 (772~520)	2.17 (1.09~3.57)	0.92 (0.8~1.04)
5~9	1,659 (857~2,747)	1.58 (0.82~1.62)	1,401 (717~2,295)	1.93 (0.99~3.16)	0.93 (0.81~1.05)
10~14	1,621 (931~585)	1.76 (1.01~2.81)	1,424 (820~2,256)	2.14 (1.23~3.4)	0.69 (0.59~0.79)
Global					
Both	62,240 (38,833~92,899)	3.55 (2.21~5.30)	20,606 (10,825~33,441)	3.21 (1.69~5.21)	−0.23 (−0.26 to −0.20)
Male	35,346 (22,187~52,469)	3.92 (2.46~5.83)	11,880 (6,170~19,101)	3.59 (1.86~5.76)	−0.23 (−0.25 to −0.20)
Female	26,895 (16,569~40,421)	3.15 (1.94~4.74)	8,726 (4,583~14,302)	2.81 (1.47~4.60)	−0.23 (−0.27 to −0.19)
Age groups					
<1	1,818 (1,003~3,042)	1.38 (0.76~2.31)	2,064 (1,123~3,497)	1.56 (0.85~2.65)	0.42 (0.40~0.45)
1~4	18,812 (10,853~29,856)	3.76 (2.17~5.97)	20,863 (11,788~33,511)	3.93 (2.22~6.31)	0.15 (0.13~0.16)
5~9	20,823 (11,438~34,459)	3.56 (1.95~5.89)	22,043 (11,987~36,886)	3.37 (1.83~5.63)	−0.24 (−0.28 to −0.2)
10~14	20,787 (11,061~33,358)	3.87 (2.06~6.22)	20,606 (10,825~33,441)	3.21 (1.69~5.21)	−0.65 (−0.71 to −0.59)

ASPR, age-specific prevalence rate; UI, uncertainty interval; EAPC, estimated annual percentage change; CI, confidential interval.

Results

Overview of the disease burden of cardiomyopathy in children aged 0–14 years in China, and comparison with global data

In 2019, the prevalent number of cardiomyopathy in children aged 0–14 in China was 4,493 [95% uncertain interval (UI): 2,687 ~ 6,838], down 16.32% compared with 1990 [5,369 (95%UI: 3221 ~ 8,164)] (Table 1); the number of deaths was 433 (95%UI: 337 ~ 565), down 70.56% compared with 1990 [1,474 (95%UI: 819 ~ 3,078)] (Table 2); the number of DALYs was 37,522 (95%UI: 29,321 ~ 48,891), down 70.74% compared with 1990 [128,224 (95%UI: 71,231 ~ 267,370)] (Table 3). In 2019, the ASPR of cardiomyopathy aged 0–14 years old was 2.00/100,000 (95%UI:1.20/100,000 ~ 3.04/100,000) in China, which was higher than in 1990 [1.66/100,000 (95%UI: 1.00/100,000 ~ 2.53/100,000)] (Table 1). In contrast, the global ASPR [3.21/100,000 (95%UI:1.69/100,000 ~ 5.21/100,000)] decreased compared with 1990 [3.55/100,000 (95%UI: 2.21/100,000 ~ 5.30/100,000)] (Table 1). ASMR and ASDR of 2019 in China were 0.19/100,000 (95%UI: 0.15/100,000 ~ 0.25/100,000) and 16.69/100,000 (95%UI: 13.04/100,000 ~ 21.75/100,000), both decreasing compared with the corresponding data of 0.46/100,000 (95%UI: 0.25/100,000 ~ 0.95/100,000) and 39.71/100,000 (95%UI: 22.06/100,000 ~ 82.80/100,000) in 1990 (Tables 2, 3). Both the ASMR and the ASDR in 2019 also declined globally compared with 1990. In 2019, the ASRs of cardiomyopathy in Chinese children aged 0–14 years old were all lower than the corresponding global averages (Tables 1–3).

Gender characteristics of the disease burden of cardiomyopathy in children aged 0–14 years in China, and comparison with global data

In 2019, the prevalence of Chinese male children aged 0–14 with cardiomyopathy was 2,711 (95%UI: 1,613–4,109), and 1782 (95%UI: 1,080–2,732) in women; the number of deaths in Chinese male children with cardiomyopathy was 260 (95%UI:185 ~ 377), and DALYs were 22,490 (95%UI: 16,058 ~ 32,629); the number of deaths in Chinese female children with cardiomyopathy was 173 (95%UI: 127 ~ 226), and DALYs were 15,033 (95%UI: 11,048 ~ 19,608) (Tables 1–3). In 2019, the ASPR, ASMR, and ASDR of cardiomyopathy in male children aged 0–14 years in China were 2.23/100,000 (95%UI: 1.33/100,000 to 3.38/100,000), 0.21/100,000 (95%UI: 0.15/100,000 to 0.31/100,000), and 18.52/100,000 (95%UI: 3.22/100,000 to 26.86/100,000), which were higher than the corresponding values of female children [1.72/100,000 (95%UI: 1.04/100,000 to 2.64/100,000), 0.17/100,000 (95%UI: 0.12/100,000 to 0.22/100,000), and 14.55/100,000 (95%UI: 10.69/100,000 to 18.98)/100,000] (Tables 1–3). In all calendar years from 1990 to 2019, the ASPR, ASMR and ASDR of Chinese children with cardiomyopathy aged 0–14 years old in males were higher than that in females; and the ASRs of cardiomyopathy in

TABLE 2 Deaths and age-specific mortality rate per 100,000 people of cardiomyopathy in children aged 0–14 years old in 1990 and 2019, and its estimated annual percentage change from 1990 to 2019.

Characteristics	1990		2019		EAPC of ASMR (95%CI) from 1990 to 2019
	Deaths (95%UI)	ASMR/100,000 (95%UI)	Deaths (95%UI)	ASMR/100,000 (95%UI)	
China					
Both	1,474 (819~3,078)	0.46 (0.25~0.95)	433 (337~565)	0.21 (0.15~0.31)	−2.32 (−2.59 to −2.05)
Male	773 (446~1,991)	0.46 (0.26~1.18)	260 (185~377)	0.17 (0.12~0.22)	−1.98 (−2.28 to −1.68)
Female	701 (329~1,687)	0.45 (0.21~1.09)	173 (127~226)	0.19 (0.15~0.25)	−2.78 (−3.02 to −2.54)
Age groups					
<1	965 (511~2,155)	4.11 (2.18~9.18)	245 (188~330)	1.62 (1.25~2.19)	−2.88 (−3.36 to −2.40)
1~4	106 (66~196)	0.33 (0.17~0.69)	59 (45~78)	0.12 (0.09~0.17)	−3.39 (−3.79 to −2.99)
5~9	102 (62~198)	0.10 (0.06~0.19)	49 (36~65)	0.07 (0.05~0.09)	−1.39 (−1.87 to −0.91)
10~14	300 (156~630)	0.10 (0.06~0.19)	81 (61~110)	0.08 (0.06~0.11)	−0.60 (−1.05 to −0.16)
Global					
Both	10,986 (7,979~16,654)	0.63 (0.46~0.95)	7,163 (5,511~9,300)	0.37 (0.28~0.47)	−1.55 (−1.68 to −1.41)
Male	5,707 (3,586~10,025)	0.63 (0.40~1.11)	3,896 (2,874~5,342)	0.39 (0.28~0.53)	−1.38 (−1.52 to −1.24)
Female	5,279 (3,828~8,453)	0.62 (0.45~0.99)	3,268 (2,455~4,137)	0.34 (0.26~0.44)	−1.74 (−1.87 to −1.61)
Age groups					
<1	6,699 (4,897~10,120)	5.09 (3.72~7.69)	3,923 (2,986~5,166)	2.97 (2.26~3.91)	−1.67 (−1.83 to −1.51)
1~4	2,500 (1,617~4,297)	0.50 (0.32~0.86)	1,600 (1,159~2,305)	0.30 (0.22~0.43)	−1.44 (−1.55 to −1.33)
5~9	884 (653~1,395)	0.15 (0.11~0.24)	792 (635~1,001)	0.13 (0.11~0.16)	−0.74 (−0.82 to −0.65)
10~14	902 (727~1,262)	0.17 (0.14~0.24)	848 (690~1,022)	0.13 (0.11~0.16)	−0.85 (−0.92 to −0.77)

ASMR, age-specific mortality rate; UI, uncertainty interval; EAPC, estimated annual percentage change; CI, confidential interval.

TABLE 3 DALYs and age-specific DALY rate per 100,000 people of cardiomyopathy in children aged 0–14 years old in 1990 and 2019, and its estimated annual percentage change from 1990 to 2019.

Characteristics	1990	2019		EAPC of ASIR (95%CI) from 1990 to 2019
	DALYs (95%UI)	ASDR/100,000 (95%UI)	DALYs (95%UI)	ASDR/100,000 (95%UI)	
China					
Both	12,8224 (71,231~267,370)	39.71 (22.06~82.8)	37,522 (29,321~48,891)	16.69 (13.04~21.75)	−2.32 (−2.59 to −2.05)
Male	67,200 (38,789~173,243)	39.89 (23.03~102.84)	22,490 (16,058~32,629)	18.52 (13.22~26.86)	−1.99 (−2.29 to −1.69)
Female	61,024 (28,609~147,143)	39.51 (18.52~95.26)	15,033 (11,048~19,608)	14.55 (10.69~18.98)	−2.77 (−3.01 to −2.54)
Age groups					
<1	85,413 (45,262~190,660)	363.89 (192.83~812.28)	21,660 (16,660~29,212)	143.75 (110.57~193.87)	−2.88 (−3.36 to −2.40)
1~4	8,297 (5,235~15,134)	28.28 (14.73~59.11)	4,660 (3,585~6,073)	10.65 (8.12~14.42)	−3.35 (−3.74 to −2.96)
5~9	8,524 (5,214~16,291)	8.14 (4.98~15.55)	4,128 (3,084~5,448)	5.68 (4.25~7.50)	−1.34 (−1.81 to −0.87)
10~14	25,991 (13,538~54,332)	8.07 (5.09~14.73)	7,075 (5,396~9,580)	6.60 (5.07~8.59)	−0.58 (−1.01 to −0.14)
Global					
Both	955,140 (693,517~1,441,833)	54.46 (39.54~82.20)	620,609 (479,373~804,032)	31.69 (24.46~41.03)	−1.55 (−1.69 to −1.42)
Male	496,340 (311,203~869,370)	55.11 (34.55~96.52)	337,397 (250,069~466,822)	33.35 (24.72~46.14)	−1.39 (−1.53 to −1.25)
Female	458,800 (333,448~734,021)	53.77 (39.08~86.02)	283,212 (212,319~358,544)	29.87 (22.40~37.82)	−1.74 (−1.87 to −1.61)
Age groups					
<1	593,190 (433,813~895,811)	450.82 (329.69~680.81)	347,514 (264,669~457,588)	263.3 0 (200.53~346.70)	−1.67 (−1.83 to −1.51)
1~4	216,833 (140,711~371,612)	43.32 (28.11~74.24)	139,589 (101,670~200,047)	26.30 (19.15~37.68)	−1.43 (−1.53 to −1.32)
5~9	74,226 (55,324~116,152)	12.68 (9.45~19.85)	66,818 (53,355~83,864)	10.21 (8.15~12.81)	−0.72 (−0.81 to −0.64)
10~14	70,891 (57,825~98,817)	13.71 (10.95~16.81)	66,689 (55,011~79,796)	10.38 (8.57~ 12.43)	−0.84 (−0.92 to −0.76)

DALY, disability-adjusted life year; ASDR, age-specific DALY rate; UI, uncertainty interval; EAPC, estimated annual percentage change; CI, confidential interval.

Chinese children aged 0–14 years old were all lower than the global averages of the corresponding genders (Figures 1–3).

Characteristics of the disease burden of cardiomyopathy in children aged 0–14 years in China in age groups, and comparison with global data

In 2019, the ASPR of cardiomyopathy of all age groups among 0–14 years old in China increased compared with 1990, while ASMR and ASDR decreased compared with 1990. The highest ASPR in 1990 and 2019 were found in the 1–4 years old group (Table 1), and the highest ASMR and ASDR were found in the <1 year age group (Tables 2, 3). It is noteworthy that the number of deaths in children in the age group less than 1 year exceeded the number of prevalence in 1990 and 2019, more obviously in 1990; while the opposite results were observed in the other age groups (Table 2). From 1990 to 2019, ASPR, ASMR and ASDR of Chinese children with cardiomyopathy in all age groups among 0–14 years old were lower than the global average of the corresponding age groups (Figures 1–3).

Annual trends in the disease burden of cardiomyopathy in children aged 0–14 years old in China, and comparison with global data

From 1990 to 2019, the ASPR of cardiomyopathy in children aged 0–14 years in China gradually increased with an EAPC of 0.82 (95% CI: 0.71–0.93); the upward trend of male children [EAPC = 0.74 (95% CI: 0.64–0.83)] is weaker than that of female children [EAPC = 0.9(95% CI: 0.78–1.02)] (Table 1). However, the ASPR of cardiomyopathy in children aged 0–14 years old has shown a downward trend globally with similar trends for both male and female children (Table 1). From 1990 to 2019, the ASMR and ASDR of cardiomyopathy in children aged 0–14 years old in China showed a downward trend with the same EAPC of [−2.32 (95% CI: −2.59 to −2.05)], which was oblivious than the global trend [EAPC = −1.55 (95% CI: −1.68 to −1.41)] (Tables 2, 3). In Chinese male children aged 0–14 years old, ASMR and ASDR showed a downward trend [EAPC = −1.98 (95% CI: −2.28 ~ −1.68) and − 1.99 (95% CI: −2.29 ~ −1.69)], with a weaker degree than in female children [EAPC = −2.78 (95% CI: −3.02 ~ −2.54) and − 2.77 (95% CI: −3.01 ~ −2.54)] (Tables 2, 3). During the period 1990–2019, the two age groups with the most obvious upward trend of ASPR were 5–9 years old and 1–4 years old; 1–4 years old and younger than 1 year old are the two age groups with the most significant downward trend in ASMR and ASDR. The changing trend of ASMR was highly consistent with ASDR in all age groups between 0 and 14 years old in China and the whole world (Figures 2, 3).

Discussion

This study found that the prevalence of children with cardiomyopathy aged 0–14 years in China decreased from 1990 to 2019, but ASPR showed an upward trend; the number of deaths, DALYs, ASMR, and ASDR all showed a downward trend. The results suggested that the overall burden of cardiomyopathy in children aged 0–14 years in China presented a downward trend during the period of 1990–2019, which was mainly due to the continuous progress of basic, translational, and clinical researches related to cardiomyopathy. Genomics technology has promoted the continuous development of precision medicine, and more and more unexplained cardiomyopathy has been unveiled (20–24). In this context, medical personnel and scientific researches have gained a deeper understanding on the causes of pediatric cardiomyopathy, and the diagnosis and treatment strategies for pediatric cardiomyopathy have also been continuously developed and improved. Meanwhile, we should also pay attention to the rising trend of ASPR in children aged 0–14 years with cardiomyopathy in China, which was mainly due to the significant decline in ASMR. The continuous progress in diagnosis and treatment significantly reduced the mortality rate of children with cardiomyopathy. The continuous improvement in precision medicine for cardiomyopathy has enabled more children with cardiomyopathy to receive timely and effective diagnosis and treatment (25). The

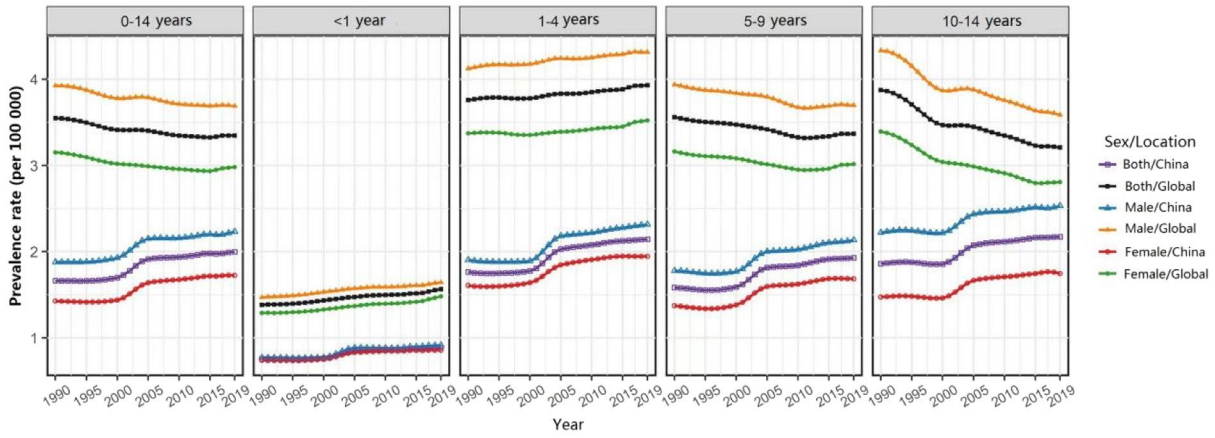


FIGURE 1
Changes in the age-specific prevalence rate of children with cardiomyopathy aged 0–14 years across all age groups and genders, China and the world, from 1990 to 2019.

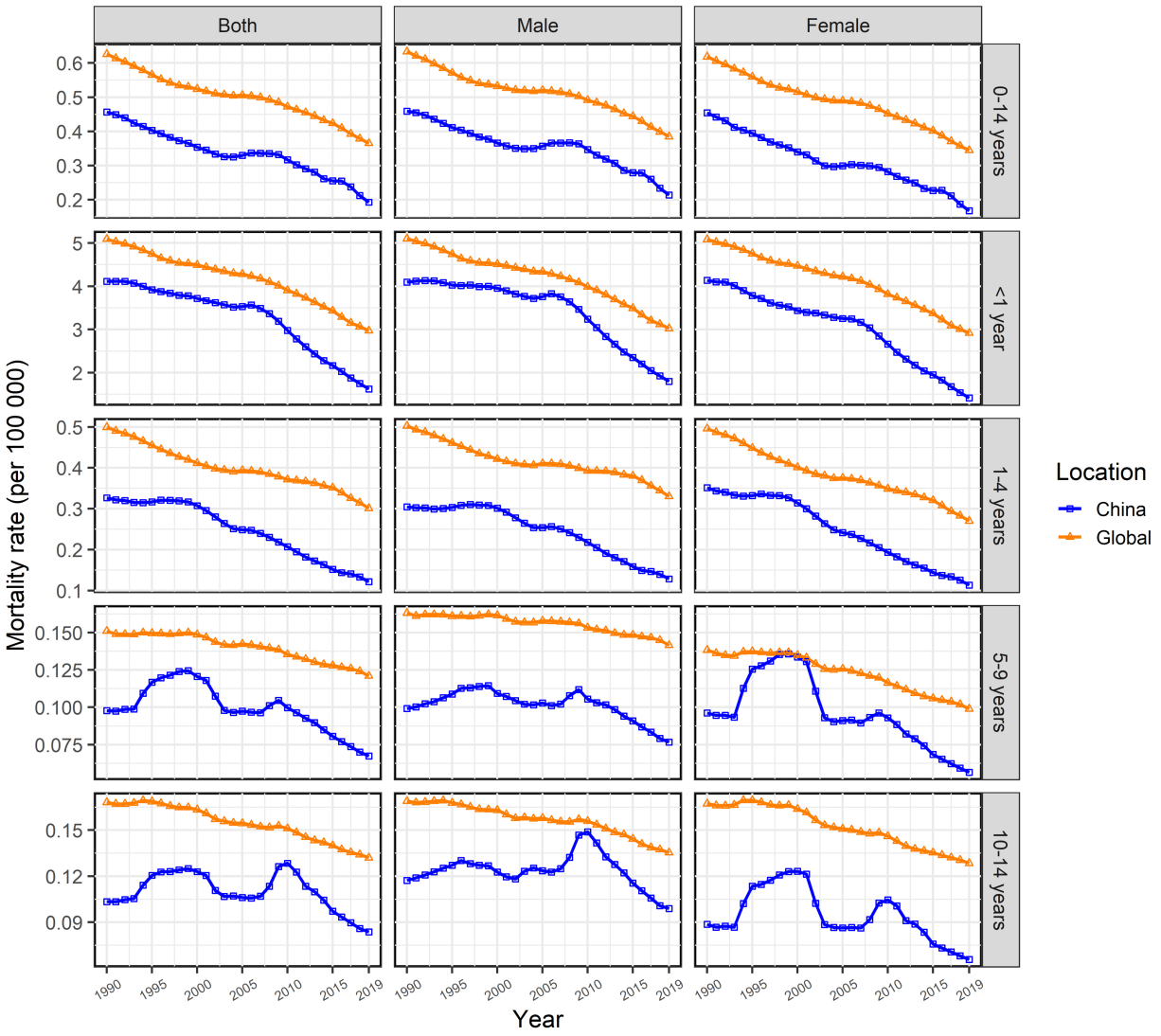


FIGURE 2
Changes in the age-specific mortality rate of children with cardiomyopathy aged 0–14 years across all age groups and genders, China and the world, from 1990 to 2019.

change in the overall size of the 0–14 year old population was another important influencing factor for the change in ASPR in China. This study also found that from 1990 to 2019, children with cardiomyopathy of all age groups and different genders in China showed the same changes as the overall trend. Namely, ASPR showed an upward trend, while ASMR and ASDR showed a highly consistent downward trend. Moreover, the overall disease burden of cardiomyopathy in Chinese children aged 0–14 years was lower than the global average. China has achieved good results in the prevention and treatment of pediatric cardiomyopathy for reducing the burden, which was mainly due to the in-depth research, experience sharing, and hard work of domestic medical and scientific researchers in the diagnosis and treatment of pediatric cardiomyopathy. The birth rate inevitably affects the number of children with cardiomyopathy, therefor different birth rate in the Chinese population compared to the global one is also an important factor affecting the discrepancies in cardiomyopathy burden. Another, the incidence rate of cardiomyopathy may vary among different ethnic groups.

Gender is an important factor affecting the burden of pediatric cardiomyopathy (26). The results of this study suggested that the burden of cardiomyopathy in Chinese male children aged 0–14 years was higher than that in female children. The number of prevalence, deaths, DALYs, and their corresponding specific rates in male children were higher than those in female children. Many children with cardiomyopathy have a familial basis, and most of the related genes are autosomal with dominant transmission mainly (27). Considering the impact of genetic patterns, the burden of disease should be similar for men and women, but this contradicts clinical statistics. The gender difference may be related to the penetrance of cardiomyopathy-related genes, mitochondrial genetics, modified genes, epigenetics, environmental factors, etc. between different sexes. Functional analysis of gene expression patterns showed that female-specific deregulation genes were mainly involved in energy metabolism, transcription, and translation regulation, while male-specific deregulation genes were related to myocardial contraction (28). Sex hormones can directly affect cardiac function by influencing

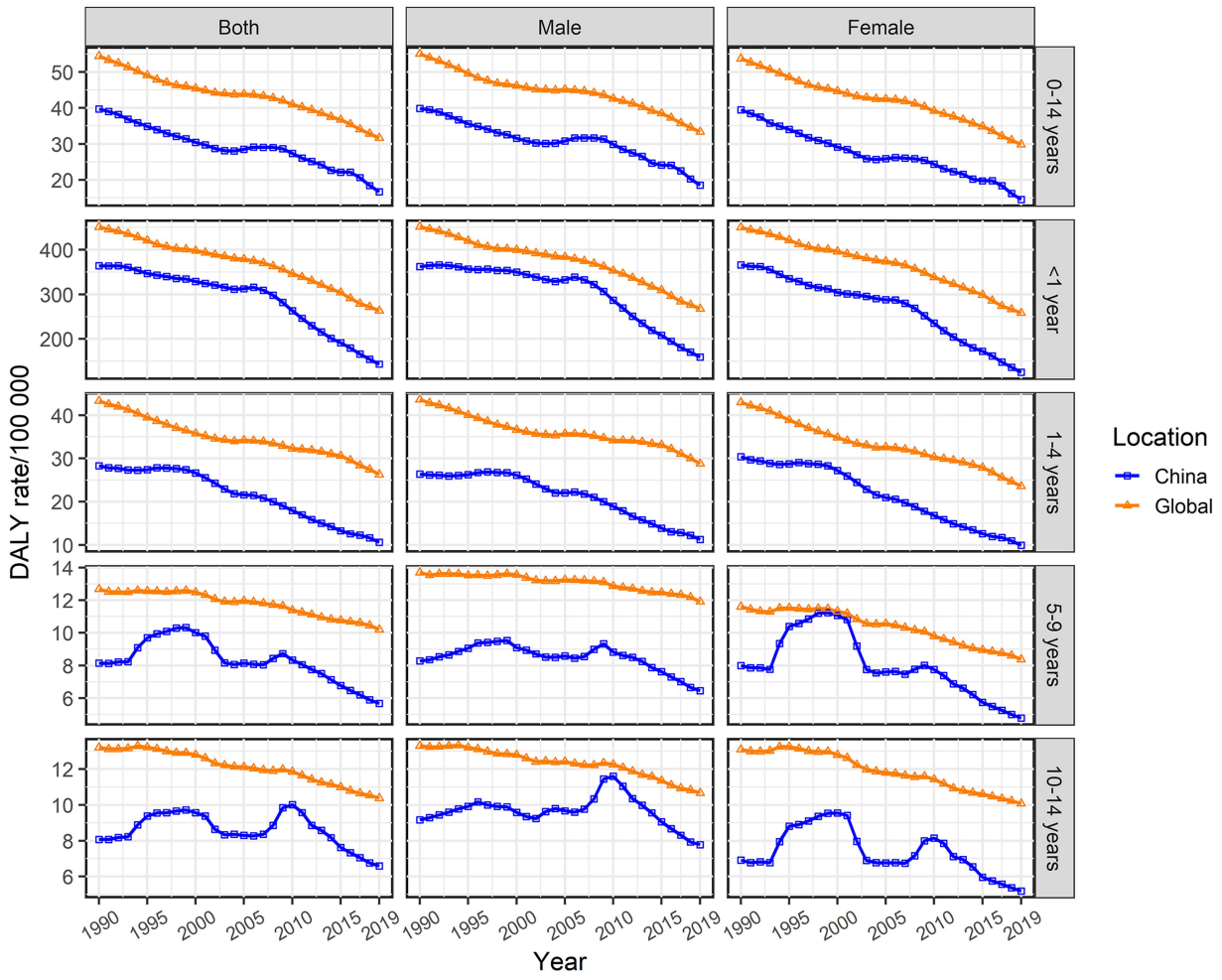


FIGURE 3
Changes in the age-specific disability-adjusted life year (DALY) rate of children with cardiomyopathy aged 0–14 years across all age groups and genders, China and the world, from 1990 to 2019.

endothelial cell function and vascular tension through androgen and estrogen receptors present in vascular endothelium, smooth muscle cells, and cardiac fibroblasts. Previous studies had found that heart failure with preserved ejection fraction was more common in women, and women experienced heart failure later than men (29). Sex hormones also have significant impacts on the immune system. Estrogen is more inclined to produce a protective immune response to the myocardium, while androgen can increase the Th1 response and promote inflammation (30). In terms of myocardial remodeling, animal studies had shown that testosterone was the cause of poor myocardial remodeling in men; elevated testosterone levels could promote myocarditis and fibrosis, leading to increased myocardial disease and heart failure (31). Currently, there is no definite evidence that standard heart failure therapies differ significantly between males and females. Overall, the prognosis of women with cardiomyopathy is better than men, but the mechanisms are complex and multifaceted. Research on the gender-specific mechanisms of cardiomyopathy can help improve diagnostic strategies and clinical management, and in-depth research on the cellular mechanisms of the "gender effect" can help find better-targeted therapies for cardiomyopathy.

The burden of childhood cardiomyopathy has significant age characteristics. This study found that the highest ASPR for cardiomyopathy in children aged 0–14 years in China in 1990 and 2019 presented in the 1–4 year old age group, while the highest ASMR and ASDR showed in the younger than 1 year old age group. It was also found that the number of deaths among children younger than 1 year old age group exceeded the prevalence in 1990 and 2019, especially in 1990; while the number of deaths among other age groups was smaller than the prevalence in both years. Cardiomyopathy is one of the most important causes of cardiac insufficiency and sudden cardiac death in children. Many children with cardiomyopathy often have severe clinical manifestations such as heart failure, malignant arrhythmia, embolism, or cardiogenic shock at the time of diagnosis, with extremely poor prognosis and high mortality. The result that the number of deaths in children younger than 1 year old was higher than the prevalence further confirmed the poor prognosis of infantile cardiomyopathy. The highest mortality and DALY rates in infants were mainly related to triggers of infant cardiomyopathy, including genetic abnormalities, genetic and metabolic diseases, and congenital factors such as intrauterine infections. In addition, there is fewer safe and effective interventions for

cardiac insufficiency that has been identified during the fetal period which is an important influencing factor for the high mortality rate of children after birth. The highest prevalence rate among children aged 1–4 years was mainly due to the stable survival of infants with cardiomyopathy after timely diagnosis and effective treatment. Also, the higher diagnostic rate among children aged 1–4 years with cardiomyopathy was another important reason. According to the survey and analysis of 4,981 hospitalized children's cardiomyopathy in 33 hospitals in China from 2006 to 2018 by the Children's Cardiology Precision Diagnosis and Treatment Cooperation Group of Pediatric Society of Chinese Medical Association, 65.15% of children with cardiomyopathy were under the age of 3 years old (32). The result suggested that the incidence rate of early childhood cardiomyopathy in China was significantly higher than that of older children, similar to foreign literature, and also similar to the statistical results of our study. In order to reduce the burden of childhood cardiomyopathy, it is necessary to pay attention to the prevention and treatment of infant cardiomyopathy, and continuously improve the status of genetic testing in the diagnosis and classification of cardiomyopathy. Emphasis should be placed on genetic counseling and eugenics, especially for high-risk families. Complete family lineage excavation and comprehensive genetic counseling should be conducted in these families.

Clinical researches and epidemiological investigations related to cardiomyopathy in children are rare, and relevant academic conferences are rarely held. In this context, our study has some strengths. First, based on the GBD 2019, the data used in our study is calculated using a robust method, and its quality is currently the best (16, 33). Second, this study firstly conducted a comprehensive analysis of the disease burden of cardiomyopathy in children aged 0–14 years in China, which is the first nationwide epidemiological survey of cardiomyopathy in children aged 0–14 years. The purpose of this study is to provide evidence-based medical evidence for future research priorities in children with cardiomyopathy in China, in order to achieve early diagnosis, ameliorate clinical outcomes, and improve the quality of life of children and their families. The epidemiological investigation of childhood cardiomyopathy has also received increasing attention in China. The Collaborative Group on Accurate Diagnosis and Treatment of Childhood Cardiomyopathy of the Cardiovascular Science Group of the Pediatrics Branch of the Chinese Medical Association conducted multicenter retrospective analyses of the clinical data of children with cardiomyopathy from 2006 to 2016 and 2008–2018, providing a reference for accurate diagnosis and treatment of children with cardiomyopathy (32, 34). Important diagnostic and therapeutic recommendations such as "Recommendations for Genetic Testing of Cardiomyopathy in Children" and "Recommendations for the Diagnosis and Treatment of Heart Failure in Children (Revised in 2020)" have also been published (35, 36). In the foreseeable future, with the continuous improvement of gene editing technology, there will also be more and better clinical plans to treat hereditary cardiomyopathy (37). We have confidence that the disease burden caused by children with cardiomyopathy in China and the world will inevitably decrease with the efforts of medical and scientific researchers.

Some limitations should be noticed. First of all, this study uses the data from GBD 2019, which has methodological limitations of GBD 2019 itself. On the other hand, the database only includes data on overall cardiomyopathy in China, which cannot clarify the epidemiological differences between different provinces and regions. Thirdly, there is no survey data for different types of cardiomyopathy in the study. Specific epidemiological investigations targeting different etiologies and types of cardiomyopathy can help to analyze the disease burden of childhood cardiomyopathy in greater depth, but the GBD 2019 does not provide a detailed classification.

In summary, from 1990 to 2019, the disease burden of cardiomyopathy in children aged 0–14 years in China showed heterogeneous changes. The burden of cardiomyopathy in male children was higher than that in female children. Moreover, the burden of cardiomyopathy among people younger than 1-year-old in China requires more attention. Policymakers, researchers, and medical personnel should develop more effective and preventive measures in terms of primary prevention, early diagnosis and treatment, disease management, improvement of public health systems, education and awareness to reduce the burden of childhood cardiomyopathy, pay attention to changes in the epidemic characteristics, and rationally allocate limited medical resources.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving human participants were reviewed and approved by the Institutional Review Boards of Qilu Hospital of Shandong University with approval number KYLL-202011(KS)-239. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Author contributions

QK, XY, and CZ contributed to the conception, design of the work, and results visualization. QK, ML, MW, HZ, XY, and CZ contributed to the acquisition and analysis of data for the work. QK and XY drafted the manuscript. All authors critically revised the manuscript, gave final approval, contributed to the interpretation of the results, and agreed to be accountable for all aspects of the work ensuring integrity and accuracy.

Funding

This work was supported by the Key Research and Development Program of Shandong Province (2019GSF108186). The funders were not involved in the collection, analysis, interpretation of data, the writing, and submitting of this report.

Acknowledgments

We would like to thank the institute for Health Metrics and Evaluation staff and its GBD collaborators who prepared these publicly available data.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2023.1198924/full#supplementary-material

References

1. Burstein DS, Gaynor JW, Griffis H, Ritter A, Connor MJO, Rossano JW, et al. Genetic variant burden and adverse outcomes in pediatric cardiomyopathy. *Pediatr Res*. (2021) 89:1470–6. doi: 10.1038/s41390-020-1101-5

2. Cheng S, Han Y, Jiang L, Lan Z, Guo J. National, regional, and global cardiomyopathy burden from 1990 to 2019. *Front Cardiovasc Med*. (2022) 9:1042448. doi: 10.3389/fcvm.2022.1042448

3. Kantor PF, Kleinman JA, Ryan TD, Wilmot I, Zuckerman WA, Addonizio LJ, et al. Preventing pediatric cardiomyopathy: a 2015 outlook. *Expert Rev Cardiovasc Ther*. (2016) 14:321–39. doi: 10.1586/14779072.2016.1129899

4. McKenna WJ, Maron BJ, Thiene G. Classification, epidemiology, and global burden of cardiomyopathies. *Circ Res*. (2017) 121:722–30. doi: 10.1161/CIRCRESAHA.117.309711

5. Liao Y, Jin H, Huang X, Gong F, Fu L. Editorial: acquired heart disease in children: pathogenesis, diagnosis and management. *Front Pediatr*. (2021) 9:725670. doi: 10.3389/fped.2021.725670

6. Yuan SM. Cardiomyopathy in the pediatric patients. *Pediatr Neonatol*. (2018) 59:120–8. doi: 10.1016/j.pedneo.2017.05.003

7. Liu YC, Yu MM, Shou ST, Chai YF. Sepsis-induced cardiomyopathy: mechanisms and treatments. *Front Immunol*. (2017) 8:1021. doi: 10.3389/fimmu.2017.01021

8. Lipshultz SE, Law YM, Asante-Korang A, Austin ED, Dipchand AI, Everitt MD, et al. Cardiomyopathy in children: classification and diagnosis: a scientific statement from the American Heart Association. *Circulation*. (2019) 140:e9–e68. doi: 10.1161/CIR.0000000000000682

9. Lipshultz SE, Sleeper LA, Towbin JA, Lowe AM, Orav EJ, Cox GF, et al. The incidence of pediatric cardiomyopathy in two regions of the United States. *N Engl J Med*. (2003) 348:1647–55. doi: 10.1056/NEJMoa021715

10. Nugent AW, Daubeney PE, Chondros P, Carlin JB, Cheung M, Wilkinson LC, et al. The epidemiology of childhood cardiomyopathy in Australia. *N Engl J Med*. (2003) 348:1639–46. doi: 10.1056/NEJMoa021737

11. Arola A, Jokinen E, Ruuskanen O, Saraste M, Pesonen E, Kuusela AL, et al. Epidemiology of idiopathic cardiomyopathies in children and adolescents: a nationwide study in Finland. *Am J Epidemiol*. (1997) 146:385–93. doi: 10.1093/oxfordjournals.aje.a009291

12. GBD 2019 Diseases and Injuries Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the global burden of disease study 2019. *Lancet*. (2020) 396:1562–222. doi: 10.1016/S0140-6736(20)32226-1

13. GBD 2019 Risk Factors Collaborators. Global burden of 87 risk factors in 204 countries and territories, 1990-2019: a systematic analysis for the global burden of disease study 2019. *Lancet*. (2020) 396:1223–49. doi: 10.1016/S0140-6736(20)30752-2

14. Murray CJ, Acharya AK. Understanding DALYs (disability-adjusted life years). *J Health Econ*. (1997) 16:703–30. doi: 10.1016/S0167-6296(97)00004-0

15. Chen H, Zhang TC, Yin XL, Man JY, Yang XR, Lu M. Magnitude and temporal trend of acne vulgaris burden in 204 countries and territories from 1990 to 2019: an analysis from the global burden of disease study 2019. *Br J Dermatol*. (2022) 186:673–83. doi: 10.1111/bjd.20882

16. Xu Q, Zhang T, Xia T, Jin B, Chen H, Yang X. Epidemiological trends of kidney Cancer along with attributable risk factors in China from 1990 to 2019 and its projections until 2030: an analysis of the global burden of disease study 2019. *Clin Epidemiol*. (2023) 15:421–33. doi: 10.2147/CLEP.S400646

17. Yang X, Man J, Chen H, Zhang T, Yin X, He Q, et al. Temporal trends of the lung cancer mortality attributable to smoking from 1990 to 2017: a global, regional and national analysis. *Lung Cancer*. (2021) 152:49–57. doi: 10.1016/j.lungcan.2020.12.007

18. Li X, Man J, Chen H, Yang X. Spatiotemporal trends of disease burden of edentulism from 1990 to 2019: a global, regional, and national analysis. *Front Public Health*. (2022) 10:940355. doi: 10.3389/fpubh.2022.940355

19. Li Z, Yang L, Chen H, Fang Y, Zhang T, Yin X, et al. Global, regional and national burden of autism spectrum disorder from 1990 to 2019: results from the global burden of disease study 2019. *Epidemiol Psychiatr Sci*. (2022) 31:e33. doi: 10.1017/S2045796022000178

20. Jordan E, Peterson L, Ai T, Asatryan B, Bronicki L, Brown E, et al. Evidence-based assessment of genes in dilated cardiomyopathy. *Circulation*. (2021) 144:7–19. doi: 10.1161/CIRCULATIONAHA.120.053033

21. Ware SM, Bhatnagar S, Dexheimer PJ, Wilkinson JD, Sridhar A, Fan X, et al. Pediatric cardiomyopathy registry study group. The genetic architecture of pediatric cardiomyopathy. *Am J Hum Genet*. (2022) 109:282–98. doi: 10.1016/j.ajhg.2021.12.006

22. Giri P, Mukhopadhyay A, Gupta M, Mohapatra B. Dilated cardiomyopathy: a new insight into the rare but common cause of heart failure. *Heart Fail Rev*. (2022) 27:431–54. doi: 10.1007/s10741-021-10125-6

23. Mehaney DA, Haghighi A, Embaby AK, Zeyada RA, Darwish RK, Elfeel NS, et al. Molecular analysis of dilated and left ventricular noncompaction cardiomyopathies in Egyptian children. *Cardiol Young*. (2022) 32:295–300. doi: 10.1017/S1047951121002055

24. Tayal U, Prasad S, Cook SA. Genetics and genomics of dilated cardiomyopathy and systolic heart failure. *Genome Med*. (2017) 9:20. doi: 10.1186/s13073-017-0410-8

25. Currie G, Delles C. Precision medicine and personalized medicine in cardiovascular disease. *Adv Exp Med Biol*. (2018) 1065:589–605. doi: 10.1007/978-3-319-77932-4_36

26. Fairweather D, Cooper LT Jr, Blauwet LA. Sex and gender differences in myocarditis and dilated cardiomyopathy. *Curr Probl Cardiol*. (2013) 38:7–46. doi: 10.1016/j.cpcardiol.2012.07.003

27. Tayal U, Prasad S, Cook SA. Genetics and genomics of dilated cardiomyopathy and systolic heart failure. *Genome Med*. (2017) 9:20. doi: 10.1186/s13073-017-0410-8

28. Haddad GE, Saunders LJ, Crosby SD, Carles M, del Monte F, King K, et al. Human cardiac-specific cDNA array for idiopathic dilated cardiomyopathy: sex-related differences. *Physiol Genomics*. (2008) 33:267–77. doi: 10.1152/physiolgenomics.00265.2007

29. Regitz-Zagrosek V, Seeland U. Sex and gender differences in myocardial hypertrophy and heart failure. *Wien Med Wochenschr*. (2011) 161:109–16. doi: 10.1007/s10354-011-0892-8

30. Frisancho-Kiss S, Davis SE, Nyland JF, Frisancho JA, Cihakova D, Barrett MA, et al. Cutting edge: cross-regulation by TLR4 and T cell Ig mucin-3 determines sex differences in inflammatory heart disease. *J Immunol*. (2007) 178:6710–4. doi: 10.4049/jimmunol.178.11.6710

31. Coronado MJ, Brandt JE, Kim E, Bucek A, Bedja D, Abston ED, et al. Testosterone and interleukin-1β increase cardiac remodeling during coxsackievirus B3 myocarditis via serpin a 3n. *Am J Physiol Heart Circ Physiol*. (2012) 302:H1726–36. doi: 10.1152/ajpheart.00783.2011

32. Cooperation Group of Precision Diagnosis and Treatment of Cardiomyopathy in Children, the Subspecialty Group of Cardiology, the Society of Pediatrics, Chinese Medical Association. Investigation and analysis of cardiomyopathy in children from 33 hospitals in China: a multicenter study of 4981 cases from 2006 to 2018. *Chin J Pract Pediatr*. (2021) 36:983–9. doi: 10.3760/cma.j.cn101070-20201108-01731, (in Chinese)

33. Wang H, Zhao S, Wang S, Zheng Y, Wang S, Chen H, et al. Global magnitude of encephalitis burden and its evolving pattern over the past 30 years. *J Infect*. (2022) 84:777–87. doi: 10.1016/j.jinf.2022.04.026

34. Cooperation Group of Precision Diagnosis and Treatment of Cardiomyopathy in Children, the Subspecialty Group of Cardiology, the Society of Pediatrics,Chinese Medical Association. A multicenter study of 1823 cases of hospitalized childhood cardiomyopathy from 2006 to 2016. *Chin J Pract Pediatr* (2019);34:393–399. doi: 10.19538/j.ek2019050616. (in Chinese)

35. The Subspecialty Group of Cardiology, The Society of Pediatrics, Chinese Medical Association, The Editorial Board, and Chinese Journal of Pediatrics. Recommendations

for gene assays for cardiomyopathy in children. *Chin J Pediatr* (2013);51:595–597. doi: 10.3760/cma.j.issn.0578-1310.2013.08.008 (in Chinese)

36. The Subspecialty Group of Cardiology, the Society of Pediatrics, Chinese Medical Association; Pediatric Cardiovascular Disease Committee, College of Cardiovascular Physicians, Chinese Medical Doctor Association, The Editorial Board, and Chinese Journal of Pediatrics. Recommendations for diagnosis and treatment of heart failure in children (2020 revised edition). *Chin J Pediatr* (2021);59:84–94. doi: 10.3760/cma.j.cn112140-20200619-00737. (in Chinese)

37. Nguyen Q, Lim KRQ, Yokota T. Genome editing for the understanding and treatment of inherited cardiomyopathies. *Int J Mol Sci.* (2020) 21:733. doi: 10.3390/ijms21030733

frontiers | Frontiers in Cardiovascular Medicine

TYPE Original Research
PUBLISHED 17 August 2023
DOI 10.3389/fcvm.2023.1236730

OPEN ACCESS

EDITED BY
Zhen-Yu Zhang,
KU Leuven, Belgium

REVIEWED BY
Mirjam Močnik,
University Clinical Centre Maribor, Slovenia
Nataša Marčun Varda,
Maribor University Medical Centre, Slovenia

*CORRESPONDENCE
Bo Xi
✉ xibo2007@126.com

RECEIVED 13 June 2023
ACCEPTED 04 August 2023
PUBLISHED 17 August 2023

CITATION
Liu Q, Wang H, Zhao M, Zhang C, Bovet P and Xi B (2023) Association between clustering of cardiovascular risk factors and left ventricular geometric remodeling in Chinese children. Front. Cardiovasc. Med. 10:1236730. doi: 10.3389/fcvm.2023.1236730

Association between clustering of cardiovascular risk factors and left ventricular geometric remodeling in Chinese children

Qin Liu[1], Huan Wang[2], Min Zhao[3], Cheng Zhang[4], Pascal Bovet[5] and Bo Xi[6]*

[1]Department of Ultrasound, Children's Hospital of the Capital Institute of Pediatrics, Beijing, China, [2]Institute of Child and Adolescent Health, School of Public Health, Peking University, Beijing, China, [3]Department of Toxicology and Nutrition, School of Public Health, Cheeloo College of Medicine, Shandong University, Jinan, China, [4]Key Laboratory of Cardiovascular Remodeling and Function Research, Chinese Ministry of Education, Chinese National Health Commission and Chinese Academy of Medical Sciences, The State and Shandong Province Joint Key Laboratory of Translational Cardiovascular Medicine, Department of Cardiology, Qilu Hospital, Cheeloo College of Medicine, Shandong University, Jinan, China, [5]Center for Primary Care and Public Health (Unisanté), University of Lausanne, Lausanne, Switzerland, [6]Department of Epidemiology, School of Public Health, Cheeloo College of Medicine, Shandong University, Jinan, China

Background: Several cardiovascular (CV) risk factors are reported to be associated with abnormal cardiac structure in children and adults. However, no study has assessed the association between clustering of multiple CV risk factors and left ventricular geometric (LVG) remodeling. We examined the association between clustering of CV risk factors and LVG remodeling among Chinese children.
Methods: This cross-sectional study included 1,406 children aged 6–11 years. Clustering of CV risk factors was quantified as the sum of the number of five CV risk factors (abdominal obesity, elevated blood pressure, high fasting blood glucose, high triglycerides and low high-density lipoprotein cholesterol). Based on left ventricular mass index and relative wall thickness (RWT), left ventricular hypertrophy (LVH), high RWT and LVG remodeling [concentric remodeling (CR), eccentric hypertrophy (EH) and concentric hypertrophy (CH)] were defined.
Results: Compared to participants without CV risk factor, those with 1, 2 and ≥3 risk factors were at increased risk of LVH [ORs (95% CIs): 3.49 (2.19–5.56), 5.53 (3.20–9.55), and 19.19 (9.67–38.08), respectively]; corresponding values for high RWT were 2.47 (1.63–3.74), 3.76 (2.25–6.27), and 5.47 (2.65–11.28). Similar associations between clustering of CV risk factors and LVG remodeling were found [CR: 1.71 (1.06–2.76), 2.83 (1.54–5.18), and 3.82 (1.37–10.62); EH: 2.42 (1.42–4.11), 4.23 (2.24–7.96), and 16.86 (7.70–36.92); CH: 14.92 (4.41–50.47), 23.15 (6.32–84.83), and 71.19 (17.09–296.56)].
Conclusion: CV risk factors in isolation and combination were associated with an increased risk of LVH, high RWT and LVG remodeling among children, emphasizing the need to consider multiple risk factors when assessing the risk of cardiac outcomes.

KEYWORDS

cardiovascular risk factor, children, geometric remodeling, left ventricle, Chinese

1. Introduction

Left ventricular hypertrophy (LVH) is a common target organ damage in youth with hypertension (1). LVH and left ventricular geometric (LVG) remodeling, which are surrogate markers of abnormal cardiac structure, and are independently associated with cardiovascular disease (CVD) morbidity and mortality (2, 3), stroke (4, 5) and cognitive impairment (6, 7).

Previous studies have documented the association between several cardiovascular (CV) risk factors separately and left ventricular structure in both children (8, 9) and adults (10, 11). Indeed, abdominal obesity (12, 13), elevated blood pressure (9, 14), triglycerides (TG) and high-density lipoprotein cholesterol (HDL-C) (15, 16) are independently associated with cardiac structural remodeling in youth. Importantly, these CV risk factors usually co-exist in the population (17, 18) and the clustering of several CV risk factors could have a larger effect on CVD than the sole presence of individual CV risk factor (19). Although the clustering of at least three CV risk factors is defined as metabolic syndrome (MetS), this definition remains controversial. MetS is a binary definition (yes: number of the CV risk factors ≥3 vs. no: number <3) while those with 1 or 2 CV risk factors cannot be simply recognized as metabolicaly healthy. In 2017, the American Academy of Pediatrics also emphasized the need to consider CV risk factors clustering rather than MetS itself (20). Furthermore, a recent review also recommended a validated and unified continuous CV risk score for children (21). Accordingly, a continuous risk score of the clustering of the same five components from MetS may better identify CVD risk. Indeed, an international study of 2,427 children and adolescents aged 6–17 years showed that clustering of CV risk factors performed better than MetS in identifying high carotid intima-media thickness (cIMT, a surrogate marker of subclinical atherosclerosis) (22).

In this study, we investigated the association of clustering of CV risk factors (including the five risk factors used in the definition of MetS) with LVH, high relative wall thickness (RWT), and LVG remodeling [including concentric remodeling (CR), eccentric hypertrophy (EH), and concentric hypertrophy (CH)] among Chinese children aged 6–11 years.

2. Materials and methods

2.1. Participants

Data came from the baseline survey of "Huantai Childhood Cardiovascular Health Cohort Study" conducted in Huantai County, Zibo City, Shandong Province, China, conducted from November 2017 to January 2018. The survey has been described elsewhere (23). In brief, 1,406 children aged 6–11 years from one primary school were included in this study. All children and their parents/guardians provided written informed consent before examinations. Collected data included demographic information (sex and age), anthropometric examinations [height, weight, waist circumference (WC) and blood pressure (BP)], lifestyle factors (sleep duration, screen time, physical activity and intake of vegetables and fruits), fasting blood assays (glucose and lipid profiles) and an echocardiogram examination. The study protocol was approved by the institutional review board at the School of Public Health, Shandong University (approval number: 20160308).

2.2. Collections of CV risk factors

Anthropometric examinations were performed by trained staff according to a standard protocol in the school setting. Height and weight were measured twice in light clothes without shoes using a calibrated scale with stadiometer (HGM-300; Shengyuan Co. Ltd., China). WC was measured twice at 1 cm distance above the horizontal level of umbilicus using a flexible plastic tape. Mean values of height, weight, and WC, as well as body mass index (BMI, kg/m^2), respectively, were calculated for data analysis. The BP in a seated position was measured three times consecutively at the heart level at about 20-second intervals, using the validated and calibrated electronic sphygmomanometer (HEM 7012; Omron, Osaka, Japan) (24). The last two BP readings were averaged for data analysis.

Venous blood samples were drawn after an overnight fast (for at least 10 h). Fasting blood glucose (FBG), TG and HDL-C were assayed using an automatic analyzer (Beckman Coulter AU480; Mishima, Shizuoka, Japan).

2.3. Measurements of left ventricular structure indices

A same experienced sonographer who was blinded with the study protocol measured the left ventricular structure using a portable color Doppler ultrasound machine (CX30; Royal Philips, Amsterdam, the Netherlands) equipped with an S4-2 convex array transducer (frequency of 2–4 MHz), according to recommendations proposed by the American Society of Echocardiography (25). Using the R-wave apex of the electrocardiogram as the standard phase, the left ventricular end-diastolic internal dimension (LVID) was obtained by measuring the echogenicity of the left ventricular septum from the left ventricular surface to the left ventricular posterior wall. In addition, the vertical distance between the two points on the time axis was measured from the upper edge of the front edge echo line to the upper edge of the rear edge echo line of the measured structure to obtain interventricular septal thickness (IVST) and left ventricular posterior wall thickness (LVPWT). Intra-observer reproducibility of IVST values [intra-class correlation coefficient (ICC) = 0.92] and LVPWT values (ICC = 0.95) was evaluated in the same 20 subjects by the same sonographer who measured twice. Left ventricular mass (LVM, g) was calculated using the Devereux's formula as $0.8 \times 1.04 \times [(\mathrm{IVST} + \mathrm{LVID} + \mathrm{LVPWT})^3 - (\mathrm{LVID})^3] + 0.6$ (26). Additionally, left ventricular mass index (LVMI, $g/m^{2.7}$) was calculated as LVM divided by height to the power of 2.7 (27). RWT was calculated as (LVPWT + IVST)/LVID (28).

2.4. Definitions of CV risk factors and LVG patterns

CV risk factors including abdominal obesity, elevated BP, high FBG, high TG and low HDL-C were defined separately as recommended by the Society of Pediatrics, Chinese Medical Association (29). Abdominal obesity was defined as WC ≥90th

percentile values for sex and age (30, 31). Elevated BP was defined as systolic and/or diastolic BP ≥95th percentile values for sex, age and height (32). High FBG (≥5.60 mmol/L), high TG (≥1.47 mmol/L) and low HDL-C (<1.03 mmol/L) were defined according to recommendations from the Society of Pediatrics, Chinese Medical Association (29). The clustering of CV risk factors was defined as the sum of the number of risk factors (abdominal obesity, elevated BP, high FBG, high TG and low HDL-C) with the range spanning from 0 to 4. As only few children had more than 3 risk factors, we combined those with 3–4 risk factors into a same group as ≥3, and the clustering was further categorized as 0, 1, 2 and ≥3. Additionally, we re-defined these CV risk factors according to the same distribution of the present study population, namely the corresponding 90th, 85th and 80th sex- and age-specific percentile values of WC, systolic/diastolic BP, FBG and TG, and 10th, 15th and 20th percentile values of HDL-C.

LVH was defined as LVMI ≥90th percentile values for sex and age of this population, and high RWT was defined as RWT ≥90th percentile values for sex and age of this population (the sex- and age-specific percentile cutoffs of LVMI and RWT are provided in **Supplementary Table S1**). LVG patterns were defined as normal geometry (normal LVMI and normal RWT), CR (normal LVMI and high RWT), EH (LVH and normal RWT) and CH (LVH and high RWT).

2.5. Statistical analysis

All statistical analyses were performed using SAS software version 9.4 (SAS Institute, Cary, NC, USA), and a two-sided $P < 0.05$ was considered statistically significant. Continuous variables were presented as means ± standard deviations and categorical variables as numbers (percentages). Students' *t* test and chi-square test were used to examine differences in characteristics by the LVH status (presence vs. absence) or the RWT status (high vs. normal). Pearson correlation analysis was performed between single CV risk factors and LVMI and RWT. Potential covariates used for adjustment included sex, age, sleep duration (<9 vs. ≥9 h per day), screen time (≤2 vs. >2 h per day), physical activity (<1 vs. ≥1 h per day), and intake of vegetables and fruits (<5 vs. ≥5 servings per day). Adjusted LVMI and RWT levels between each CV risk factor status (abnormal vs. normal) and across the number of CV risk factors (0, 1, 2 and ≥3) were compared using covariance analysis. We also conducted trend analysis for LVMI and RWT levels according to the number of CV risk factors using multivariate linear regression analysis. Binary logistic regression analysis was used to calculate adjusted odds ratios (ORs) and 95% confidence intervals (CIs) of LVH and high RWT, and multi-class logistic regression analysis for LVG remodeling with the normal geometry as the reference category.

3. Results

3.1. Characteristics of study participants

A total of 1,406 children (boys: 52.8%) aged 6–11 years were included in this study. Characteristics of children by the LVH status are shown in **Table 1**. Children with LVH ($n = 133$) had higher levels of BMI, WC, systolic and diastolic BP, and TG, and a lower level of HDL-C than those without LVH ($n = 1,273$). Similar characteristics were found between children with high RWT and those with normal RWT (**Supplementary Table S2**).

3.2. Association of single CV risk factor with LVG remodeling

Abdominal obesity, high TG and low HDL-C were associated with the risk of LVH irrespective of definitions of CV risk factors (**Table 2**). Elevated BP was associated with LVH when using percentile values of this population (**Table 2**). High FBG was associated with LVH when using recommended guideline (**Table 2**). Similarly, regardless of definitions of CV risk factors, abdominal obesity and high TG were associated with increased risk of high RWT, while associations of elevated BP, high FBG and low HDL-C with high RWT varied slightly based on different definitions of CV risk factors (**Table 2**). Besides, there were positive correlations between specific CV risk factors (including WC, SBP, DBP, FBG, and TG; **Supplementary Table S3**) and LVMI and RWT, and HDL-C was related inversely with LVMI ($r = -0.12$, $P < 0.001$; **Supplementary Table S3**). Additionally, covariance analysis showed significant associations of each CV risk factor with LVMI and RWT levels (**Supplementary Table S4**).

TABLE 1 Characteristics of the children according to the LVH status.

Characteristics	Total ($n = 1,406$)	LVH status		
		Presence ($n = 133$)	Absence ($n = 1,273$)	*P* value[a]
Age, years	8.93 ± 1.50	8.87 ± 1.53	8.93 ± 1.50	0.613
Height, cm	136.40 ± 10.67	135.73 ± 12.72	136.46 ± 10.44	0.524
Body mass index, kg/m^2	18.21 ± 3.46	22.54 ± 4.41	17.76 ± 3.01	<0.001
Waist circumference, cm	63.03 ± 9.78	73.05 ± 12.94	61.98 ± 8.75	<0.001
Systolic BP, mmHg	106.43 ± 9.20	108.68 ± 9.75	106.19 ± 9.11	0.003
Diastolic BP, mmHg	63.60 ± 6.66	65.31 ± 7.47	63.42 ± 6.55	0.006
FBG, mmol/L	4.73 ± 0.56	4.81 ± 0.59	4.72 ± 0.55	0.104
TG, mmol/L	0.76 ± 0.35	0.97 ± 0.47	0.74 ± 0.32	<0.001
HDL-C, mmol/L	1.58 ± 0.38	1.44 ± 0.36	1.60 ± 0.38	<0.001
Abdominal obesity, *n* (%)	440 (31.29)	96 (72.18)	344 (27.02)	<0.001
Elevated BP, *n* (%)	215 (15.29)	28 (21.05)	187 (14.69)	0.052
High FBG, *n* (%)	88 (6.26)	15 (11.28)	73 (5.73)	0.012
High TG, *n* (%)	64 (4.55)	19 (14.29)	45 (3.53)	<0.001
Low HDL-C, *n* (%)	76 (5.41)	16 (12.03)	60 (4.71)	<0.001
Short sleep duration, *n* (%)	229 (16.29)	11 (8.27)	218 (17.12)	0.009
Long screen time, *n* (%)	62 (4.41)	9 (6.77)	53 (4.16)	0.164
Insufficient physical activity, *n* (%)	796 (56.61)	78 (58.65)	718 (56.40)	0.619
Insufficient intake of fruits and/or vegetables, *n* (%)	1,142 (81.22)	115 (86.47)	1,027 (80.68)	0.104

Continuous variables are presented as means ± standard deviations. BP, blood pressure; FBG, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; LVH, left ventricular hypertrophy; TG, triglycerides.
[a]Group differences between the LVH status.

TABLE 2 Associations of each CV risk factor with LVH and high RWT.

CV risk factors	LVH			High RWT		
	n (%)[b]	OR (95% CI)	*P* value	*n* (%)[b]	OR (95% CI)	*P* value
Abdominal obesity						
Recommended[a] (*n* = 440)	96 (21.82)	6.85 (4.58–10.24)	<0.001	79 (17.95)	3.42 (2.38–4.91)	<0.001
P90 (*n* = 146)	53 (36.30)	8.52 (5.62–12.93)	<0.001	37 (25.34)	4.10 (2.66–6.33)	<0.001
P85 (*n* = 216)	68 (31.48)	8.10 (5.49–11.95)	<0.001	53 (24.54)	4.40 (2.99–6.47)	<0.001
P80 (*n* = 286)	84 (29.37)	9.08 (6.16–13.39)	<0.001	65 (22.73)	4.26 (2.95–6.15)	<0.001
Elevated BP						
Recommended[a] (*n* = 215)	28 (13.02)	1.48 (0.95–2.32)	0.087	26 (12.09)	1.31 (0.83–2.07)	0.240
P90 (*n* = 234)	34 (14.53)	1.77 (1.16–2.69)	0.008	37 (15.81)	2.00 (1.33–3.00)	0.001
P85 (*n* = 341)	44 (12.90)	1.57 (1.07–2.31)	0.022	48 (14.08)	1.75 (1.20–2.55)	0.003
P80 (*n* = 446)	53 (11.88)	1.46 (1.01–2.11)	0.044	56 (12.56)	1.50 (1.05–2.16)	0.026
High FBG						
Recommended[a] (*n* = 88)	15 (17.05)	2.21 (1.21–4.06)	0.010	15 (17.05)	1.94 (1.06–3.53)	0.031
P90 (*n* = 148)	19 (12.84)	1.52 (0.90–2.56)	0.118	20 (13.51)	1.48 (0.89–2.46)	0.132
P85 (*n* = 217)	25 (11.52)	1.34 (0.84–2.14)	0.219	30 (13.82)	1.56 (1.01–2.42)	0.044
P80 (*n* = 288)	34 (11.81)	1.43 (0.94–2.18)	0.091	41 (14.24)	1.71 (1.15–2.53)	0.008
High TG						
Recommended[a] (*n* = 64)	19 (29.69)	5.15 (2.83–9.38)	<0.001	12 (18.75)	2.18 (1.12–4.26)	0.022
P90 (*n* = 150)	32 (21.33)	3.10 (1.99–4.84)	<0.001	25 (16.67)	1.98 (1.23–3.17)	0.005
P85 (*n* = 220)	42 (19.09)	2.88 (1.93–4.31)	<0.001	33 (15.00)	1.80 (1.18–2.74)	0.007
P80 (*n* = 291)	54 (18.56)	3.02 (2.07–4.40)	<0.001	41 (14.09)	1.71 (1.15–2.52)	0.008
Low HDL-C						
Recommended[a] (*n* = 76)	16 (21.05)	2.90 (1.61–5.25)	<0.001	16 (21.05)	2.71 (1.51–4.86)	0.001
P10 (*n* = 132)	27 (20.45)	2.89 (1.80–4.63)	<0.001	19 (14.39)	1.67 (0.99–2.82)	0.055
P15 (*n* = 200)	31 (15.50)	2.03 (1.31–3.15)	0.002	25 (12.50)	1.41 (0.89–2.25)	0.143
P20 (*n* = 277)	40 (14.44)	1.90 (1.28–2.83)	0.002	37 (13.36)	1.57 (1.05–2.35)	0.028

Binary logistic regression models were performed separately for each cardiovascular risk factor adjusting for sex, age, sleep duration, screen time, physical activity, and intake of vegetables and fruits. P90, P85 and P80 represented the corresponding sex- and age-specific percentile values of waist circumference, systolic/diastolic BP, FBG and TG based on the present population, and P10, P15 and P20 for HDL-C. BP, blood pressure; CI, confidence interval; CV, cardiovascular; FBG, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; LVH, left ventricular hypertrophy; OR, odds ratio; RWT, relative wall thickness; TG, triglycerides.
[a]Recommended guideline from the Society of Pediatrics, Chinese Medical Association.
[b]Percentages are calculated as: (the number of subjects with LVH or high RWT)/(the number of those with specific CV risk factors)×100%.

Abdominal obesity (OR = 2.34, 95% CI: 1.53–3.59) and low HDL-C (OR = 2.36, 95% CI: 1.12–4.97) were associated with CR. Elevated BP (90th or 85th) and high TG (85th) defined using the percentiles were also associated with CR (**Supplementary Table S5**). Abdominal obesity, elevated BP, high TG, and low HDL-C increased the risk of EH with ORs (95% CIs) of 5.26 (3.34–8.29), 1.72 (1.03–2.89), 5.92 (2.92–11.98), and 2.58 (1.21–5.47), respectively; these associations were mostly similar when defining CV risk factors based on the percentiles (**Supplementary Table S5**). Abdominal obesity, high FBG, high TG, and low HDL-C also increased the risk of CH, with ORs (95% CIs) of 20.96 (8.13–54.03), 3.33 (1.38–8.06), 4.82 (1.86–12.52), and 4.58 (1.92–10.92), respectively; similar associations were found when CV risk factors were defined using the percentiles for definitions (**Supplementary Table S5**).

3.3. Association of clustering of CV risk factors with LVG remodeling

There were 787 (55.97%) children without CV risk factor, 413 (29.37%) with one, 156 (11.10%) with two, and 50 (3.56%) with at least three. LVMI and RWT levels were higher along increasing number of CV risk factors (*P* for linear trend <0.001), after adjustment for sex, age, sleep duration, screen time, physical activity, and intake of vegetables and fruits (**Figures 1**, **2**).

The prevalence of LVH and high RWT increased progressively across the clustering of CV risk factors (**Table 3**). Compared with children without CV risk factor, those with 1, 2 and ≥3 CV risk factors were associated with an increased risk of LVH, with ORs (95% CIs) of 3.49 (2.19–5.56), 5.53 (3.20–9.55), and 19.19 (9.67–38.08), respectively (**Table 3**). Similarly, the more number of CV risk factors was associated with a higher risk of high RWT [2.47 (1.63–3.74) for 1, 3.76 (2.25–6.27) for 2, and 5.47 (2.65–11.28) for ≥3, **Table 3**]. Similar associations were found when CV risk factors were defined based on the percentiles (**Table 3**).

The clustering of CV risk factors was associated with LVG remodeling including CR, EH and CH (**Table 4**). The corresponding ORs (95% CIs) of CR were 1.71 (1.06–2.76), 2.83 (1.54–5.18), and 3.82 (1.37–10.62), respectively, for children with 1, 2 and ≥3 CV risk factors; those of EH were 2.42 (1.42–4.11), 4.23 (2.24–7.96), and 16.86 (7.70–36.92), respectively; those of CH were 14.92 (4.41–50.47), 23.15 (6.32–84.83), and 71.19 (17.09–296.56), respectively. Similar associations of the clustering

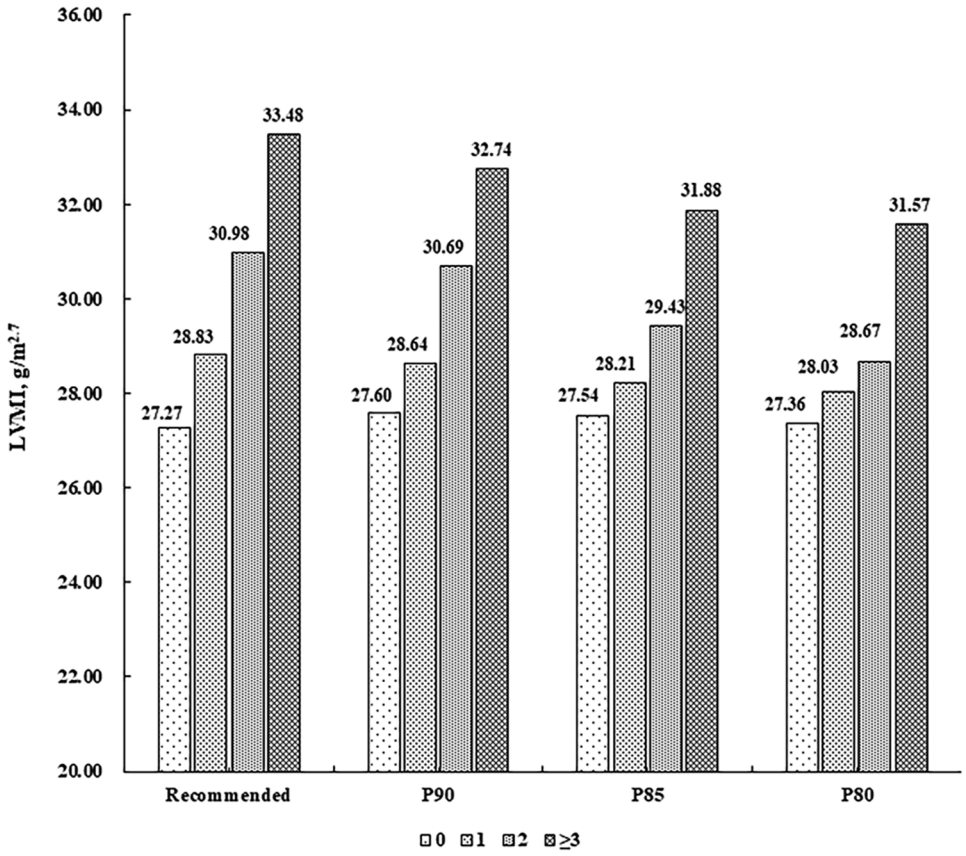


FIGURE 1
Mean levels of LVMI (g/m$^{2.7}$) according to the number of cardiovascular risk factors. Cardiovascular risk factors were defined according to the recommended guideline from the Society of Pediatrics, Chinese Medical Association and the corresponding sex- and age-specific percentile values based on the present population, respectively (P90, P85 and P80 for waist circumference, systolic/diastolic blood pressure, fasting blood glucose, and triglycerides, and P10, P15 and P20 for high-density lipoprotein cholesterol). LVMI, left ventricular mass index.

of CV risk factors with CR, EH and CH were found when using the percentiles for definitions.

4. Discussion

In this cross-sectional study among 1,406 children aged 6–11 years from China, we found that increased numbers of CV risk factors were associated with the higher levels of LVMI and RWT. The clustering of CV risk factors progressively increased the risk of LVH, high RWT and LVG remodeling (CR, EH and CH). These findings indicate a strong association between the number of CV risk factors and the risk of LVG remodeling among children.

Consistent with previous studies, we found that specific CV risk factors were significantly associated with LVMI and RWT. A retrospective study including 160 overweight and obese children and adolescents aged 6–18 years found that WC above the 90th percentile values was associated with increased LVMI and CH (33). A cross-sectional study of 303 adolescents (mean age 15.6 years) showed an independent relationship between BP and LVMI (9). A cross-sectional study of 70 children with obesity (median age 14 years) found positive correlations of TG and the TG-to-HDL-C ratio with LVMI and RWT (15). Associations of the TG-to-HDL-C ratio with LVMI and RWT were also found in a study including 884 outpatient children and adolescents aged 6–16 years (16). In the present study, WC, SBP, DBP, FBG, and TG were positively related with LVMI and RWT, along with inverse correlation between HDL-C and LVMI. Our findings, combined with prior research, may suggest that monitoring CV risk factors among children holds practical value for the prevention of subclinical target organ damage.

Comparatively, abdominal obesity among all five CV risk factors had the largest effect on the cardiac remodeling. Obesity has been considered as a state of chronic metabolic disorder (34), and obesity-related hemodynamic factors (e.g., increased circulating blood volume and cardiac output) and metabolic factors (e.g., insulin resistance, visceral fat deposition and secretion of adipokines) may contribute to a series of adaptations/alterations in cardiac structure and function (35). Besides, obesity frequently promotes other CV risk factors such as hypertension, dyslipidemia, and glucose intolerance (36), and there is also an additive effect between obesity and BP on cardiac remodeling (37). Evidence shows that elevated BP is a prominent contributor to cardiac remodeling (38), however, a weaker association between elevated BP (vs. abdominal obesity) and cardiac remodeling was found in our study. This may suggest

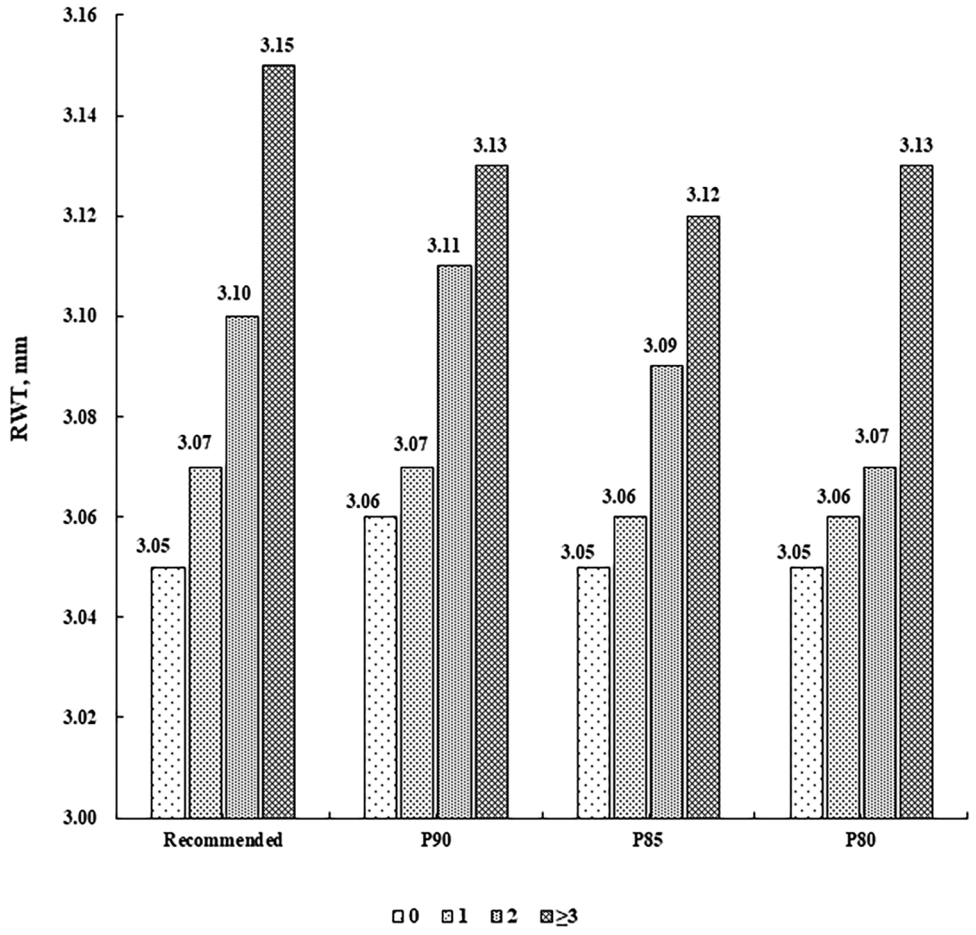


FIGURE 2
Mean levels of RWT (mm) according to the number of cardiovascular risk factors. Cardiovascular risk factors were defined according to the recommended guideline from the Society of Pediatrics, Chinese Medical Association and the corresponding sex- and age-specific percentile values based on the present population, respectively (P90, P85 and P80 for waist circumference, systolic/diastolic blood pressure, fasting blood glucose, and triglycerides, and P10, P15 and P20 for high-density lipoprotein cholesterol). RWT, relative wall thickness.

that other underlying mechanisms other than BP-related responses may play a vital role. Further studies are warranted to clarify the pathophysiologic mechanisms.

Furthermore, our study also showed that LVMI and RWT levels increased markedly according to the number of CV risk factors. Similarly, a cross-sectional study of 830 young US adults aged 24–43 years found that LVMI levels increased according to the number of abnormal MetS components (39). In another cross-sectional study of 291 children (mean age 11.7 years), a comprehensive CV risk score based on five MetS components had a positive correlation with cIMT levels (40). Overall, these findings support an additive effect of these risk factors on continuous subclinical CVD markers.

A recent combined analysis of three population-based studies of 2,427 children and adolescents aged 6–17 years showed that a graded risk score based on five MetS components was superior to dichotomous classification of MetS to predict high cIMT (22). Additionally, our findings that having ≥3 CV risk factors was associated with the highest risk of LVG remodeling, followed by having two and one CV risk factors, indicate a dose-response association between the clustering of CV risk factors and LVG remodeling. Of note, children who did not meet the definition of MetS (i.e., number of CV risk factors as 1 or 2) were also at an increased risk of LVG remodeling, re-emphasizing the continuous nature of the association between CV risk factors and cardiac outcomes. Therefore, our findings supported that it is important to focus on clustering of CV risk factors among children and adolescents rather than the arbitrarily defined MetS (20). Moreover, irrespective of what are cutoffs of CV risk factors, it is essential to keep an optimal levels of health factors. As exemplified in a child cohort study from China, the ideal levels of four behavior factors (i.e., diet, physical activity, nicotine exposure, sleep heath) as well as four health indicators (i.e., BMI, blood lipids, blood glucose, and blood pressure) were conducive to reducing the abnormal cardiovascular structures (41).

To our knowledge, this is the first study examining the association between the clustering of CV risk factors and LVG remodeling among Chinese children. Meanwhile, there are several limitations in this study that should be considered. First, this study included children aged 6–11 years from only one

TABLE 3 Associations of the clustering of CV risk factors with LVH and high RWT.

Cut-offs	Number of CV risk factors	LVH		High RWT	
		n (%)	OR (95% CI)	*n* (%)	OR (95% CI)
Recommended[a]	0 ($n = 787$)	31 (3.94)	Reference	45 (5.72)	Reference
	1 ($n = 413$)	52 (12.59)	3.49 (2.19–5.56)	54 (13.08)	2.47 (1.63–3.74)
	2 ($n = 156$)	29 (18.59)	5.53 (3.20–9.55)	28 (17.95)	3.76 (2.25–6.27)
	≥3 ($n = 50$)	21 (42.00)	19.19 (9.67–38.08)	12 (24.00)	5.47 (2.65–11.28)
P90	0 ($n = 853$)	42 (4.92)	Reference	53 (6.21)	Reference
	1 ($n = 367$)	43 (11.72)	2.54 (1.62–3.96)	49 (13.35)	2.34 (1.56–3.54)
	2 ($n = 129$)	27 (20.93)	5.11 (3.00–8.69)	26 (20.16)	3.89 (2.32–6.52)
	≥3 ($n = 57$)	21 (36.84)	11.19 (5.96–20.98)	11 (19.30)	3.73 (1.82–7.65)
P85	0 ($n = 684$)	32 (4.68)	Reference	40 (5.85)	Reference
	1 ($n = 398$)	35 (8.79)	2.03 (1.23–3.34)	43 (10.80)	1.95 (1.25–3.07)
	2 ($n = 209$)	31 (14.83)	3.43 (2.03–5.79)	30 (14.35)	2.69 (1.62–4.45)
	≥3 ($n = 115$)	35 (30.43)	9.23 (5.38–15.83)	26 (22.61)	4.87 (2.83–8.39)
P80	0 ($n = 529$)	18 (3.40)	Reference	31 (5.86)	Reference
	1 ($n = 413$)	35 (8.47)	2.78 (1.55–5.01)	34 (8.23)	1.42 (0.86–2.36)
	2 ($n = 282$)	27 (9.57)	2.96 (1.59–5.49)	34 (12.06)	2.20 (1.32–3.68)
	≥3 ($n = 182$)	53 (29.12)	12.08 (6.81–21.44)	40 (21.98)	4.50 (2.71–7.47)

Binary logistic regression models were performed with adjustment for sex, age, sleep duration, screen time, physical activity, and intake of vegetables and fruits. P90, P85 and P80 represented the corresponding sex- and age-specific percentile values of waist circumference, systolic/diastolic blood pressure, fasting blood glucose and triglycerides based on the present population, and P10, P15 and P20 for high-density lipoprotein cholesterol. CI, confidence interval; CV, cardiovascular; LVH, left ventricular hypertrophy; OR, odds ratio; RWT, relative wall thickness.
[a]Recommended guideline from the Society of Pediatrics, Chinese Medical Association.

TABLE 4 Association of the clustering of CV risk factors with LVG.

Cut-offs	Number of CV risk factors	CR		EH		CH	
		n (%)	OR (95% CI)	*n* (%)	OR (95% CI)	*n* (%)	OR (95% CI)
Recommended[a]	0 ($n = 787$)	42 (5.34)	Reference	28 (3.56)	Reference	3 (0.38)	Reference
	1 ($n = 413$)	33 (7.99)	1.71 (1.06–2.76)	31 (7.51)	2.42 (1.42–4.11)	21 (5.08)	14.92 (4.41–50.47)
	2 ($n = 156$)	17 (10.90)	2.83 (1.54–5.18)	18 (11.54)	4.23 (2.24–7.96)	11 (7.05)	23.15 (6.32–84.83)
	≥3 ($n = 50$)	5 (10.00)	3.82 (1.37–10.62)	14 (28.00)	16.86 (7.70–36.92)	7 (14.00)	71.19 (17.09–296.56)
P90	0 ($n = 853$)	46 (5.39)	Reference	35 (4.10)	Reference	7 (0.82)	Reference
	1 ($n = 367$)	31 (8.45)	1.79 (1.11–2.89)	25 (6.81)	1.85 (1.09–3.16)	18 (4.90)	6.63 (2.74–16.05)
	2 ($n = 129$)	13 (10.08)	2.55 (1.32–4.92)	14 (10.85)	3.52 (1.81–6.84)	13 (10.08)	15.46 (5.97–40.02)
	≥3 ($n = 57$)	7 (12.28)	4.33 (1.79–10.48)	17 (29.82)	13.12 (6.52–26.41)	4 (7.02)	14.49 (3.99–52.65)
P85	0 ($n = 684$)	34 (4.97)	Reference	26 (3.80)	Reference	6 (0.88)	Reference
	1 ($n = 398$)	31 (7.79)	1.70 (1.03–2.83)	23 (5.78)	1.72 (0.97–3.07)	12 (3.02)	3.77 (1.40–10.15)
	2 ($n = 209$)	19 (9.09)	2.23 (1.23–4.03)	20 (9.57)	2.95 (1.60–5.45)	11 (5.26)	6.62 (2.40–18.28)
	≥3 ($n = 115$)	13 (11.30)	3.71 (1.86–7.41)	22 (19.13)	8.23 (4.39–15.45)	13 (11.30)	20.24 (7.41–55.30)
P80	0 ($n = 529$)	27 (5.10)	Reference	14 (2.65)	Reference	4 (0.76)	Reference
	1 ($n = 413$)	26 (6.30)	1.30 (0.74–2.27)	27 (6.54)	2.85 (1.47–5.53)	8 (1.94)	2.81 (0.84–9.44)
	2 ($n = 282$)	27 (9.57)	2.19 (1.25–3.84)	20 (7.09)	3.06 (1.51–6.19)	7 (2.48)	3.48 (1.00–12.06)
	≥3 ($n = 182$)	17 (9.34)	2.70 (1.42–5.15)	30 (16.48)	9.75 (4.97–19.10)	23 (12.64)	24.82 (8.39–73.46)

Multi-class logistic regression models were performed with adjustment for sex, age, sleep duration, screen time, physical activity, and intake of vegetables and fruits. P90, P85 and P80 represented the corresponding sex- and age-specific percentile values of waist circumference, systolic/diastolic blood pressure, fasting blood glucose and triglycerides based on the present population, and P10, P15 and P20 for high-density lipoprotein cholesterol. CH, concentric hypertrophy; CI, confidence interval; CR, concentric remodeling; CV, cardiovascular; EH, eccentric hypertrophy; LVG, left ventricular geometric; OR, odds ratio.
[a]Recommended guideline from the Society of Pediatrics, Chinese Medical Association.

primary school, making our results less generalizable. Further studies in children with different ages from other regions are needed to further validate the associations observed in this study. Second, the cross-sectional data used in this study preclude concluding on the causal link of CV risk factors on cardiac outcomes. Third, although different CV risk factors had different effects on the cardiac structure, and we did not allocate different weights to specific risk factors because of unavailable weights, we partially addressed this issue by considering these CV risk factors along percentile values of the present population.

5. Conclusion

CV risk factors in isolation and combination were associated with an increased risk of LVH, high RWT and LVG remodeling

among children, emphasizing the need to consider multiple risk factors when assessing the risk of cardiac outcomes.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by School of Public Health, Shandong University (approval number: 20160308). The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

QL contributed to writing of the original draft, formal analysis, reviewing and editing. HW contributed to data curation, formal analysis, reviewing and editing. CZ, MZ, and PB contributed to conceptualization, methodology, reviewing and editing. BX contributed to conceptualization, methodology, reviewing and editing. All authors contributed to the article and approved the submitted version.

Funding

This work was supported by the National Natural Science Foundation of China (81673195, 81722039). The funders had no role in the design, analysis, or submission of the prepared manuscript.

Acknowledgments

We thank all the participants in this study.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2023.1236730/full#supplementary-material

References

1. National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. *Pediatrics*. (2004) 114:555–76. doi: 10.1542/peds.114.s2.iv

2. Eskerud I, Gerdts E, Larsen TH, Lonnebakken MT. Left ventricular hypertrophy contributes to myocardial ischemia in non-obstructive coronary artery disease (the microcad study). *Int J Cardiol*. (2019) 286:1–6. doi: 10.1016/j.ijcard.2019.03.059

3. Akintoye E, Mahmoud K, Shokr M, Sandio A, Mallikethi-Reddy S, Sheikh M, et al. Racial/ethnic differences in the prognostic utility of left ventricular mass Index for incident cardiovascular disease. *Clin Cardiol*. (2018) 41:502–9. doi: 10.1002/clc.22914

4. Wang S, Xue H, Zou Y, Sun K, Fu C, Wang H, et al. Left ventricular hypertrophy, abnormal ventricular geometry and relative wall thickness are associated with increased risk of stroke in hypertensive patients among the Han Chinese. *Hypertens Res*. (2014) 37:870–4. doi: 10.1038/hr.2014.88

5. O'Neal WT, Almahmoud MF, Qureshi WT, Soliman EZ. Electrocardiographic and echocardiographic left ventricular hypertrophy in the prediction of stroke in the elderly. *J Stroke Cerebrovasc Dis*. (2015) 24:1991–7. doi: 10.1016/j.jstrokecerebrovasdis.2015.04.044

6. Norby FL, Chen LY, Soliman EZ, Gottesman RF, Mosley TH, Alonso A. Association of left ventricular hypertrophy with cognitive decline and dementia risk over 20 years: the atherosclerosis risk in communities-neurocognitive study (Aric-Ncs). *Am Heart J*. (2018) 204:58–67. doi: 10.1016/j.ahj.2018.07.007

7. Moazzami K, Ostovaneh MR, Ambale Venkatesh B, Habibi M, Yoneyama K, Wu C, et al. Left ventricular hypertrophy and remodeling and risk of cognitive impairment and dementia: mesa (multi-ethnic study of atherosclerosis). *Hypertension*. (2018) 71:429–36. doi: 10.1161/HYPERTENSIONAHA.117.10289

8. Jing L, Nevius CD, Friday CM, Suever JD, Pulenthiran A, Mejia-Spiegeler A, et al. Ambulatory systolic blood pressure and obesity are independently associated with left ventricular hypertrophic remodeling in children. *J Cardiovasc Magn Reson*. (2017) 19:86. doi: 10.1186/s12968-017-0401-3

9. Urbina EM, Mendizabal B, Becker RC, Daniels SR, Falkner BE, Hamdani G, et al. Association of blood pressure level with left ventricular mass in adolescents. *Hypertension*. (2019) 74:590–6. doi: 10.1161/HYPERTENSIONAHA.119.13027

10. Kishi S, Gidding SS, Reis JP, Colangelo LA, Venkatesh BA, Armstrong AC, et al. Association of insulin resistance and glycemic metabolic abnormalities with lv structure and function in middle age: the cardia study. *JACC Cardiovasc Imaging*. (2017) 10:105–14. doi: 10.1016/j.jcmg.2016.02.033

11. Pietri P, Georgiopoulos G, Tsiachris D, Kordalis A, Vlachopoulos C, Vyssoulis G, et al. Triglycerides are related to left ventricular mass in hypertensive patients independently of other cardiometabolic risk factors: the effect of gender. *Sci Rep*. (2020) 10:13253. doi: 10.1038/s41598-020-70237-1

12. Rodicio MM, Domenech de Miguel V, Guinda Jimenez M, Cigarran Guldris S, Lopez Franco MM, Estany Gestal A, et al. Early cardiac abnormalities in obese children and their relationship with adiposity. *Nutrition*. (2018) 46:83–9. doi: 10.1016/j.nut.2017.09.001

13. Mehta SK. Waist circumference to height ratio and left ventricular mass in children and adolescents. *Cardiol Young*. (2016) 26:658–62. doi: 10.1017/S1047951115000803

14. Maugeri A, Hruskova J, Jakubik J, Barchitta M, Lo Re O, Kunzova S, et al. Independent effects of hypertension and obesity on left ventricular mass and geometry: evidence from the cardiovision 2030 study. *J Clin Med*. (2019) 8:370. doi: 10.3390/jcm8030370

15. Bjelakovic B, Stefanutti C, Vukovic V, Kavaric N, Saranac L, Klisic A, et al. Lipid profile and left ventricular geometry pattern in obese children. *Lipids Health Dis*. (2020) 19:109. doi: 10.1186/s12944-020-01285-9

16. Di Bonito P, Moio N, Scilla C, Cavuto L, Sibilio G, Sanguigno E, et al. Usefulness of the high triglyceride-to-hdl cholesterol ratio to identify cardiometabolic risk factors and preclinical signs of organ damage in outpatient children. *Diabetes Care*. (2012) 35:158–62. doi: 10.2337/dc11-1456

17. Camhi SM, Katzmarzyk PT. Tracking of cardiometabolic risk factor clustering from childhood to adulthood. *Int J Pediatr Obes*. (2010) 5:122–9. doi: 10.3109/17477160903111763

18. Smoak CG, Burke GL, Webber LS, Harsha DW, Srinivasan SR, Berenson GS. Relation of obesity to clustering of cardiovascular disease risk factors in children and young adults: the Bogalusa heart study. *Am J Epidemiol*. (1987) 125:364–72. doi: 10.1093/oxfordjournals.aje.a114543

19. Chung ST, Onuzuruike AU, Magge SN. Cardiometabolic risk in obese children. *Ann N Y Acad Sci*. (2018) 1411:166–83. doi: 10.1111/nyas.13602

20. Magge SN, Goodman E, Armstrong SC, Committee on Nutrition, Section on Endocrinology, Section on Obesity. The metabolic syndrome in children and adolescents: shifting the focus to cardiometabolic risk factor clustering. *Pediatrics*. (2017) 140:e20171603. doi: 10.1542/peds.2017-1603

21. Kamel M, Smith BT, Wahi G, Carsley S, Birken CS, Anderson LN. Continuous cardiometabolic risk score definitions in early childhood: a scoping review. *Obes Rev*. (2018) 19:1688–99. doi: 10.1111/obr.12748

22. Zhao M, Caserta CA, Medeiros CCM, Lopez-Bermejo A, Kollias A, Zhang Q, et al. Metabolic syndrome, clustering of cardiovascular risk factors and high carotid intima-media thickness in children and adolescents. *J Hypertens*. (2020) 38:618–24. doi: 10.1097/HJH.0000000000002318

23. Yang LL, Zhang Q, Zhang YQ, Sun JH, Zhao M, Xi B. Design of huantai childhood cardiovascular health cohort study. *Chin J Prev Med*. (2020) 54:1461–4. doi: 10.3760/cma.j.cn112150-20200610-00857

24. Meng LH, Hou DQ, Shan XY, Mi J. Accuracy evaluation of omron hem-7012 electronic sphygmomanometers in measuring blood pressure of children and adolescents. *Chin J Hypertens*. (2013) 21:158–62. doi: 10.16439/j.cnki.1673-7245.2013.02.036

25. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, et al. Recommendations for chamber quantification: a report from the American society of echocardiography's guidelines and standards committee and the chamber quantification writing group, developed in conjunction with the European association of echocardiography, a branch of the European society of cardiology. *J Am Soc Echocardiogr*. (2005) 18:1440–63. doi: 10.1016/j.echo.2005.10.005

26. Devereux RB, Alonso DR, Lutas EM, Gottlieb GJ, Campo E, Sachs I, et al. Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. *J Am Soc Echocardiogr*. (1986) 57:450–8. doi: 10.1016/0002-9149(86)90771-X

27. de Simone G, Daniels SR, Devereux RB, Meyer RA, Roman MJ, Dedivitiis O, et al. Left-ventricular mass and body size in normotensive children and adults-assessment of allometric relations and impact of overweight. *J Am Coll Cardiol*. (1992) 20:1251–60. doi: 10.1016/0735-1097(92)90385-z

28. Reichek N, Devereux RB. Reliable estimation of peak left ventricular systolic pressure by M-mode echographic-determined End-diastolic relative wall thickness: identification of severe valvular aortic stenosis in adult patients. *Am Heart J*. (1982) 103:202–3. doi: 10.1016/0002-8703(82)90493-8

29. The Society of Pediatrics, , The Subspecialty Group of Endocrinologic Hereditary and Metabolic Diseases, , The Subspecialty Group of Cardiology, , The Subspecialty Group of Child Health Care, Chinese Medical Association. The definition and prevention recommends of metabolic syndrome in Chinese children and adolescents. *Chin J Pediatr*. (2012) 50:420–2. doi: 10.3760/cma.j.issn.0578-1310.2012.06.005

30. Zong XN, Li H, Zhang YQ. Percentile reference value of waist circumference for Chinese children aged 3-7 years. *Chin J Epidemiol*. (2020) 41:1286–90. doi: 10.3760/cma.j.cn112338-20190827-00629

31. Ma GS, Ji CY, Ma J, Mi J, Sung RY, Xiong F, et al. Waist circumference reference values for screening cardiovascular risk factors in Chinese children and adolescents aged 7-18 years. *Chin J Epidemiol*. (2010) 31:609–15. doi: 10.3760/cma.j.issn.0254-6450.2010.06.003

32. Fan H, Yan YK, Mi J. Updating blood pressure references for Chinese children aged 3-17 years. *Chin J Hypertens*. (2017) 25:428–35. doi: 10.16439/j.cnki.1673-7245.2017.05.009

33. Trandafir LM, Russu G, Moscalu M, Miron I, Lupu VV, Leon Constantin MM, et al. Waist circumference a clinical criterion for prediction of cardio-vascular complications in children and adolescences with overweight and obesity. *Medicine*. (2020) 99:e20923. doi: 10.1097/MD.0000000000020923

34. Poirier P, Giles TD, Bray GA, Hong Y, Stern JS, Pi-Sunyer FX, et al. Obesity and cardiovascular disease: pathophysiology, evaluation, and effect of weight loss: an update of the 1997 American heart association scientific statement on obesity and heart disease from the obesity committee of the council on nutrition, physical activity, and metabolism. *Circulation*. (2006) 113:898–918. doi: 10.1161/CIRCULATIONAHA.106.171016

35. Brady TM. The role of obesity in the development of left ventricular hypertrophy among children and adolescents. *Curr Hypertens Rep*. (2016) 18:3. doi: 10.1007/s11906-015-0608-3

36. Bastien M, Poirier P, Lemieux I, Despres JP. Overview of epidemiology and contribution of obesity to cardiovascular disease. *Prog Cardiovasc Dis*. (2014) 56:369–81. doi: 10.1016/j.pcad.2013.10.016

37. Woodiwiss AJ, Norton GR. Obesity and left ventricular hypertrophy: the hypertension connection. *Curr Hypertens Rep*. (2015) 17:539. doi: 10.1007/s11906-015-0539-z

38. Yildiz M, Oktay AA, Stewart MH, Milani RV, Ventura HO, Lavie CJ. Left ventricular hypertrophy and hypertension. *Prog Cardiovasc Dis*. (2020) 63:10–21. doi: 10.1016/j.pcad.2019.11.009

39. Patel DA, Srinivasan SR, Chen W, Berenson GS. Influence of the metabolic syndrome versus the sum of its individual components on left ventricular geometry in young adults (from the Bogalusa heart study). *Am J Cardiol*. (2009) 104:69–73. doi: 10.1016/j.amjcard.2009.02.063

40. Gooty VD, Sinaiko AR, Ryder JR, Dengel DR, Jacobs DR Jr, Steinberger J. Association between carotid intima media thickness, age, and cardiovascular risk factors in children and adolescents. *Metab Syndr Relat Disord*. (2018) 16:122–6. doi: 10.1089/met.2017.0149

41. Shu W, Li M, Xiao H, Amaerjiang N, Khattab NM, Zunong J, et al. Validation of "life's essential 8" metrics with cardiovascular structural Status in children: the PROC study in China. *J Am Heart Assoc*. (2023) 12:e029077. doi: 10.1161/JAHA.122.029077

frontiers | Frontiers in Cardiovascular Medicine

TYPE Original Research
PUBLISHED 15 September 2023
DOI 10.3389/fcvm.2023.1216976

OPEN ACCESS

EDITED BY
Shikai Yu,
Tongji University, China

REVIEWED BY
Roman A. Gebauer,
Leipzig University, Germany
Gaetano Thiene,
University of Padua, Italy
Andreas Brodehl,
Heart and Diabetes Center North Rhine-Westphalia, Germany
Samira Kalayinia,
Shaheed Rajaei Cardiovascular Medical and Research Center, Iran

*CORRESPONDENCE
Olga Kofeynikova
✉ kofeolyaa@gmail.com

RECEIVED 04 May 2023
ACCEPTED 04 September 2023
PUBLISHED 15 September 2023

CITATION
Kofeynikova O, Alekseeva D, Vershinina T, Fetisova S, Peregudina O, Kovalchuk T, Yakovleva E, Sokolnikova P, Klyushina A, Chueva K, Kostareva A, Pervunina T and Vasichkina E (2023) The phenotypic and genetic features of arrhythmogenic cardiomyopathy in the pediatric population.
Front. Cardiovasc. Med. 10:1216976.
doi: 10.3389/fcvm.2023.1216976

The phenotypic and genetic features of arrhythmogenic cardiomyopathy in the pediatric population

Olga Kofeynikova[1]*, Daria Alekseeva[1], Tatiana Vershinina[1], Svetlana Fetisova[1], Olga Peregudina[1], Tatiana Kovalchuk[1], Elena Yakovleva[1], Polina Sokolnikova[1], Alexandra Klyushina[1], Kseniia Chueva[2], Anna Kostareva[3,4], Tatiana Pervunina[5] and Elena Vasichkina[1]

[1]World-Class Research Centre for Personalized Medicine, Almazov National Medical Research Centre, Saint Petersburg, Russia, [2]Department of Pediatric Cardiology, Almazov National Medical Research Centre, Saint Petersburg, Russia, [3]Institute of Molecular Biology and Genetics, Almazov National Medical Research Centre, Saint Petersburg, Russia, [4]Department of Women's and Children's Health and Center for Molecular Medicine, Karolinska Institutet (KI), Solna, Sweden, [5]Institute of Perinatology and Pediatrics, Almazov National Medical Research Centre, Saint Petersburg, Russia

Introduction: The present study aimed to describe the phenotypic features and genetic spectrum of arrhythmogenic cardiomyopathy (ACM) presented in childhood and test the validity of different diagnostic approaches using Task Force Criteria 2010 (TFC) and recently proposed Padua criteria.

Patients and methods: Thirteen patients (mean age at diagnosis 13.6 ± 3.7 years) were enrolled using "definite" or "borderline" diagnostic criteria of ACM according to the TFC 2010 and the Padua criteria in patients <18 years old. Clinical data, including family history, 12-lead electrocardiogram (ECG), signal-averaged ECG, 24-h Holter monitoring, imaging techniques, genetic testing, and other relevant information, were collected.

Results: All patients were classified into three variants: ACM of right ventricle (ACM-RV; $n = 6$, 46.1%), biventricular ACM (ACM-BV; $n = 3$, 23.1%), and ACM of left ventricle (ACM-LV; $n = 4$, 30.8%). The most common symptoms at presentations were syncope ($n = 6$; 46.1%) and palpitations ($n = 5$; 38.5%). All patients had more than 500 premature ventricular contractions per day. Ventricular tachycardia was reported in 10 patients (76.9%), and right ventricular dilatation was registered in 8 patients (61.5%). An implantable cardiac defibrillator was implanted in 61.5% of cases, and three patients with biventricular involvement underwent heart transplantation. Desmosomal mutations were identified in 8 children (53.8%), including four patients with *PKP2* variants, two with *DSP* variants, one with *DSG2* variant, and one with *JUP*. Four patients carried compound heterozygous variants in desmosomal genes associated with left ventricular involvement.

Conclusion: Arrhythmias and structural heart disease, such as chamber dilatation, should raise suspicion of different ACM phenotypes. Diagnosis of ACM might be difficult in pediatric patients, especially for ACM-LV and ACM-BV forms. Our study confirmed that using "Padua criteria" in combination with genetic testing improves the diagnostic accuracy of ACM in children.

KEYWORDS

arrhythmogenic cardiomyopathy, children, sudden cardiac death, ventricular arrhythmia, task force criteria, Padua criteria

1. Introduction

Arrhythmogenic cardiomyopathy (ACM) (PS107970) is a genetic cardiac disorder characterized by progressive fibro-fatty replacement of the ventricular myocardium. The disease's natural causes include the gradual progression of ventricular arrhythmias (VA), right (RV) or, rarely, left ventricular (LV) dilation, and a decrease in systolic heart function with a high risk of sudden cardiac death (SCD) (1, 2). Initially, the disease was described as predominantly involving the right ventricle (ACM-RV). However, over the years, the definition of ACM has been extended, and currently, the disease is classified into three subtypes: ACM-RV, ACM-LV, and ACM-BV (3).

Diagnosing ACM can be challenging and is typically based on a combination of criteria, including a detailed family history, electrocardiogram (ECG), Holter monitoring (HM), echocardiography (echo), magnetic resonance imaging (CMR), endomyocardial biopsy (EMB), and genetic screening (1, 4). These clinical tests were summarized in a criterial-based diagnostic algorithm known as the revised Task Force Criteria (TFC) (5). However, the 2010 TFC are exclusively concerned with the right phenotypic manifestations of ACM, and as such, have several important limitations (1). To improve the diagnostic approach to ACM, the Padua criteria were proposed in 2020. These criteria include clinical examination on both ventricles (5–8).

Additionally, the Padua criteria take into account genotype information, which is especially important in the case of ACM-LV and ACM-BV. With current genotyping technologies, various groups of genes have been identified, predominantly associated with defined forms of ACM. For example, the most frequent ACM-RV is mainly associated with variants in desmosomal genes such as *PKP2*, *JUP*, *DSC2*, *DSG2*, *DSP*, and *SCN5A* (4–6). On the other hand, patients with ACM-LV or biventricular phenotype often harbor pathogenic variants in *LMNA*, *DSP*, *FLNC*, *TMEM43*, and rarely other genes such as *LDB3*, *DES*, *ACTN2*, *BAG3*, *PLN*, *TTN*, *NKX2-5*, *RBM20*, *SCN5A*, *KCNQ1*, *KCNH2*, *TRPM4*, *LEMD2*, *ILK* and mitochondrial DNA mutations (4–6, 9).

Although ACM mainly manifests in adulthood, it can be very aggressive in children, albeit very rarely. Several recently published extensive meta-analysis and clinical summaries regarding ACM in pediatric patients have confirmed this fact (10–12). However, data on the pediatric phenotype of ACM and its association with genetic background is still limited. Defining the phenotypic features of pediatric ACM in connection to the genetic background is crucial for clinical prognosis and risk stratification, genetic counseling, and decisions on device implantation. Therefore, the aim of the current study is to describe the phenotypic features and genetic spectrum of ACM presented in childhood and to test the validity of different diagnostic approaches using TFC 2010 and recently proposed Padua criteria in pediatric patients with ACM.

2. Materials and methods

2.1. Patient cohort

The study cohort consisted of pediatric ACM patients who were admitted to the Almazov National Medical Research Center between 2010 and 2022. Patients were included in the study if they had either a "definite" or "borderline" ACM diagnosis before the age of 18 years, as per revised TFC 2010 criteria and the new Padua criteria, with subdivision to ACM-RV, ACM-LV, or ACM-BV (7, 8). The clinical data analyzed included physical examination, laboratory tests such as electrolytes and enzymes, 12-lead ECG, signal-averaged ECG, HM, cardiac magnetic resonance (CMR, performed in 9 patients) and echocardiography. Echocardiography criteria of RV/RV outflow tract (RVOT)/LV dilatation and/or dysfunction were as follows: following: RV dilatation >2 *z*-score (13), FAC <35%, PLAX RVOT/BSA ≥16 mm/m^2, PSAX RVOT/BSA ≥18 mm/m^2, LV dilatation > *z*-score 2 (14), ejection fraction LV <50% and wall motion abnormalities of LV or RV. LV dilatation and/or dysfunction by CRM was defined by identification of the following: end-diastolic volume ≥120 ml/m^2, EF <50%; RV—RVEF <40%, end-diastolic volume ≥120 ml/m^2 in male and ≥110 ml/m^2 in female subjects and wall motion abnormalities. Histopathological examination was performed in 5 patients (patients 3, 4, 7, 9, 10): the samples were stained with hematoxylin and eosin and van Gieson stain. We performed immunohistochemical analysis with antibodies to CD3, CD68, HLA-DR to exclude myocarditis. Morphometric study of the residual area of cardiomyocytes and calculation of cell infiltrate were carried out using an image analyzer Image Scope Color M (Russia).

The study was performed in accordance with the Declaration of Helsinki, and approval was obtained from the local ethical committee of Almazov National Medical Research Center (15). Written informed consent was obtained from the parents of the minors before the investigation.

2.2. Genetic testing

Genotyping was performed using a target sequencing panel that included the 172 cardiomyopathy-related genes as previously described (16). In brief, target panel of 172 cardiomyopathy-associated genes was designed and processed with the SureSelect Target Enrichment System (Agilent; Waldbronn, Germany) with an Illumina MiSeq instrument (see **Supplementary Material**), probeset regions were extended by 100 bp in both directions to capture variants in non-coding areas during downstream analysis.

Alignment, data processing, and variant calling were performed according to GATK BestPractice recommendations using hg38 human genome reference and following tools were used: nextflow v22.10.2, python v3.10.6, fastp v0.23.2, fastqc v0.11.9, bwa v0.7.17, bcftools v1.16, samtools v1.16.1, mosdepth v0.3.3, gatk4 v4.3.0.0, vcftools v0.1.16. For variant calling HaplotypeCaller

v4.3.0.0 and Deepvariant v1.4.0 were used. Filtered variants were annotated with Variant Effect Predictor (VEP) v.104 using frequency data from gnomAD, TOPMed and ExAC databases. Additionally, CADD v1.6 and dbNSFP v4.2 databases were used to assign pathogenicity prediction scores to variants. Variant annotation was performed using ANNOVAR (Philadelphia, PA, USA). The variants were filtered based on their functional consequences. To assess the influence of variants on splicing, we utilized Sequence Ontology (SO) classifications provided by VEP, along with precomputed SpliceAI scores from Gencode v24 by Illumina and dbscSNV v1.1 scores from dbscSNV. These resources were integrated as plugins within VEP. New ClinVar records were also incorporated during analysis. Before undergoing manual curation, variants were selected based on the following criteria: genotype quality >20, coverage depth >5 for SNPs and >10 for InDels, AF in gnomAD <0.01, CADD score >20, non-Benign classification in ClinVar, protein sequence altering or splicing altering consequences. Finally, bidirectional Sanger sequencing was performed to validate all reported variants. Genetic variants were classified according to the 2015 American College of Medical Genetics and Genomics criteria (ACMG) (17).

3. Results

3.1. Patient cohort

The study cohort consisted of 13 children with confirmed ACM, according to the TFC 2010 criteria and Padua criteria, who were admitted to the Almazov National Medical Research Center. The cohort comprised: 5 females (38.5%) and 8 males (61.5%) (Table 1), with a mean age at diagnosis of 13.6 ± 3.7 years. Twelve patients had a "definite" diagnosis according to both TFC 2010 criteria and Padua criteria, while one patient had a "borderline" diagnosis (Table 2). All patients were classified into three variants: ACM-RV (6 patients, 46.1%), ACM-BV (3 patients, 23.1%), and ACM-LV (4 patients, 30.8%) (Table 1).

Table 1 shows the clinical characteristics of the patients. The mean age of symptom onset was 12 ± 3.95 years (range 4–17), with syncope reported in 6 patients (46.1%), palpitations in 5 patients (38.5%), and chest pain in 5 patient (38.5%). Only 1 patient (7.7%) remained asymptomatic at the time of diagnosis and was examined due to premature ventricular contractions (PVCs) at 12-lead ECG baseline screening during a routine cardiology visit. Importantly, a "hot phase" of clinical presentation with chest pain episodes and high troponin I and/or CPK values was documented in 5 children (38.5%) after thorough exclusion of myocarditis according to MRI, cardiac biopsy and serum data. Heart failure was present in all pediatric patients at the time of the first admission, with 10 patients (76.9%) classified as NYHA functional class II.

All patients had available ECG and HM for analysis. ECG abnormalities were evident in all cases (100%). More than 500 PVCs per day were documented in all pediatric patients, and ventricular tachycardia (VT) was reported in 10 patients (76.9%), including 6 cases (46.1%) of polymorphic VT. The origin of monomorphic VT in the remaining 3 (23.1%) patients was in the RVOT with left bundle branch block (LBBB) morphology with inferior axis, one patient had monomorphic VT with left bundle branch block (LBBB) morphology with superior axis (7.7%), all of which met the major criteria of TFC 2010. Negative T waves in the right chest leads (V1–V2, V1–V4) were observed in 2 adolescents (15.4%) at the age of 16, but only one of them had it as the main criterion. None of the 13 patients had a defined and clear visualization of the epsilon wave while late potentials were seen in 9 patients (69.2%), no patient presented with low ECG including those with ACM-BV or ACM-LV. Regardless of the ACM phenotype, VA was the most prevalent symptom leading to the diagnosis of ACM. Children diagnosed with ACM-BV or ACM-LV had a poorer prognosis due to severe heart failure (Table 1).

3.2. Imaging and visualization

Echocardiographic abnormalities were detected in all 13 cases after the initial clinical presentation. Dilatation of the RV was registered in 8 patients (61.5%), 6 of whom had dilatation of the RVOT, LV dilatation was observed in 8 patients (61.5%). Biventricular involvement was documented in 3 out of 13 pediatric cases (23.1%), and aneurysms of the LV and RV were described in only 2 patients (15.4%). CMR was available for only 9 children and confirmed the diagnosis in 6 of them. Regional RV wall motion abnormalities, such as dyskinesia or akinesia, were noted in 4 patients (30.7%), two of whom had RV aneurysm. Late gadolinium enhancement (LGE) evidence of fibrosis was registered in 6 children (46.1%), including 2 cases (15.4%) where it was solely in the RV, 2 cases (15.4%) where it was solely in the LV, and 2 cases (15.4%) where it was present in both ventricles. Only 3 patients (23.1%) presented with LV regional wall motion abnormalities (hypo/akinesia), according to CMR data.

3.3. Histopathological examination

Histopathological examination was performed in 5 patients (Table 3); of those, 2 patients underwent a diagnostic EMB during radiofrequency ablation and 3 patients underwent histopathological examination of native heart. The morphological diagnosis of ACM was confirmed in all 5 patients. In all cases, the residual cardiomyocyte area was less than 40%. In 1 patient who had a biventricular phenotype, the residual cardiomyocyte area corresponded to 5%–10%. In 3 cases, fibro-fatty replacement were detected.

3.4. Management of patients

All patients received antiarrhythmic therapy, including beta-blockers in 7 patients (53.8%), sotalol in 4 children (30.8%),

10.3389/fcvm.2023.1216976

TABLE 1 Genetic and phenotypic characteristics of patients.

	Pt.1	Pt.2	Pt.3	Pt.4	Pt.5	Pt.6	Pt.7	Pt.8	Pt.9	Pt.10	Pt.11	Pt.12	Pt.13
Gender	m	m	m	m	m	m	m	f	f	f	f	f	m
Phenotype	RV	RV	RV	RV	RV	LV	LV	LV	BV	BV	BV	BV	LV
Genotype	*RYR2* LP	*PKP2/PKP2* LP/LP	*PKP2* LP	*SYNE1* VUS	*DSG2* P	*DSP/DSP* P/P	*FLNC* VUS	*JUP* VUS	*MYH7/FKTN/ANK2* P/ VUS/VUS	*PKP2/PKP2* LP/ VUS	*PKP2/PKP2* LP/P	*DSP* VUS	*SCN5A/ANK2* P/VUS
Outcome	-	ICD	ICD HT	-	ICD	ICD	ICD	-	ICD HT	ICD HT	ICD	-	-
Age at diagnosis (years)	12	17	15	16	13	5	17	17	16	13	8	12	16
Age at first symptoms	11	15	14	12	13	4	14	17	12	12	4	12	16
Family histoty													
SDD	-	Maternal grandfather	Father	-	-	-	Father	-	-	-	-	-	-
Phenotype of parents	n/a	-	n/a	n/a	n/a	-	n/a	n/a	-	-	-	n/a	n/a
Genotype of parents	n/a	Mother PKP2 Father PKP2	n/a	n/a	n/a	n/a	n/a	n/a	n/a	Mother PKP2	Mother PKP2 Father PKP2	n/a	n/a
First symptoms													
Syncope	+	–	+	–	–	–	+	+	–	–	–	+	–
Palpitations	–	+	–	–	–	–	–	–	+	+	+	–	+
Chest pain	–	–	–	+	+	–	–	+	+	+	–	–	–
"Hot phase"	–	–	–	+	+	–	–	+	+	+	–	–	–
Functional class of heart failure (at the first admission)	II	-	II	II	II	II	II	-	II	II	II	II	-
ECG anomalies													
Negantive T wave in V1–V3	–	–	–	–	–	–	–	–	+	–	–	–	–
Epsilon wave	–	–	–	–	–	–	–	–	–	–	–	–	–
Late potentials	+	+	–	+	+	–	–	+	+	–	+	+	+
>500 PVCs/24 h	+	+	+	+	+	+	+	+	+	+	+	+	+
VT	+	+	+	–	+	+	–	–	+	+	+	+	+
VT polymorphic	+	–	+	–	–	+	–	–	–	+	+	–	+
Echocardiographic findings													
RV dilatation	+	+	+	–	+	–	–	–	+	+	+	+	–
LV dilatation	–	–	–	+	–	+	+	+	+	+	+	–	+
Aneurysm of RV and LV	–	–	–	–	–	–	–	–	+	+	–	–	–
CMR features													
RV dysfunction	+	–	n/a	–	+	–	–	–	+ Aneurysm	n/a	+ Aneurysm	n/a	n/a
LV dysfuction	–	–	n/a	–	–	+	+	–	+	n/a	–	n/a	n/a
Fibrosis (LGE)	+	–	n/a	–	+	+	+	–	+	n/a	+	n/a	n/a

BV, biventricular; f, female; HT, heart transplantation; ICD, implantable cardioverter-defibrillator; LV, left ventricle; CMR, magnetic resonance imaging; PVCs, premature ventricular complexes; RV, right ventricle; SDD, sudden cardiac death; VT, ventricular tachycardia; n/a, not available or not performed; P, pathogenic; LP, likely pathogenic; VUS, variant of unknown significance.

TABLE 2 ACM criteria (comparison of the TFC 2010 and the Padua criteria).

Patient	Task force criteria 2010							The Padua criteria						
	Structural	Tissue	Repolarization	Depolarization	Arrhythmias	Family history and Genetics	Diagnosis	ECG	Arrhythmia	Imaging	CMR	Biopsy	Genetics	Diagnosis
Pt.1	M (CMR)	–	–	m	m	–	Definitive RV	–	m	M	M	–	–	Definitive RV
Pt.2	–	–	–	m	m, m	M	Definitive RV	–	m	–	–	–	M	Borderline RV
Pt.3	M (Echo)	–	–	–	m	M	Definitive RV	–	m	M	–	–	M	Definitive RV
Pt.4	–	M	m	m	m	–	Definitive RV	m	m	–	–	M	–	Definitive RV
Pt.5	M (CMR)	–	–	m	m, m	M	Definitive RV	–	m	M	M	–	M	Definitive RV
Pt.6	–	–	–	–	–	M	Possible RV	–	m	m	M	–	M	Definitive LV
Pt.7	–	–	–	–	m	M	Possible RV	–	m	M	M	–	M	Definitive LV
Pt.8	–	–	–	m	–	M	Possible RV	m	m	m	–	–	M	Definitive LV
Pt.9	M	M	M	m	m	–	Definitive RV	m	m	M	M	M	–	Definitive BV
Pt.10	M	M	–	–	m	M	Definitive RV	–	m	M	–	M	M	Definitive BV
Pt.11	M	–	–	m	m	M	Definitive RV	–	m	M	M	–	M	Definitive BV
Pt.12	m	–	–	m	m, m	M	Definite RV	–	m	m	–	–	M	Definitive RV
Pt.13	–	–	–	m	–	M	Possible RV	–	m	M	–	–	M	Definitive LV

BV, biventricular; echo, echocardiography; LV, left ventricle; M, major criteria; m, minor criteria; CMR, magnetic resonance imaging; RV, right ventricle.

amiodarone in 1 patient, and a combination of propafenone and sotalol in 1 patient. Almost half of the patients (7 of 13, 53.8%) required heart failure therapy, including diuretics and ACE inhibitors. Radiofrequency ablation of VT was attempted in 4 patients but was unsuccessful. Implantable cardioverter-defibrillators (ICDs) were implanted in 8 children (61.5%). Overall, 3 (23.1%) patients underwent cardiac transplantation before the age of 18 (at the age of 16 years), and one of them needed prolonged mechanical support prior to heart transplantation. All transplanted patients were followed in the outpatient department even after achieving 18 years of age and have remained stable until now.

3.5. Genetic testing

Genetic testing was performed in all 13 patients using a targeted new-generation sequencing approach with a broad spectrum of genes examined [**Supplementary File**, (13)]. This led to the identification of the genetic cause in all 13 patients. Desmosomal mutations were detected in 8 children (53.8%), including 4 patients with *PKP2* variants, 2 patients with *DSP* variants, 1 patient with *DSG2* variant, and 1 patient with *JUP* (**Table 1**). Three patients were compound heterozygous and carried two *PKP2* variants, and 1 patient carried two variants in *DSP* with the corresponding clinical features of Carvajal syndrome. Genetic variants in non-desmosomal genes, such as *FLNC*, *MYH7*, *RYR2*, *SCN5A*, and *SYNE1*, were found in 5 patients (38%).

3.6. Family screening

None of the patients had a family history of ACM, but SCD was reported in three families (23.1%). Clinical cardiac screening was performed in 5 out of 13 (38.5%) families and all relatives (parents and siblings) were asymptomatic for the moment. The data of genetic screening were available only in three families with compound PKP2 variants detected in the probands (patient 2, 10 and 11). In all three cases one or two parents were carriers of single PKP2 variant, still, remained asymptomatic for the time of clinical investigation (**Table 1**, **Figure 1**).

4. Discussion

According to the 2019 HRS expert consensus document, ACM-RV is considered to be extremely rare in children under the age of 10 years. Therefore, diagnosing ACM in childhood is quite challenging (18, 19). It is still under debate to what extent the TFC 2010 and Padua criteria of ACM are sensitive and specific in the pediatric population, taking into account that many of their components, such as CMR and EMB, often cannot be performed in children. Meanwhile some criteria, such as T-wave inversion or epsilon wave, may not provide enough information.

TABLE 3 Data of histopathological examination.

	Condition	Residual myocardium (%)	Fibrosis	Lipomatosis	Inflammation
Pt3	Native heart	37%	+	–	+
Pt4	Diagnostic EMB	38%	+	+	–
Pt7	Diagnostic EMB	-	+	–	–
Pt9	Native heart	5%–10%	+	+	+
Pt10	Native heart	<40%	+	+	+

EMB, endomyocardial biopsy.

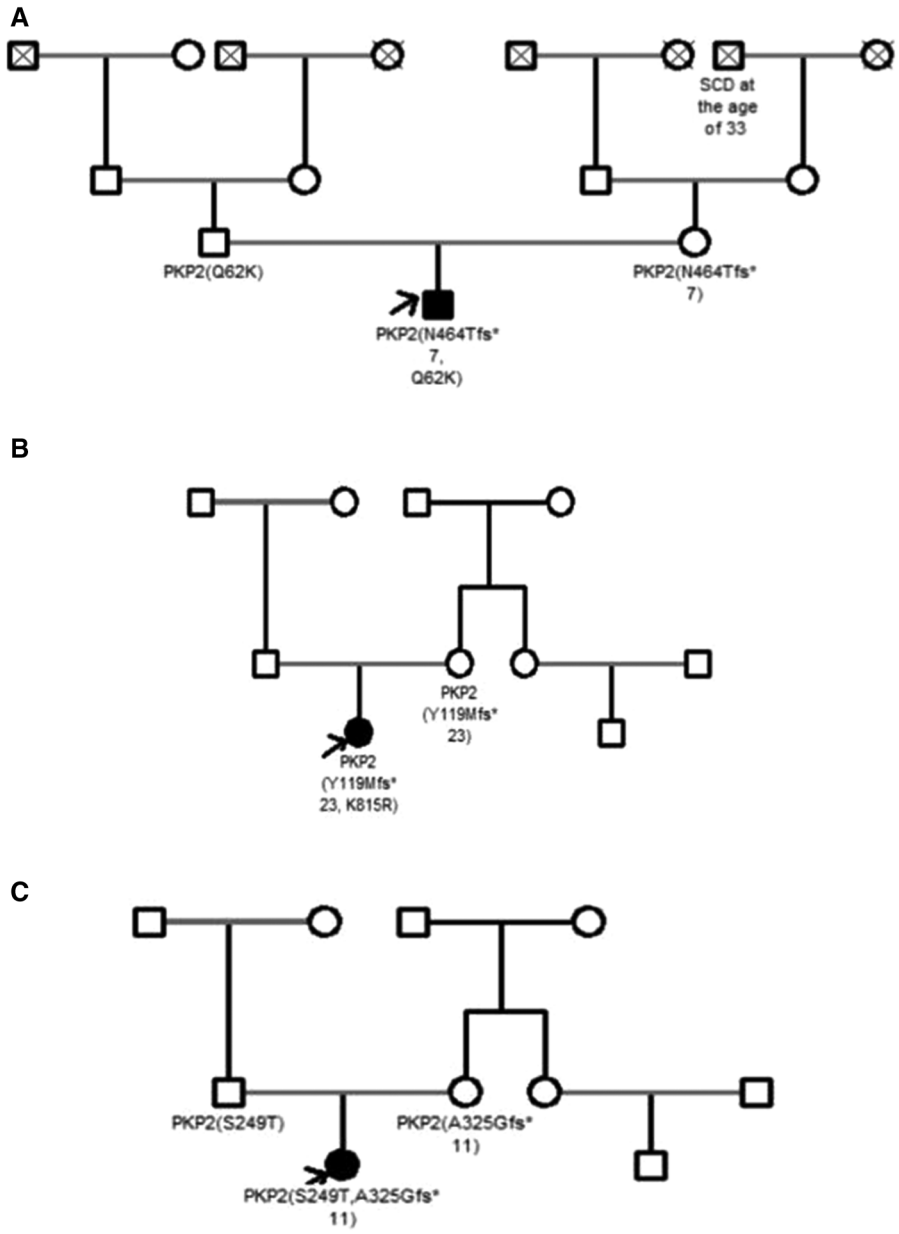


FIGURE 1
Pedigrees of the family A (patient 2), family B (patient 10) and family C (patient 11). ACM patients are shown with solid symbols and unaffected with white symbols, the arrow indicates the proband. Dead people are shown with a cross. SCD, sudden cardiac death.

In this regard, comparing the specificity and sensitivity of these criteria, especially for various forms of ACM, remains an important clinical task in pediatric cardiology.

We used the TFC 2010 and Padua criteria for the diagnosis of ACM. In patients with ACM-RV, the application of TFC 2010 and Padua criteria yielded consistent results. Padua criteria confirmed

the definitive diagnosis in 5 out of 6 patients with ACM-RV (patients 1, 2, 3, 5, and 12). Only in 1 patient (patient 4), the diagnosis of definite ACM-RV was slightly weakened but still confirmed as borderline. In addition, in the other 3 patients (patients 9, 10, and 11), the ACM-RV suggested by TFC 2010 was revised to ACM-BV after reassessment using Padua criteria. In addition to 4 patients (6, 7, 8, and 13) initially diagnosed with ACM-LV using only Padua criteria, a total of 7 patients received a non-ACM-RV diagnosis when solely applying Padua criteria. Considering the prevalence of non-ACM-RV in half of the pediatric patients in our group and its worse prognosis compared to ACM-RV, the implementation of Padua criteria in children becomes more favorable, leading to a more precise diagnosis and risk stratification. This is in line with recent data published by Cicenia et al. on a group of 21 children, which also confirmed the superior performance of Padua criteria in establishing ACM diagnosis in children (12).

Of note, despite the early and severe clinical course, none of our patients reported a family history of ACM, which is a well-known hereditary disease. Even when considering 3 cases of SCD in close relatives, this may correspond to only 23% of familial cases. This fact can potentially be explained by several reasons. First, compound heterozygosity forms suggest that at least one of the parents carries a pathogenic variant which can be non-penetrant or lead to the late manifestation. This phenomenon is widely described for ACM variant carriers (18–21). In this case, only a compound heterozygous combination of variants can lead to the early and severe manifestation being asymptomatic in parents with single variants (as in patients 6 and 10). Another explanation is the potential *de novo* status of the variants, the most likely mechanism in non-desmosomal gene variants (*LMNA*, *MYH7*, *FLNC*), leading to the ACM-BV. Thus, Klauke et al. confirmed the association between *de novo* status in *DES* and ACM through both clinical and functional characterization (22). Therefore, the inability to confirm the *de novo* or allelic status of the mutations due to the unavailability of parental DNA can be an important limitations of our study.

Riele et al. showed that clinical phenotype and ARVC course were similar between pediatric and adult cases, and ACM may be fully manifested in pediatric patients with VA, cardiac failure, and SCD (23). Our study confirmed the prevalence of arrhythmic symptoms in pediatric ACM since arrhythmogenic manifestations (VA, including VT) were reported in all children from our study group. However, only 1 patient had VT of LBBB with a superior axis, which met the major criteria according to the TFC 2010. All other patients initially had VT of different morphology, so the diagnosis of ACM was confirmed using other criteria. These results questioned the sensitivity of arrhythmic criteria in the pediatric population and suggested that any type of VT could be a sign of ACM in children. This notion was previously underlined by Shriprasad et al., providing a further argument for establishing modified ACM diagnostic criteria in children (24). In most cases, arrhythmia preceded structural changes in the heart. Therefore, establishing a diagnosis in time to work on SCD prevention is extremely important (10, 25–27). Our results showed that children with ACM-RV and ACM-BV forms had the most pronounced and difficult-to-treat VA; 8 out of 9 children in this group required ICD implantation. In this light, it is necessary to provide dynamic monitoring of children with cardiac arrhythmias with or without any structural myocardial pathology to establish ACM diagnosis on time.

One the most challenging criteria to apply in children when diagnosing ACM is depolarizing abnormalities, since inverted T waves is a common finding in this population (28). As expected, only 1 child in our cohort met the main criterion for repolarization, which was a negative T wave in V1, V2, V3, and V4 leads. Additionally, epsilon waves are extremely rare in pediatric patients (26, 29). To confirm this, none of our patients had a clear visualization of the epsilon wave, which questions its reliability as a diagnostic criterion in pediatric patients.

Undoubtedly, CMR is a highly valuable in diagnosing ACM, and its high specificity in children has been validated by several studies (10–13, 26). In our cohort, dilatation of the RV or LV was detected in all patients, and signs of fibrosis on CMR were major criteria in 6 out of 9 patients, in whom CMR was available. However, performing CMR in young children can often be challenging due to the need for anesthesia, and the risk of severe cardiac arrhythmia (30, 31). It is worth noting that, the commonly used CMR parameters of TFC 2010 have not yet been validated in pediatric patients (26). Similar limitations are associated with EMB performance. While EMB can be very informative in establishing the diagnosis of ACM, its utility is rather limited in children due to the high risk of complications (24).

Since children lack a gold standard for diagnosing ACM, genetic testing can play a key diagnostic role, especially in cases of ACM-BV and ACM-LV (8, 32). Similar to adult groups, mutations in one of the desmosomal genes were the most frequent genetic causes in our study group, with 8 out of 13 patients having such mutations (*PKP2*, *DSP*, *DSG2*, and *JUP*) (1, 3, 33, 34). Of note, in half of the cases caused by desmosomal gene mutations, compound heterozygosity was detected mainly in association with LV involvement (patients 6, 10, and 11). In contrast, most of the isolated desmosomal gene mutations (3 out of 4) were associated with ACM-RV (Patients 2, 5, and 12). Even considering the small number of patients studied, one can suggest that compound heterozygosity in desmosomal genes is associated with a poor prognosis and early involvement of the LV in pediatric patients with ACM (35). Non-desmosomal genes (*FLNC*, *RYR2*, *MYH7*, *SCN5A*, and *SYNE1*) were detected in more than one-third of the children in our group. While some of these genes are well-known to be associated with ACM (*SCN5A*), the causative role of others, such as, *SYNE1*, needs further verification.

The present study evaluates the usefulness of TFC 2010 and Padua criteria in diagnosing ACM in a cohort of 13 pediatric patients. Interestingly, in 2 patients diagnosed with ACM, pathogenic variants were identified in genes that are well-known to be associated with other types of inherited cardiac disorders, *MYH7*, *FLNC* and RYR2 (6, 36, 37). These molecular

mechanisms can differ from those in desmosome-associated ACM, potentially, leading to different clinical approaches. Both patients met the TFC 2010, and one of them, who carried the *RYR2* variant, had one major CMR criterion of ACM. This highlights the clinical and genetic overlap between ACM and other inherited cardiac disorders, emphasizing the need for long-term close follow-up for a better understanding of such phenotypes (6).

Protonotario et al. reported that the sensitivity and specificity of the ACM-risk prediction model depend on the genotype with different factor weights depending on the causative gene (30). DeWitt et al. showed that ACM-RV is associated with a high proportion of PKP2 variants, while ACM-LV is associated with DSP (11). Although this study mainly includes desmosomal gene mutations, similar patterns, even to a greater extent, can be useful for ACM associated with non-desmosomal genes. Similar to other reports, we confirmed that ACM-LV and ACM-BV in children have some important clinical features. Thus, an earlier onset of the disease was noted in children with ACM-LV and ACM-BV. ACM-BV was the most severe and 2 out of 3 patients in the group required heart transplantation in childhood, mainly due to the rapid progression of biventricular heart failure. This notion was previously reported by Somprasong et al., who confirmed that the involvement of the LV in children is a stronger predictor of adverse outcomes, including the need for heart transplantation (38). Given the severity of ACM-LV- and ACM-BV and the difficulties in their accurate diagnosis, we emphasize the need for the proper use of Padua criteria in children, in combination with extensive genetic screening in order to establish this clinical form in a timely manner and to ensure the appropriate risk management, family screening, and genetic counseling.

5. Conclusion

Using a cohort of 13 pediatric patients diagnosed with ACM, we assessed the utility of TFC 2010 and Padua criteria. We demonstrated that VT of any morphology, in combination with chamber dilatation, should raise the suspicion of different ACM phenotypes. Age-related electrocardiographic features in children do not allow for the reliable use of the existing ECG diagnostic criteria for ACM in pediatric patients. The proportion of non-ACM-RV forms in pediatric patients is close to 50% and is associated with multiple gene mutations, LV involvement, and poor prognosis. Further analysis of larger pediatric cohorts with ACM due to different genetic backgrounds will allow for establishing more reliable genotype-phenotype correlations and creating new, more sensitive diagnostic criteria for ACM children with different phenotypes.

6. Study limitations

The study has some limitations that need to be acknowledged. First, it was a retrospective study that was limited to a small cohort of patients. Second, some clinical data were not available to all patients, for example, CMR was missed for 4 out of 13 patients, and EMB was not possible to perform in some of them. Another important limitation is the unavailability of parental DNA in most cases, which made establishing the *de novo* or inherited status of a genetic variant and its penetrance in parents impossible. This absence of detailed segregation analysis underlines the need for further research and functional studies for the new described variants and genes.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/**Supplementary Material**.

Ethics statement

The study was performed in accordance with the Declaration of Helsinki, and approval was obtained from the local ethical committee of Almazov National Medical Research Center. Written informed consent was obtained from the parents of the minors before the investigation. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements. Written informed consent was obtained from the individual(s), and minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article.

Author contributions

DA, EY, SF, and TK contributed to the conception and design of the study, analysis, and interpretation of the data and drafting of the manuscript. OK contributed to the study concept and research design and wrote the manuscript. AKo, TP, and EV made contributions to the conception and design of the study and revision of the manuscript critically. OP, TV, and KC took part in the analysis and interpretation of the data and have been involved in revising the manuscript critically. PS and AKl conducted the experiments and performed the analysis and interpretation of the data. All authors contributed to the article and approved the submitted version.

Funding

This work was financially supported by the Ministry of Science and Higher Education of the Russian Federation (Agreement No. 075-15-2022-301).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2023.1216976/full#supplementary-material

References

1. Corrado D, Basso C, Judge D. Arrhythmogenic cardiomyopathy. *Circ Res*. (2017) 121:784–802. doi: 10.1161/CIRCRESAHA.117.309345

2. Pilichou K, Thiene G, Bauce B, Rigato I, Lazzarini E, Migliore F, et al. Arrhythmogenic cardiomyopathy. *Orphanet J Rare Dis*. (2016) 11:33. doi: 10.1186/s13023-016-0407-1

3. Vaikhanskaya TG, Sivitskaya LN, Kurushko TV, Rusak TV, Levdansky OD, Danilenko NG, et al. A paradigm shift in the concept of arrhythmogenic cardiomyopathy: expanding the clinical and genetic spectrum, new diagnostic criteria for left ventricular phenotypes. *Russ J Cardiol*. (2020) 25(10):3863. doi: 10.15829/1560-4071-2020-3863

4. Murray B, James CA. Genotype-phenotype correlates in arrhythmogenic cardiomyopathies. *Curr Cardiol Rep*. (2022) 24:1557–65. doi: .org/10.1007/s11886-022-01777-3

5. Giacca M. Gene editing for cardiomyopathy takes a step forward. *Cardiovasc Res*. (2022) 118:3011–2. doi: 10.1093/cvr/cvac164

6. Towbin JA, McKenna WJ, Abrams DJ, Ackerman MJ, Calkins H, Darrieux FCC, et al. 2019 HRS expert consensus statement on evaluation, risk stratification, and management of arrhythmogenic cardiomyopathy. *Heart Rhythm*. (2019) 16:e301–72. doi: 10.1016/j.hrthm.2019.05.007

7. Marcus FI, McKenna WJ, Sherrill D, Basso C, Bauce B, Bluemke DA, et al. Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: proposed modification of the task force criteria. *Eur Heart J*. (2010) 31:806–14. doi: 10.1093/eurheartj/ehq025

8. Corrado D, Perazzolo Marra M, Zorzi A, Beffagna G, Cipriani A, Lazzari M, et al. Diagnosis of arrhythmogenic cardiomyopathy: the Padua criteria. *Int J Cardiol*. (2020) 319:106–14. doi: 10.1016/j.ijcard.2020.06.005

9. Abdelfatah N, Chen R, Duff HJ, Seifer CM, Buffo I, Huculak C, et al. Characterization of a unique form of arrhythmic cardiomyopathy caused by recessive mutation in LEMD2. *JACC Basic Transl Sci*. (2019) 4(2):204–21. doi: 10.1016/j.jacbts.2018.12.001

10. Surget E, Maltret A, Raimondi F, Fressart V, Bonnet D, Gandjbakhch E, et al. Clinical presentation and heart failure in children with arrhythmogenic cardiomyopathy. *Circ Arrhythm Electrophysiol*. (2022) 15(2):e010346. doi: 10.1161/CIRCEP.121.010346

11. DeWitt ES, Chandler SF, Hylind RJ, Beausejour Ladouceur V, Blume ED, VanderPluym C, et al. Phenotypic manifestations of arrhythmogenic cardiomyopathy in children and adolescents. *J Am Coll Cardiol*. (2019) 74(3):346–58. doi: 10.1016/j.jacc.2019.05.022

12. Cicenia M, Cantarutti N, Adorisio R, Silvetti MS, Secinaro A, Ciancarella P, et al. Arrhythmogenic cardiomyopathy in children according to "Padua criteria": single pediatric center experience. *Int J Cardiol*. (2022) 350:83–9. doi: 10.1016/j.ijcard.2022.01.008

13. Koestenberger M, Nagel B, Ravekes W, Avian A, Burmas A, Grangl G, et al. Reference values and calculation of z-scores of echocardiographic measurements of the normal pediatric right ventricle. *Am J Cardiol*. (2014) 114(10):1590–8. doi: 10.1016/j.amjcard.2014.08.028

14. Calculate BSA-adjusted z-scores of the aortic annulus and sinuses of Valsalva using data published by Boston Children's Hospital (Updated 11/2008: added percentiles). Available at: http://zscore.chboston.org (Accessed January 20, 2023).

15. Website World Medical Association. Available at: https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects (Accessed March 15, 2023).

16. Jorholt J, Formicheva Y, Vershinina T, Kiselev A, Muravyev A, Demchenko E, et al. Two new cases of hypertrophic cardiomyopathy and skeletal muscle features associated with ALPK3 homozygous and compound heterozygous variants. *Genes*. (2020) 11:1201. doi: 10.3390/genes11101201

17. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, et al. Standards and guidelines for the interpretation of sequence variants. *Genet Med*. (2015) 17:405–24. doi: 10.1038/gim.2015.30

18. Kapplinger JD, Landstrom AP, Salisbury BA, Callis TE, Pollevick GD, Tester DJ, et al. Distinguishing arrhythmogenic right ventricular cardiomyopathy/dysplasia-associated mutations from background genetic noise. *J Am Coll Cardiol*. (2011) 57(23):2317–27. doi: 10.1016/j.jacc.2010.12.036

19. Haggerty CM, James CA, Calkins H, Tichnell C, Leader JB, Hartzel DN, et al. Electronic health record phenotype in subjects with genetic variants associated with arrhythmogenic right ventricular cardiomyopathy: a study of 30,716 subjects with exome sequencing. *Genet Med*. (2017) 19(11):1245–52. doi: 10.1038/gim.2017.40

20. Headrick AT, Rosenfeld JA, Yang Y, Tunuguntla H, Allen HD, Penny DJ, et al. Incidentally identified genetic variants in arrhythmogenic right ventricular cardiomyopathy-associated genes among children undergoing exome sequencing reflect healthy population variation. *Mol Genet Genomic Med*. (2019) 7(6):e593. doi: 10.1002/mgg3.593

21. Hylind RJ, Pereira AC, Quiat D, Chandler SF, Roston TM, Pu WT, et al. Population prevalence of premature truncating variants in plakophilin-2 and association with arrhythmogenic right ventricular cardiomyopathy: a UK biobank analysis. *Circ Genom Precis Med*. (2022) 15(3):e003507. doi: 10.1161/CIRCGEN.121.003507

22. Klauke B, Kossmann S, Gaertner A, Brand K, Stork I, Brodehl A, et al. De novo desmin-mutation N116S is associated with arrhythmogenic right ventricular cardiomyopathy. *Hum Mol Genet*. (2010) 19(23):4595–607. doi: 10.1093/hmg/ddq387

23. Te Riele ASJM, James CA, Sawant AC, Bhonsale A, Groeneweg JA, Mast TP, et al. Arrhythmogenic right ventricular dysplasia/cardiomyopathy in the pediatric population: clinical characterization and comparison with adult-onset disease. *JACC Clin Electrophysiol*. (2015) 1:551–60. doi: 10.1016/j.jacep.2015.08.004

24. Shriprasad R, Deshpande SR, Herman HK, Quigley PC, Shinnick JK, Cundiff CA, et al. Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D): review of 16 pediatric cases and a proposal of modified pediatric criteria. *Pediatr Cardiol*. (2016) 37(4):646–55. doi: 10.1007/s00246-015-1327-x

25. Etoom Y, Govindapillai S, Hamilton R, Manlhiot C, Yoo SJ, Farhan M, et al. Importance of CMR within the task force criteria for the diagnosis of ARVC in children and adolescents. *J Am Coll Cardiol*. (2015) 65(10):987–95. doi: 10.1016/j.jacc.2014.12.041

26. Saguner AM, Ganahl S, Kraus A, Baldinger SH, Akdis D, Saguner AR, et al. Electrocardiographic features of disease progression in arrhythmogenic right ventricular cardiomyopathy/dysplasia. *BMC Cardiovasc Disord*. (2015) 15:4. doi: 10.1186/1471-2261-15-4

27. Mattesi G, Zorzi A, Corrado D, Cipriani A. Natural history of arrhythmogenic cardiomyopathy. *J Clin Med*. (2020) 9(3):878. doi: 10.3390/jcm9030878

28. Dickinson DF. The normal ECG in childhood and adolescence. *Heart*. (2005) 91(12):1626–30. doi: 10.1136/hrt.2004.057307

29. Zhang L, Liu L, Kowey PR, Fontaine GH. The electrocardiographic manifestations of arrhythmogenic right ventricular dysplasia. *Curr Cardiol Rev*. (2014) 10(3):237–45. doi: 10.2174/1573403x10666140514102928

30. Scottish Intercollegiate Guidelines Network. Safe sedation of children undergoing diagnostic and therapeutic procedures. A National Clinical Guideline. (2004) (Accessed June 7, 2011).

31. The Royal College of Radiologists. Safe sedation, analgesia and anaesthesia within the radiology department. (2003) (Accessed May 30, 2011).

32. Cicenia M, Drago F. Arrhythmogenic cardiomyopathy: diagnosis, evolution, risk stratification and pediatric population—where are we? *J Cardiovasc Dev Dis*. (2022) 9:98. doi: 10.3390/jcdd9040098

33. Bhonsale A, Groeneweg JA, James CA, Dooijes D, Tichnell C, Jongbloed JDH, et al. Impact of genotype on clinical course in arrhythmogenic right ventricular dysplasia/cardiomyopathy-associated mutation carriers. *Eur Heart J*. (2015) 36:847–55. doi: 10.1093/eurheartj/ehu509

34. Brodehl A, Meshkov A, Myasnikov R, Kiseleva A, Kulikova O, Klauke B, et al. Hemi- and homozygous loss-of-function mutations in DSG2 (desmoglein-2) cause recessive arrhythmogenic cardiomyopathy with an early onset. *Int J Mol Sci*. (2021) 22(7):3786. doi: 10.3390/ijms22073786

35. Protonotarios A, Bariani R, Cappelletto C, Pavlou M, García-García A, Cipriani A, et al. Importance of genotype for risk stratification in arrhythmogenic right ventricular cardiomyopathy using the 2019 ARVC risk calculator. *Eur Heart J*. (2022) 43(32):3053–67. doi: 10.1093/eurheartj/ehac235

36. Muravyev A, Vershinina T, Tesner P, Sjoberg G, Fomicheva Y, Čajbiková NN, et al. Rare clinical phenotype of filaminopathy presenting as restrictive cardiomyopathy and myopathy in childhood. *Orphanet J Rare Dis*. (2022) 17 (1):358. doi: 10.1186/s13023-022-02477-5

37. Ader F, De Groote P, Réant P, Rooryck-Thambo C, Dupin-Deguine D, Rambaud C, et al. FLNC pathogenic variants in patients with cardiomyopathies: prevalence and genotype-phenotype correlations. *Clin Genet*. (2019) 96(4):317–29. doi: 10.1111/cge.13594

38. Chungsomprasong P, Hamilton R, Luining W, Fatah M, Yoo SJ, Grosse-Wortmann L. Left ventricular function in children and adolescents with arrhythmogenic right ventricular cardiomyopathy. *Am J Cardiol*. (2016) 119:778–84. doi: 10.1016/j.amjcard.2016.11.020

frontiers | Frontiers in Pediatrics

TYPE Study Protocol
PUBLISHED 18 October 2023
DOI 10.3389/fped.2023.1256815

OPEN ACCESS

EDITED BY
Shikai Yu,
Tongji University, China

REVIEWED BY
Gabriela Corina Zaharie,
University of Medicine and Pharmacy Iuliu Hatieganu, Romania
Alexandre A. da Silva,
University of Mississippi Medical Center, United States

*CORRESPONDENCE
Hannibal Troensegaard
✉ hannibal.troensegaard@medisin.uio.no

RECEIVED 11 July 2023
ACCEPTED 02 October 2023
PUBLISHED 18 October 2023

CITATION
Troensegaard H, Khoury J, Westerberg AC, Tonstad S, Roeters van Lennep J, Veierød MB, Iversen PO, Holven KB and Retterstøl K (2023) Protocol for a 20-year follow-up after a randomized controlled trial of a Mediterranean diet in pregnancy: maternal and offspring risk factors for cardiovascular disease.
Front. Pediatr. 11:1256815.
doi: 10.3389/fped.2023.1256815

Protocol for a 20-year follow-up after a randomized controlled trial of a Mediterranean diet in pregnancy: maternal and offspring risk factors for cardiovascular disease

Hannibal Troensegaard[1]*, Janette Khoury[1], Ane C. Westerberg[2,3], Serena Tonstad[4], Jeanine Roeters van Lennep[5], Marit B. Veierød[6], Per Ole Iversen[1,7], Kirsten B. Holven[1,8] and Kjetil Retterstøl[1,9]

[1]Department of Nutrition, Institute of Basic Medical Sciences, University of Oslo, Oslo, Norway, [2]Department of Obstetrics, Division of Obstetrics and Gynaecology, Oslo University Hospital Rikshospitalet, Oslo, Norway, [3]School of Health Sciences, Kristiania University College, Oslo, Norway, [4]Department of Preventive Cardiology, Oslo University Hospital, Oslo, Norway, [5]Department of Internal Medicine, Erasmus MC Cardiovascular Institute, University Medical Centre Rotterdam, Rotterdam, Netherlands, [6]Oslo Centre for Biostatistics and Epidemiology, Department of Biostatistics, Institute of Basic Medical Sciences, University of Oslo, Oslo, Norway, [7]Department of Haematology, Oslo University Hospital, Oslo, Norway, [8]Norwegian National Advisory Unit on Familial Hypercholesterolemia, Oslo University Hospital, Oslo, Norway, [9]The Lipid Clinic, Department of Medicine, Oslo University Hospital, Oslo, Norway

Background: An inadequate maternal diet during pregnancy can impair offspring health and may increase the risk of cardiovascular disease later in life. The purpose of the proposed study is to assess the risk factors associated with cardiovascular disease in both mothers and their offspring 20 years following their participation in a Mediterranean diet intervention trial during pregnancy.

Methods: The "Cardiovascular Risk Reduction Diet In Pregnancy" (CARRDIP) study was a randomized controlled trial performed between 1999 and 2001. The participants were randomized to adhere to either a Mediterranean diet or their regular diet during pregnancy. An extensive amount of data such as diet information, ultrasound measurements, anthropometry, and biomarkers from these mothers during pregnancy and their offspring in the neonatal period were collected. The mother–offspring pairs ($n = 269$) from the CARRDIP study will be invited to participate in a clinical examination and blood sample collection. This follow-up study, conducted 20 years after the original CARRDIP study, will investigate cardiovascular risk factors in mothers and offspring. The primary outcome will be the blood pressure of the offspring. In addition, the study will explore various aspects of cardiovascular health, including metabolic and inflammatory status, clinical history, and body composition of the participants.

Abbreviations
CARRDIP, Cardiovascular Risk Reduction Diet In Pregnancy; CARRDIP20, 20-year follow-up of Cardiovascular Risk Reduction Diet In Pregnancy.

Discussion: Previous studies investigating the effects of nutrition during pregnancy on maternal and offspring health have been either observational studies, animal studies, or randomized controlled trials with a follow-up period of less than 5 years. This project aims to study the long-term effects of dietary intervention during pregnancy on maternal and offspring cardiovascular risk markers.

Clinical Trial Registration: Clinicaltrials.gov, identifier (NCT05030922).

KEYWORDS

cardiovascular risk factors, offspring health, antenatal care, lifestyle intervention, Mediterranean diet, long-term follow-up, pregnancy, randomized controlled trial

1. Introduction

Cardiovascular disease (CVD) accounts for about a third of all deaths worldwide (1). Numerous studies have demonstrated that lifestyle interventions, such as smoking, physical inactivity, and dietary habits, can reduce cardiovascular risk factors. Lifestyle intervention, as primordial and primary prevention, is a cost-effective way of combatting the burden of CVD morbidity and mortality (2, 3). Although the main goals for primary and secondary prevention are well established, the targets of primordial prevention for CVD are not as clear. Nevertheless, initiating CVD prevention as early as possible, including during childhood or even *in utero*, holds significant potential (3, 4).

One of the main causes of CVD is atherosclerosis, a progressive, lifelong process resulting in plaque accumulation and inflammation within the arterial wall, which in turn may lead to thrombosis and stenosis, thereby impeding local blood flow (5). Lifestyle changes, specifically diet, influence the progression of atherosclerosis and stenosis (6, 7). For example, strong evidence demonstrates that replacing saturated fatty acids with polyunsaturated fatty acids in adults reduces the risk of coronary heart disease, as discussed in a systematic review of current evidence by the Secretary of Health and Human Services in the United States (8).

A Mediterranean diet has been shown to alter the atherosclerotic process and protect against CVD (9–12). There are several variations of the Mediterranean diet, but all are based in principle on increased intakes of whole grain bread, fruit, vegetables, legumes, and sources of polyunsaturated fat such as nuts, fish oil, and olive oil. In addition, this dietary approach involves reducing the intake of pastries, meat, and fat-rich dairy products.

The development and progression of atherosclerotic lesions are dependent on individual lifestyle choices. Notably, epigenetic factors promoting atherosclerosis may be passed on from a pregnant mother to her fetus. A pronounced maternal hypercholesterolemia during pregnancy may adversely affect both the mother and the fetus. Increased levels of cholesterol in the maternal bloodstream can accelerate the development of atherosclerotic lesions in the child during the early stages of life. Observational studies have shown that fatty streak formations in the fetal aorta are modulated by maternal hypercholesterolemia. Some observational studies have shown that signs of atherosclerosis appear in early adulthood (13–17). Furthermore, maternal cholesterol levels correlate with offspring cholesterol levels at many stages of development, including 6 months, 1 year, 2 years, and 6 years, which may increase the long-term risk of CVD (18–20).

Observational studies have found associations between maternal dietary intake during pregnancy and the body composition and cardiovascular health of the child. The composition of fatty acids in the maternal blood has been suggested to be related to childhood adiposity, and a Mediterranean dietary pattern during pregnancy has been linked to lower waist circumference in childhood (21–24). Although several randomized controlled trials (RCTs) have examined the short-term effect of dietary and lifestyle interventions in pregnancy on the health status of infants, there is a lack of long-term follow-up examining these relations in an RCT setting. According to a Cochrane review of interventions in pregnancy, a long-term follow-up is rarely done, and we were unable to identify any RCT with dietary interventions during pregnancy with a follow-up period of longer than 5 years (25).

The Cardiovascular Risk Reduction Diet in Pregnancy (CARRDIP) study was an RCT that examined the effects of a Mediterranean diet intervention on both maternal and fetal outcomes among healthy pregnant women (26–30). Some important study findings were identified in this study, including differences in the fatty acid composition in the blood and a reduction of low-density lipoprotein levels in the serum during pregnancy. In addition, the intervention group exhibited a decrease in the instances of premature births compared with the control group. While the CARRDIP study focused on the immediate health effects, we now want to examine the long-term health effects on both mothers and offspring in the CARRDIP cohort. In this study, we describe the protocol for CARRDIP20, a follow-up study conducted 20 years after the original randomized controlled trial involving dietary intervention in pregnancy.

2. Methods and analyses

2.1. Aim

This study aims to examine cardiovascular risk factors in mothers and their offspring 20 years after the mothers participated in the CARRDIP study (**Figure 1**) (26–28).

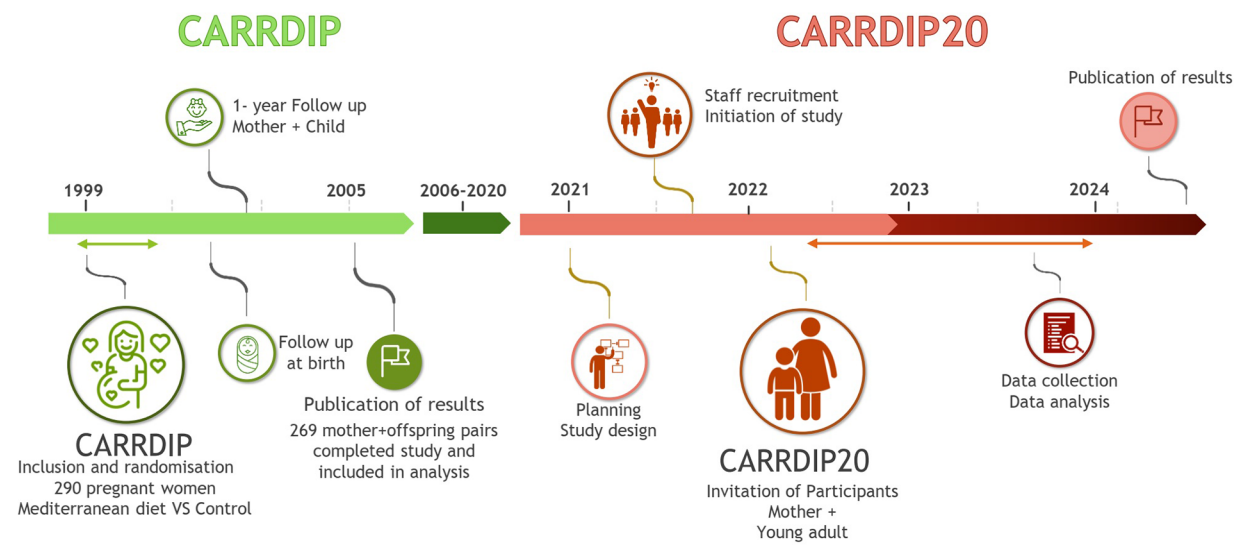


FIGURE 1
Illustration of the timeline of the original CARRDIP study and the proposed CARRDIP20 study.

2.2. Design and setting

The CARRDIP study was an RCT with dietary intervention in pregnancy performed between 1999 and 2001. The participating mothers were allocated to either the intervention group ($n = 141$) or the control ($n = 149$) group. The aim of the intervention group was to limit dietary cholesterol to 150 mg/day and reduce the intake of saturated fat to 8% of the total energy intake. The intended composition of the total energy intake consisted of 32% from total fat, 16%–17% from protein, and 50%–51% from carbohydrates. The intervention group was encouraged to increase the intake of fatty fish, olive oil, nuts, and avocado to replace meat, butter, and fatty dairy products and to replace full-fat dairy products with skimmed or low-fat ones. The control group consumed their usual diet and did not introduce oils or low-fat meat or dairy products, aiming at 32% of energy from total fat (including 12% from saturated fat), 16%–17% of energy from protein, and 50%–51% of energy from carbohydrates. Total energy intake aimed at a weight gain of 8–14 kg during pregnancy in both study groups (26). The participants were monitored several times during pregnancy with planned follow-up visits at gestation weeks 24, 30, and 36. Mothers and offspring were followed up, both to ensure adherence to the Mediterranean diet in the intervention group and to monitor the health status of both the mother and the fetus (fetal biometric measurements and Doppler measurements). Blood lipid levels, markers of endothelial activation, and inflammation were measured in maternal samples during pregnancy and in cord blood at birth. Several pregnancy and birth outcomes were recorded, and neonatal lipid levels were measured. The CARRDIP study found a significant reduction in the umbilical artery pulsatile index, reflecting decreased placental vascular resistance (27). This reduction in the index between gestational weeks 24 and 30 was a significant predictor of higher systolic blood pressure at 6 months of age, supporting the concept of fetal origins in the development of cardiovascular risk factors (30).

The current CARRDIP20 study will be a long-term follow-up of all mothers and their offspring separately, comparing the effects of intervention against control in both groups.

2.3. Participants

The CARRDIP study included healthy, low-risk pregnancies to minimize possible confounding factors related to later CVD risk in the offspring. Eligible participants were included after an ultrasound showing a single healthy fetus in gestational weeks 17–20. The inclusion criteria were non-smoking pregnant women aged 21–38 years with a body mass index (BMI) of 19–32 kg/m^2. The exclusion criteria were high-risk pregnancy due to diabetes mellitus, endocrine disease, chronic hypertension, drug abuse, history of thromboembolic disease, or significant gastrointestinal, cardiac, pulmonary, or hematologic disease. Of the 290 women included in the CARRDIP study, 21 women withdrew their consent before or during the intervention, leaving a final number of 269 mother–offspring pairs. All mothers and their offspring from the CARRDIP cohort will be invited to participate in the follow-up.

2.4. Data collection

The mother–offspring pairs from the original CARRDIP study will be invited to participate in a clinical examination and sample collection at the Department of Nutrition, Institute of Basic Medical Sciences, University of Oslo. Study investigators will be blinded to the original study group allocation. Data to be collected during the visit are presented in **Table 1**.

TABLE 1 Data to be collected in the CARRDIP20 study both from the mothers and their offspring.

Data to be collected	Analysis/methodology
Blood biomarkers	Lipid profiles (total cholesterol, non-high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, and apolipoprotein A + B including ratio, lipoprotein(a)), markers of glucose metabolism, ferritin, liver transaminases, TSH, creatinine, tissue plasminogen activator antigen, cellular adhesion molecules, proinflammatory markers (e.g., CRP, TNFα, interleukins, interferons), hemostatic markers (e.g., fibrinogen, tissue factor, D-dimer), and differential white blood cell count
Peripheral blood mononuclear cells (PBMC) transcriptomics	PBMC will be isolated, and gene expression analysis will be performed. We will investigate both the global gene expression profile and targeted gene expression analysis, particularly investigating genes involved in lipid metabolism and inflammatory pathways
Blood pressure	Systolic and diastolic blood pressure as recorded ambulatory with appropriate devices
Dietary intake and health score	Dietary intake will be assessed with a validated food frequency questionnaire (31). Health score will be determined with the Cardiovascular Health Score of the American Heart Association (32).
Anthropometry	Weight, height, waist circumference, and hip circumference using scales and non-stretch tapes
Body composition	Fat percentage of body weight and skeletal muscle mass.
Intima-media thickness (IMT) and liver fat content	An ultrasound investigation of the IMT of the carotid artery offers a possibility to early identify the risk of atherosclerotic lesions. An ultrasound of the liver will reveal fat deposition (which is associated with several non-communicable diseases)

2.5. Outcomes

The primary and secondary outcomes will be based on the findings and sampling methods of the original study and of similar studies on nutritional status during pregnancy (23, 26–28, 30, 33–39). The assessment, analysis, and reporting of outcomes will follow relevant CONSORT guidelines for clinical trials, and the current study protocol will adhere to the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines (40, 41).

The primary outcome of the study will be the difference in the mean arterial blood pressure between the control and intervention groups in the CARRDIP offspring group due to hypertension being one of the most important CVD risk factors (42). Maternal exposures during pregnancy have been found to potentially influence offspring's blood pressure and contribute to the development of CVD risk factors later in life. Factors such as maternal smoking, alcohol consumption, or diet have been associated with an increased risk of elevated blood pressure levels in the offspring. In addition, these maternal exposures have been linked to developing other CVD risk factors in the offspring, including dyslipidemia, insulin resistance, obesity, and impaired glucose metabolism (33, 43, 44). Moreover, we have previously collected blood pressure measurements among the offspring at both 1-year and 3-year follow-up visits. Thus, the blood pressure variable presents an opportunity for further analysis on parameters tracking from birth, through childhood, and into early adulthood.

The following secondary outcomes will be differences in the intervention and control groups in both mothers and offspring: lipid profile, fasting glucose and insulin, HbA1c, markers of endothelial activation and inflammation such as tissue plasminogen activator antigen (tPAag), von Willebrand factor (vWF), plasminogen activator inhibitor-1 (PAI-1) activity, plasminogen activator inhibitor-2 (PAI2) antigen, C-reactive protein (CRP), and differential white blood cell (WBC) count. We will use appropriate cardiovascular risk scores to estimate cardiovascular risk status and compare control and intervention in both the mothers and offspring separately. Additional secondary outcomes will include differences in intima-media thickness in the carotid artery and liver fat content measured by ultrasound, variations in body composition indicators by analyzing fat percentage, and skeletal muscle mass measured by bio-impedance. In addition, measurements of waist circumference, hip circumference, and body mass index will be conducted.

2.5.1. Sample size

The CARRDIP randomized trial was designed to detect a clinically relevant difference in maternal cholesterol levels at week 36 in pregnancy and in neonatal cholesterol levels (26). In the CARRDIP20 study, we examined differences in CVD risk factors, which are typically in the range of 0.5–0.7 standard deviations (SDs) in intervention trials with groups randomized to different diets (45), requiring a sample size of approximately 64–100 per group with 80% power at a 5% significance level. Thus, despite the expected loss to follow-up, we most likely have statistical power to detect clinically relevant differences between the groups (46). If we assume an average difference in the systolic blood pressure of 5 mmHg, with SD = 10 mmHg, we will need 128 participants (64 in each group; power 80%, significance level 5%). This corresponds to 47% of the mothers that participated in the CARRDIP trial.

2.5.2. Data analysis

The differences between the intervention and control group in primary and secondary outcomes will be analyzed separately for the mothers and offspring. We will follow the CONSORT guidelines (47–49). The primary outcome, blood pressure, and the majority of the secondary outcomes are continuous with two time points: baseline and a 20-year follow-up. Analysis of covariance will be used to analyze the data (50). There may be some selection of participants in a long-term follow-up. We can adjust for variables that differ between the intervention and control group and are associated with the outcome of interest (48). However, the use of analysis of covariance (i.e., adjustment for the baseline value) may have to be evaluated if there are major indications of selective drop-out. In that case, we will analyze the difference between the values observed at the 20-year follow-up and the baseline using a multivariable linear regression model and adjust for potential covariates.

3. Discussion

The existing evidence suggests that maternal diet during pregnancy may impact the health status of the offspring. Moreover, observational studies support the significance of the *in utero* metabolic environment on the risk of CVD in the offspring later in life (51, 52). The data from the randomized controlled CARRDIP trial with significant clinical effects in both mother and offspring offer a unique possibility to study possible mechanisms for the observed differences. Furthermore, it is crucial to identify possible targets for appropriate dietary intervention during pregnancy to optimize the health of the offspring, both *in utero* and later in life. Ideally, these potential targets should be investigated through long-term follow-ups of RCTs.

To date, studies investigating the effects and mechanisms of diet on the long-term health of the child have primarily been observational and animal studies. Thus, the proposed CARRDIP20 study of the long-term (20 years) effects of a Mediterranean diet during pregnancy on offspring health is unique and of potential great clinical and scientific interest.

Pregnancy may be regarded as a "window of opportunity" where interventions can promote the long-term health outcomes of both the mother and the offspring. Further identification of mechanisms responsible for fetal programming of adult CVD may identify possibilities for targeted treatment among groups at risk of CVD, as well as improved dietary recommendations and policy strategies to improve health in the general population.

Data availability statement

The datasets generated and analyzed during the current study will not be publicly available due to privacy concerns of participants in the study. Restrictions apply to the availability of these data, which were used under license for the current study, but are available from the corresponding author on reasonable request and with permission from Committees for Medical and Health Research Ethics, Norway.

Ethics statement

The studies involving human participants were reviewed and approved by the Regional Committees for Medical and Health Research Ethics, Norway. The patients/participants provided written informed consent to participate in this study.

Author contributions

HT: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Validation, Writing – Original draft, Writing – Review and editing. JK: Conceptualization, Investigation, Methodology, Supervision, Writing – Review and editing. AW: Conceptualization, Methodology, Supervision, Writing – Review and editing. ST: Writing – Review and editing. JR: Writing – Review and editing. MV: Methodology, Writing – Review and editing. PI: Conceptualization, Funding acquisition, Methodology, Project administration, Resources, Supervision, Writing – Review and editing. KH: Conceptualization, Methodology, Project administration, Supervision, Writing – Review and editing. KR: Conceptualization, Methodology, Project administration, Supervision, Writing – Review and editing.

Funding

The authors declare that financial support was received for the research, authorship, and/or publication of this article.

This study was supported by The South-Eastern Norway Regional Health Authority and the University of Oslo.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. World Health Organization. WHO Cardiovascular Diseases (2023). Available at: https://www.who.int/en/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds) (Accessed June 13, 2023).

2. Franco OH, der Kinderen AJ, De Laet C, Peeters A, Bonneux L. Primary prevention of cardiovascular disease: cost-effectiveness comparison. *Int J Technol Assess Health Care*. (2007) 23(1):71–9. doi: 10.1017/S0266462307051598

3. Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. *Circulation*. (2019) 140(11): e596–646. doi: 10.1161/CIR.0000000000000678.

4. Thornburg KL. The programming of cardiovascular disease. *J Dev Orig Health Dis*. (2015) 6(5):366–76. doi: 10.1017/S2040174415001300

5. Gimbrone MA Jr., Garcia-Cardena G. Endothelial cell dysfunction and the pathobiology of atherosclerosis. *Circ Res* (2016) 118(4):620–36. doi: 10.1161/CIRCRESAHA.115.306301

6. Hjermann I, Velve Byre K, Holme I, Leren P. Effect of diet and smoking intervention on the incidence of coronary heart disease. Report from the Oslo study group of a randomised trial in healthy men. *Lancet*. (1981) 2(8259):1303–10. doi: 10.1016/S0140-6736(81)91338-6

7. Leren P. The Oslo diet-heart study: eleven-year report. *Circulation*. (1970) 42 (5):935–42. doi: 10.1161/01.CIR.42.5.935

8. Committee DGA. *Scientific report of the 2020 dietary guidelines advisory committee: Advisory report to the secretary of agriculture and the secretary of health and human services*. Washington, DC: U.S. Department of Agriculture ARS (2020).

9. de Lorgeril M, Salen P, Martin JL, Monjaud I, Delaye J, Mamelle N. Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: final report of the Lyon diet heart study. *Circulation*. (1999) 99(6):779–85. doi: 10.1161/01.CIR.99.6.779

10. Estruch R, Ros E, Salas-Salvado J, Covas MI, Corella D, Aros F, et al. Primary prevention of cardiovascular disease with a Mediterranean diet supplemented with extra-virgin olive oil or nuts. *N Engl J Med*. (2018) 378(25):e34. doi: 10.1056/NEJMoa1800389

11. Maki KC, Dicklin MR. Is there an optimal diet for primordial prevention of atherosclerosis? *Eur Heart J*. (2022) 43(34):3189–91. doi: 10.1093/eurheartj/ehac434

12. Snetselaar L, Bailey R, Sabate J, Van Horn L, Schneeman B, Bahnfleth C, et al. *Types of dietary fat and cardiovascular disease: a systematic review. US department of agriculture, food and nutrition service, center for nutrition policy and promotion, nutrition evidence systematic review*. Washington, USA: US Department of Agriculture, Food and Nutrition Service, Center for Nutrition Policy and Promotion (2020). doi: 10.52570/NESR.DGAC2020.SR0501

13. Avis HJ, Hutten BA, Twickler MT, Kastelein JJ, van der Post JA, Stalenhoef AF, et al. Pregnancy in women suffering from familial hypercholesterolemia: a harmful period for both mother and newborn? *Curr Opin Lipidol*. (2009) 20(6):484–90. doi: 10.1097/MOL.0b013e3283319127

14. Napoli C, Glass CK, Witztum JL, Deutsch R, D'Armiento FP, Palinski W. Influence of maternal hypercholesterolaemia during pregnancy on progression of early atherosclerotic lesions in childhood: Fate of Early Lesions in Children (FELIC) study. *Lancet*. (1999) 354(9186):1234–41. doi: 10.1016/S0140-6736(99)02131-5

15. Stary HC. Evolution and progression of atherosclerotic lesions in coronary arteries of children and young adults. *Arteriosclerosis*. (1989) 9(1 Suppl):I19–32.

16. Stary HC. Lipid and macrophage accumulations in arteries of children and the development of atherosclerosis. *Am J Clin Nutr*. (2000) 72(5 Suppl):1297S–306S. doi: 10.1093/ajcn/72.5.1297s

17. Khoury JC, Dolan LM, Vandyke R, Rosenn B, Feghali M, Miodovnik M. Fetal development in women with diabetes: imprinting for a life-time? *J Matern Fetal Neonatal Med*. (2012) 25(1):11–4. doi: 10.3109/14767058.2012.626921

18. Oyri LKL, Bogsrud MP, Kristiansen AL, Myhre JB, Astrup H, Retterstol K, et al. Cholesterol at ages 6, 12 and 24 months: tracking and associations with diet and maternal cholesterol in the infant cholesterol study. *Atherosclerosis*. (2021) 326:11–6. doi: 10.1016/j.atherosclerosis.2021.04.017

19. Christensen JJ, Retterstol K, Godang K, Roland MC, Qvigstad E, Bollerslev J, et al. LDL cholesterol in early pregnancy and offspring cardiovascular disease risk factors. *J Clin Lipidol*. (2016) 10(6):1369–78.e7. doi: 10.1016/j.jacl.2016.08.016

20. Jacobs DR Jr., Woo JG, Sinaiko AR, Daniels SR, Ikonen J, Juonala M, et al. Childhood cardiovascular risk factors and adult cardiovascular events. *N Engl J Med*. (2022) 386(20):1877–88. doi: 10.1056/NEJMoa2109191

21. Vidakovic AJ, Gishti O, Voortman T, Felix JF, Williams MA, Hofman A, et al. Maternal plasma PUFA concentrations during pregnancy and childhood adiposity: the generation R study. *Am J Clin Nutr*. (2016) 103(4):1017–25. doi: 10.3945/ajcn.115.112847

22. Fernandez-Barres S, Romaguera D, Valvi D, Martinez D, Vioque J, Navarrete-Munoz EM, et al. Mediterranean dietary pattern in pregnant women and offspring risk of overweight and abdominal obesity in early childhood: the INMA birth cohort study. *Pediatr Obes*. (2016) 11(6):491–9. doi: 10.1111/ijpo.12092

23. Brion MJ, Ness AR, Rogers I, Emmett P, Cribb V, Davey Smith G, et al. Maternal macronutrient and energy intakes in pregnancy and offspring intake at 10 Y: exploring parental comparisons and prenatal effects. *Am J Clin Nutr*. (2010) 91(3):748–56. doi: 10.3945/ajcn.2009.28623

24. Stratakis N, Conti DV, Borras E, Sabido E, Roumeliotaki T, Papadopoulou E, et al. Association of fish consumption and mercury exposure during pregnancy with metabolic health and inflammatory biomarkers in children. *JAMA Netw Open*. (2020) 3(3):e201007. doi: 10.1001/jamanetworkopen.2020.1007

25. Teune MJ, van Wassenaer AG, Malin GL, Asztalos E, Alfirevic Z, Mol BW, et al. Long-term child follow-up after large obstetric randomised controlled trials for the evaluation of perinatal interventions: a systematic review of the literature. *BJOG*. (2013) 120(1):15–22. doi: 10.1111/j.1471-0528.2012.03465.x

26. Khoury J, Henriksen T, Christophersen B, Tonstad S. Effect of a cholesterol-lowering diet on maternal, cord, and neonatal lipids, and pregnancy outcome: a randomized clinical trial. *Am J Obstet Gynecol*. (2005) 193(4):1292–301. doi: 10.1016/j.ajog.2005.05.016

27. Khoury J, Haugen G, Tonstad S, Froslie KF, Henriksen T. Effect of a cholesterol-lowering diet during pregnancy on maternal and fetal Doppler velocimetry: the CARRDIP study. *Am J Obstet Gynecol*. (2007) 196(6):549.e1–7. doi: 10.1016/j.ajog.2007.01.017

28. Khoury J, Henriksen T, Seljeflot I, Mørkrid L, Frøslie K, Tonstad S. Effects of an antiatherogenic diet during pregnancy on markers of maternal and fetal endothelial activation and inflammation: the CARRDIP study. *BJOG*. (2007) 114(3):279–88. doi: 10.1111/j.1471-0528.2006.01187.x

29. Amundsen AL, Khoury J, Sandset PM, Seljeflot I, Ose L, Tonstad S, et al. Altered hemostatic balance and endothelial activation in pregnant women with familial hypercholesterolemia. *Thromb Res*. (2007) 120(1):21–7. doi: 10.1016/j.thromres.2006.07.001

30. Khoury J, Knutsen M, Stray-Pedersen B, Thaulow E, Tonstad S. A lower reduction in umbilical artery pulsatility in mid-pregnancy predicts higher infant blood pressure six months after birth. *Acta Paediatr*. (2015) 104(8):796–800. doi: 10.1111/apa.13020

31. Carlsen MH, Lillegaard IT, Karlsen A, Blomhoff R, Drevon CA, Andersen LF. Evaluation of energy and dietary intake estimates from a food frequency questionnaire using independent energy expenditure measurement and weighed food records. *Nutr J*. (2010) 9:37. doi: 10.1186/1475-2891-9-37

32. Enserro DM, Vasan RS, Xanthakis V. Twenty-year trends in the American Heart Association cardiovascular health score and impact on subclinical and clinical cardiovascular disease: the Framingham offspring study. *J Am Heart Assoc*. (2018) 7 (11):1–9. doi: 10.1161/JAHA.118.008741

33. Campbell DM, Hall MH, Barker DJ, Cross J, Shiell AW, Godfrey KM. Diet in pregnancy and the offspring's blood pressure 40 years later. *Br J Obstet Gynaecol*. (1996) 103(3):273–80. doi: 10.1111/j.1471-0528.1996.tb09718.x

34. Amati F, Hassounah S, Swaka A. The impact of Mediterranean dietary patterns during pregnancy on maternal and offspring health. *Nutrients*. (2019) 11(5):1–20. doi: 10.3390/nu11051098

35. Chatzi L, Rifas-Shiman SL, Georgiou V, Joung KE, Koinaki S, Chalkiadaki G, et al. Adherence to the Mediterranean diet during pregnancy and offspring adiposity and cardiometabolic traits in childhood. *Pediatr Obes*. (2017) 12(Suppl 1):47–56. doi: 10.1111/ijpo.12191

36. Stratakis N, Roumeliotaki T, Oken E, Barros H, Basterrechea M, Charles MA, et al. Fish intake in pregnancy and child growth: a pooled analysis of 15 European and US birth cohorts. *JAMA Pediatr*. (2016) 170(4):381–90. doi: 10.1001/jamapediatrics.2015.4430

37. Murrin C, Shrivastava A, Kelleher CC. Maternal macronutrient intake during pregnancy and 5 years postpartum and associations with child weight status aged five. *Eur J Clin Nutr*. (2013) 67(6):670–9. doi: 10.1038/ejcn.2013.76

38. Moon RJ, Harvey NC, Robinson SM, Ntani G, Davies JH, Inskip HM, et al. Maternal plasma polyunsaturated fatty acid status in late pregnancy is associated with offspring body composition in childhood. *J Clin Endocrinol Metab*. (2013) 98 (1):299–307. doi: 10.1210/jc.2012-2482

39. Shiell AW, Campbell DM, Hall MH, Barker DJ. Diet in late pregnancy and glucose-insulin metabolism of the offspring 40 years later. *BJOG*. (2000) 107 (7):890–5. doi: 10.1111/j.1471-0528.2000.tb11088.x

40. Boutron I, Altman DG, Moher D, Schulz KF, Ravaud P, Group CN. Consort statement for randomized trials of nonpharmacologic treatments: a 2017 update and a consort extension for nonpharmacologic trial abstracts. *Ann Intern Med*. (2017) 167(1):40–7. doi: 10.7326/M17-0046

41. Butcher NJ, Monsour A, Mew EJ, Chan AW, Moher D, Mayo-Wilson E, et al. Guidelines for reporting outcomes in trial protocols: the SPIRIT-outcomes 2022 extension. *JAMA*. (2022) 328(23):2345–56. doi: 10.1001/jama.2022.21243

42. Schnohr P, Jensen JS, Scharling H, Nordestgaard BG. Coronary heart disease risk factors ranked by importance for the individual and community. A 21 year follow-up of 12 000 men and women from the Copenhagen city heart study. *Eur Heart J*. (2002) 23(8):620–6. doi: 10.1053/euhj.2001.2842

43. Brion MJ, Leary SD, Lawlor DA, Smith GD, Ness AR. Modifiable maternal exposures and offspring blood pressure: a review of epidemiological studies of maternal age, diet, and smoking. *Pediatr Res*. (2008) 63(6):593–8. doi: 10.1203/PDR.0b013e31816fdbd3

44. Leary SD, Ness AR, Emmett PM, Davey Smith G, Headley JE, Team AS. Maternal diet in pregnancy and offspring blood pressure. *Arch Dis Child*. (2005) 90 (5):492–3. doi: 10.1136/adc.2004.070698

45. Reynolds A, Mann J, Cummings J, Winter N, Mete E, Te Morenga L. Carbohydrate quality and human health: a series of systematic reviews and meta-analyses. *Lancet*. (2019) 393(10170):434–45. doi: 10.1016/S0140-6736(18)31809-9

46. Fewtrell MS, Kennedy K, Singhal A, Martin RM, Ness A, Hadders-Algra M, et al. How much loss to follow-up is acceptable in long-term randomised trials and prospective studies? *Arch Dis Child*. (2008) 93(6):458–61. doi: 10.1136/adc.2007.127316

47. Schulz KF, Altman DG, Moher D, Group C. Consort 2010 statement: updated guidelines for reporting parallel group randomised trials. *Br Med J*. (2010) 340:c332. doi: 10.1136/bmj.c332

48. Moher D, Hopewell S, Schulz KF, Montori V, Gotzsche PC, Devereaux PJ, et al. Consort 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. *Br Med J*. (2010) 340:c869. doi: 10.1136/bmj.c869

49. Butcher NJ, Monsour A, Mew EJ, Chan AW, Moher D, Mayo-Wilson E, et al. Guidelines for reporting outcomes in trial reports: the consort-outcomes 2022 extension. *JAMA*. (2022) 328(22):2252–64. doi: 10.1001/jama.2022.21022

50. Vickers AJ, Altman DG. Statistics notes: analysing controlled trials with baseline and follow up measurements. *Br Med J*. (2001) 323(7321):1123–4. doi: 10.1136/bmj.323.7321.1123

51. Gaillard R. Maternal obesity during pregnancy and cardiovascular development and disease in the offspring. *Eur J Epidemiol*. (2015) 30(11):1141–52. doi: 10.1007/s10654-015-0085-7

52. Poston L. Maternal obesity, gestational weight gain and diet as determinants of offspring long term health. *Best Pract Res Clin Endocrinol Metab*. (2012) 26(5):627–39. doi: 10.1016/j.beem.2012.03.010

frontiers | Frontiers in Pediatrics

TYPE Original Research
PUBLISHED 06 November 2023
DOI 10.3389/fped.2023.1302750

OPEN ACCESS

EDITED BY
Shikai Yu,
Tongji University, China

REVIEWED BY
Donald Lee Batisky,
University of Cincinnati, United States
Arcady A. Putilov,
Federal Research Center of Fundamental and Translational Medicine, Russia

*CORRESPONDENCE
Bo Ban
✉ banbo2011@163.com

RECEIVED 02 October 2023
ACCEPTED 25 October 2023
PUBLISHED 06 November 2023

CITATION
Zhao Q, He M, Zhang M, Chu Y and Ban B (2023) Non-linear relationship between sleep duration and blood pressure in children with short stature.
Front. Pediatr. 11:1302750.
doi: 10.3389/fped.2023.1302750

Non-linear relationship between sleep duration and blood pressure in children with short stature

Qianqian Zhao[1,2], Mingming He[1,2], Mei Zhang[1,2], Yuntian Chu[3] and Bo Ban[1,2]*

[1]Department of Endocrinology, Affiliated Hospital of Jining Medical University, Jining Medical University, Jining, China, [2]Department of National Telemedicine Center of China, Chinese Research Center for Behavior Medicine in Growth and Development, Jining, China, [3]National Telemedicine Center of China, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China

Background: Evidence regarding the relationship between sleep duration and blood pressure is controversial. Therefore, the aim of this study was to investigate the relationship between sleep duration and blood pressure in children with short stature.
Methods: A total of 1,085 participants with short stature were enrolled from the Affiliated Hospital of Jining Medical University in China. The variables involved in this study included sleep duration, anthropometric indicators and biochemical parameters. Sleep duration was evaluated in a face-to-face interview.
Results: The average age of the 1,085 selected participants was 10.2 ± 3.5 years old, and approximately 763 (70.32%) of them were male. The results of adjusted linear regression showed that sleep duration was negatively associated with systolic blood pressure *z* scores (SBP-Z) and diastolic blood pressure *z* scores (DBP-Z) after adjusting for confounders (β −0.07, 95% CI −0.13, −0.01 $P = 0.038$; β −0.05, 95% CI −0.10, −0.01 $P = 0.035$, respectively). A nonlinear relationship was detected between sleep duration and blood pressure, including SBP-Z, DBP-Z and mean arterial pressure *z* scores (MAP-Z). The inflection point of the nonlinear relationship between sleep duration and SBP-Z is 10 h, and the inflection point of DBP-Z and MAP-Z is 8 h.
Conclusion: This study revealed a nonlinear relationship between sleep duration and blood pressure in children with short stature. The findings suggest that the optimal sleep duration in children with short stature was 8–10 h, and sleep durations either too short or too long were associated with increased blood pressure levels.

KEYWORDS

systolic blood pressure, diastolic blood pressure, sleep duration, cardiovascular disease, short stature

Introduction

Childhood hypertension is considered an important risk factor for advanced cardiovascular disease (CVD) (1). There is growing evidence that high blood pressure continues from childhood into adulthood, which indicates that children with high blood pressure are more likely to suffer from hypertension later in life (2). Considering that there is not a single cut-off point to define high blood pressure in children and adolescents (3), it is more difficult for young people to be recognized as having high blood pressure compared to adults. A growing number of studies have given considerable attention to screening for elevated blood pressure and have confirmed relevant factors in youths, especially in obese children, who are prone to having unfavourable blood pressure levels (4–6). However, there is increasing evidence that short stature is also a risk factor

for CVD, and recent studies have reported that an inverse relationship between height and blood pressure is also exists in children (7, 8). Therefore, these studies suggest the need to analyse the blood pressure status and the associated factors, especially in children and adolescents with short stature.

Previous studies have demonstrated that elevated blood pressure as assessed in childhood is a predictor of increased risk of CVD in adults (9, 10). The assessment of childhood CVD risk based on elevated blood pressure may be useful for preventing CVD in adulthood (11). Previous studies have evaluated numerous factors that influence blood pressure levels, and major risk factors for hypertension have been identified, including age, body mass index (BMI), dyslipidaemia, diet and lifestyle habits (12); however, sleep is an often overlooked factor. Sleep plays an important role in the daily life of adults and the growth of children and adolescents, and adequate sleep is essential for everyday functioning and health. However, sleep deprivation is very common, with up to 30% of people affected by sleep deprivation during childhood and adolescence (13). Sleep deprivation in children increases the likelihood of poor behaviour and physical health consequences. In particular, an association between short sleep duration and an increased risk of cardiovascular events has been well established (14). Recent studies have suggested that the effect of sleep duration on CVD may be related to elevated blood pressure (15). Studies on the relationship between sleep duration and blood pressure have gradually increased (16). However, findings from previous studies regarding the relationship between sleep duration and blood pressure have been controversial in both children and adults (17–26), and the relationship between sleep duration and blood pressure has been found to be U-shaped (26), negatively correlated (19) or unrelated (20, 26). However, evidence of a relationship between sleep duration and blood pressure is lacking in children with short stature. Therefore, the aim of this study was to investigate the relationship between sleep duration and blood pressure in Chinese children with short stature.

Methods

Study population

The present study is a secondary analysis of our prospective cohort study. All the subjects enrolled were in the GDDSD study (http://www.chictr.org.cn, ChiCTR1900026510), an ongoing prospective, observational, open cohort study that is evaluating the aetiology of growth and development diseases and the long-term safety and effectiveness of growth hormone therapy in a real-life clinical setting (27). A total of 1,085 children and adolescents with short stature (763 males and 322 females) from the Affiliated Hospital of Jining Medical University between March 2013 and October 2020 were recruited. The average age of the participants was 10.2 ± 3.5 years. Subjects were eligible if their height standard deviation scores (SDS) were more than 2 SDS lower than the average of individuals of the same race, age and sex. The exclusion criteria were as follows: (1) chronic diseases; (2) skeletal dysplasia; (3) chromosomal abnormalities, including Noonan syndrome and Turner syndrome; and (4) missing data on sleep duration and blood pressure.

Anthropometric measurement

Height and weight were measured using a standard procedure with the participants wearing no shoes or coats. Height was measured using a stadiometer (Nantong Best Industrial Co., Ltd., Jiangsu, China), which is accurate to 0.1 cm. An electronic scale (Wuxi Weigher Factory Co., Ltd., Jiangsu, China) was used to measure weight to the nearest 0.1 kg. Body mass index (BMI) was calculated as weight (kg)/height squared (m^2). The SDS of height and BMI were calculated based on the growth charts of normal Chinese children (28, 29). Blood pressure measurements were performed after a 10-min rest with the children in a seated position, and the blood pressure was measured three times on the right arm with an electronic sphygmomanometer (Omron HBP-1300, Dalian, China). The average of the three measurements was used in the analyses. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were also expressed in SBP *z* scores (SBP-Z) and DBP *z* scores (DBP-Z) related to age, gender and height for every individual (30). The mean arterial pressure (MAP) was calculated as DBP plus one-third of the pulse pressure. Pubertal maturity was assessed by a trained physician who performed a physical examination and assigned each child a maturity level according to the Tanner stage (31). Boys with testicular volume less than 4 ml and no pubic hair and girls with undeveloped breasts and no pubic hair were considered prepubescent. Sleep duration was determined by parental report or self-report.

Laboratory measurements

All participants fasted for at least eight hours before blood samples were taken for biochemical measurements. The serum insulin-like growth factor-1 (IGF-1) concentration was measured by chemiluminescence assay (DPC IMMULITE 1,000 analyser, Siemens, Germany), and the intra- and inter-assay coefficients of variation (CVs) were 3.0% and 6.2%, respectively. Fasting plasma glucose (FPG), triglycerides (TG), total cholesterol (TC), high-density lipoprotein-cholesterol (HDL-C), and low-density lipoprotein-cholesterol (LDL-C) were analysed by an autobiochemical analyser (Cobas c702, Roche; Shanghai, China). The IGF-1 SDS was calculated using the reference values of healthy children of the same age and sex (32).

Statistical analysis

Continuous variables are expressed as the mean ± standard deviation or median (interquartile range), while categorical variables are presented as numbers and percentages. Univariate analysis was performed to estimate the association between SBP-Z and sleep duration as well as the other variables. Smooth curve

fitting was applied to explore nonlinear associations between sleep duration and SBP-Z. In addition, smooth curve fitting was also used to analyse the relationship between sleep duration and DBP-Z, MAP z scores (MAP-Z). Furthermore, to examine the independent association of sleep duration and SBP-Z, we used multivariate linear regression and two piecewise linear regressions. A two-sided $P < 0.05$ was considered statistically significant. Data were analysed using R 3.6.1 (https://www.R-project.org) and EmpowerStats (https://www.Empowerstats.com, X&Y Solutions, Inc.; Boston, MA).

Results

Baseline characteristics of participants

Table 1 shows the descriptive characteristics of the study population at baseline. A total of 1,085 individuals participated in the study. The average age of the children was 10.2 ± 3.5 years old, and 763 (70.32%) of them were boys. The mean height SDS of the participants was −2.70 ± 0.63. Among the study population, 737 participants were prepubescent, accounting for 67.93% of the sample. The assessment of sleep habits showed that the average sleep duration per night in the population study sample was 9.20 ± 0.96 h. The mean SBP-Z and SBP level were 0.73 (0.08–1.45) and 105.71 ± 11.98 mmHg, respectively. The mean DBP-Z and DBP level were 0.35 (−0.07–0.84) and 62.22 ± 8.72 mmHg, respectively.

TABLE 1 Clinical and biochemical characteristics.

Variables	All
Number	1,085
Sex (male %)	763 (70.32%)
Age (years)	10.2 ± 3.5
Height (cm)	125.43 ± 17.94
Height SDS	−2.70 ± 0.63
Body weight (kg)	27.72 ± 11.49
BMI (kg/m^2)	18.01 ± 3.47
BMI SDS	0.12 (−0.69–1.03)
Sleep duration (hours)	9.20 ± 0.96
IGF-1 (ng/ml)	168.00 (98.25–252.75)
IGF-1 SDS	−0.96 (−1.74–0.11)
SBP (mmHg)	105.71 ± 11.98
SBP-Z	0.73 (0.08–1.45)
DBP (mmHg)	62.22 ± 8.72
DBP-Z	0.35 (−0.07–0.84)
MAP (mmHg)	76.71 ± 8.60
MAP-Z	0.50 (0.07–0.95)
FPG (mmol/L)	4.86 ± 2.11
TG (mmol/L)	0.65 (0.51–0.86)
TC (mmol/L)	3.86 ± 0.73
HDL-C (mmol/L)	1.45 ± 0.30
LDL-C (mmol/L)	2.11 ± 0.59
Pubertal stage	
In prepuberty (%)	737 (67.93%)
In puberty (%)	348 (32.07%)

Height SDS, height standard deviation scores; BMI SDS, body mass index standard deviation scores; IGF-1 SDS, insulin like growth factor-1 standard deviation scores; SBP-Z, systolic blood pressure z scores; DBP-Z, diastolic blood pressure z scores; MAP-Z, mean arterial pressure z scores; FPG, fasting plasma glucose; TG, triglyceride; TC, total cholesterol; HDL-C, high density lipoprotein-cholesterol; LDL-C, low density lipoprotein cholesterol. Continuous variables are presented as the mean ± standard deviation or median (interquartile range). Categorical variables are displayed as number (percentage).

Variables associated with blood pressure in the participants

The analysis results of the relationship between blood pressure and clinical parameters are provided in Table 2. In the univariate linear regression analysis, we observed a significant negative association between sleep duration and SBP-Z and DBP-Z (both $P < 0.05$). In addition, the relationship between age, sex and SBP-Z and DBP-Z remained negative, while other variables, including height SDS, body weight, IGF-1 SDS, TG, TC and LDL-C, were positively associated with SBP-Z (all $P < 0.05$). However, there were no significant associations between SBP-Z and pubertal stage, BMI SDS, FPG or HDL-C (all $P > 0.05$).

Independent association between sleep duration and blood pressure

To explore whether there was a nonlinear relationship between sleep duration and blood pressure, smooth curve fitting was performed. The results showed that there was a nonlinear relationship between sleep duration and blood pressure (SBP-Z, DBP-Z and MAP-Z) after adjusting for potential confounding factors, and there was an inflection point (Figures 1, 2). Before the inflection point, sleep duration and blood pressure were negatively associated, and after the inflection point, sleep duration and blood pressure were positively associated. To investigate this finding further, we conducted linear regression and two piecewise linear regressions.

As presented in Table 3, it was observed through linear regression that after adjusting for confounding variables, sleep duration was independently negatively associated with SBP-Z (β −0.07, 95% CI −0.13, −0.01; $P = 0.038$). Moreover, in the two piecewise regressions, the results showed that the inflection point of sleep duration was 10 h. If sleep duration was less than 10 h, there was a negative association between sleep duration and SBP-Z (β −0.10, 95% CI −0.17, −0.03; $P = 0.004$), while if the sleep duration was greater than 10 h, there was a positive association between sleep duration and SBP-Z (β 0.34, 95% CI 0.04, 0.64; $P = 0.025$). In addition, we also analyzed DBP-Z, whose inflection point is 8 h, which is consistent with the relationship between SBP-Z and sleep duration.

Furthermore, we analyzed the relationship between sleep duration and mean arterial pressure. Sleep duration was independently negatively associated with MAP-Z (β −0.05, 95% CI −0.10, −0.01; $P = 0.021$). Moreover, in the two piecewise regressions, the results showed that the inflection point of sleep duration was 8 h. If sleep duration was less than 8 h, there was a negative association between sleep duration and MAP-Z

TABLE 2 Association between blood pressure and different variables.

Variables	SBP-Z			DBP-Z		
	β	(95% CI)	*P*-value	β	(95% CI)	*P*-value
Age (years)	−0.02	(−0.03, −0.01)	0.041	−0.03	(−0.04, −0.01)	<0.001
Height SDS	0.13	(0.05, 0.21)	0.002	0.15	(0.09, 0.22)	<0.001
Body weight (kg)	0.01	(0.01, 0.01)	0.001	0.01	(0.01, 0.01)	0.003
BMI SDS	0.04	(−0.01, 0.09)	0.081	0.03	(−0.01, 0.07)	0.144
Sleep duration (hours)	−0.07	(−0.13, −0.01)	0.034	−0.03	(−0.08, −0.01)	0.048
IGF-1 SDS	0.11	(0.07, 0.16)	<0.001	0.06	(0.02, 0.10)	0.001
FPG (mmol/L)	−0.01	(−0.04, 0.02)	0.394	−0.01	(−0.03, 0.02)	0.721
TG (mmol/L)	0.19	(0.05, 0.34)	0.010	0.01	(−0.11, 0.12)	0.936
TC (mmol/L)	0.09	(0.01, 0.18)	0.024	0.03	(−0.04, 0.09)	0.436
HDL-C (mmol/L)	−0.01	(−0.02, 0.01)	0.402	−0.01	(−0.01, 0.01)	0.803
LDL-C (mmol/L)	0.16	(0.06, 0.26)	0.002	0.03	(−0.05, 0.11)	0.450
Sex						
Male		Reference			Reference	
Female	−0.28	−0.28 (−0.41, −0.15)	< 0.001	−0.17	(−0.27, −0.06)	0.002
Pubertal stage						
In prepuberty (%)		Reference			Reference	
In puberty (%)	−0.08	−0.08 (−0.20, 0.05)	0.224	−0.13	(−0.23, −0.03)	0.009

Height SDS, height standard deviation scores; BMI SDS, body mass index standard deviation scores; IGF-1 SDS, insulin like growth factor-1 standard deviation scores; SBP-Z, systolic blood pressure *z* scores; DBP-Z, diastolic blood pressure *z* scores; FPG, fasting plasma glucose; TG, triglyceride; TC, total cholesterol; HDL-C, high density lipoprotein-cholesterol; LDL-C, low density lipoprotein cholesterol. $P < 0.05$ is considered to be statistically significant.

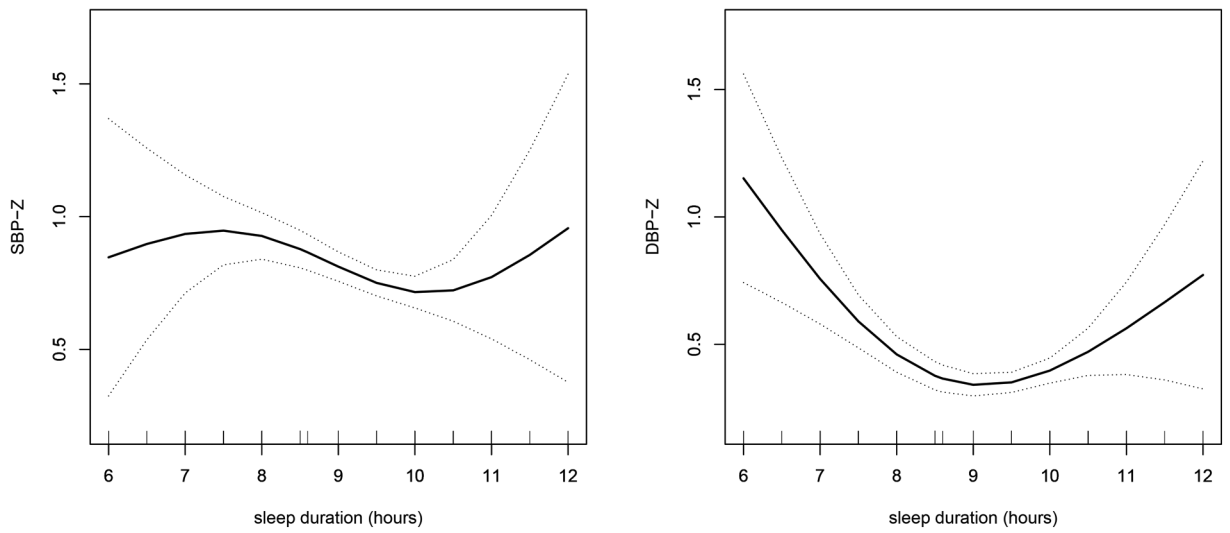


FIGURE 1
The relationship between sleep duration and blood pressure was determined by smooth curve fitting. Adjustment variables: age, sex, height, weight, IGF-1, TG and TC. SBP-Z, systolic blood pressure *z* scores; DBP-Z, diastolic blood pressure *z* scores; IGF-1, insulin like growth factor-1; TG, triglyceride; TC, total cholesterol.

(β −0.43, 95% CI −0.64, −0.22; $P < 0.001$), while if the sleep duration was greater than 8 h, there was a positive association between sleep duration and MAP-Z (β 0.03, 95% CI 0.06, 0.01; $P = 0.046$) (Table 4).

The log-likelihood ratio test was used to evaluate whether linear regression or two piecewise linear regressions could better represent the relationship between sleep duration and blood pressure. $P < 0.05$ indicated that piecewise linear regression could better reflect the true relationship between sleep duration and blood pressure. The results showed that *P* for the log-likelihood ratio test were all less than 0.05, so the two-piecewise linear regression used to fit the association between sleep duration and blood pressure could accurately represent the relationship (Tables 3, 4).

Discussion

In this study, we observed a significant negative relationship between sleep duration and blood pressure in children with short

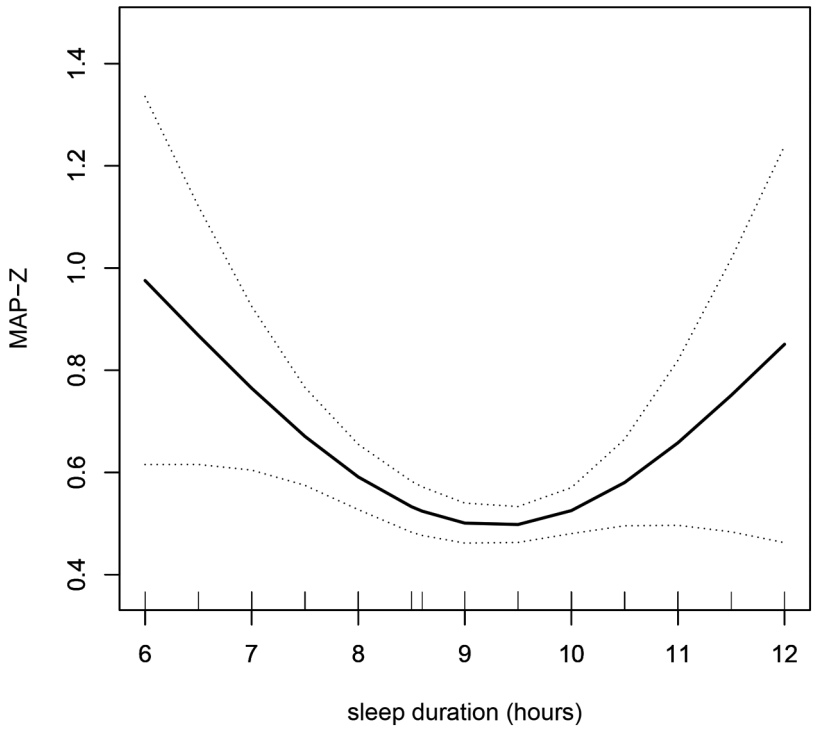


FIGURE 2
The relationship between sleep duration and MAP-Z was determined by smooth curve fitting. Adjustment variables: age, sex, height, weight, IGF-1, TG and TC. MAP-Z, mean arterial pressure *z* scores; IGF-1, insulin like growth factor-1; TG, triglyceride; TC, total cholesterol.

stature. Furthermore, there was a nonlinear relationship between sleep duration and blood pressure. The optimal amount of sleep in children with short stature was found to be 8–10 h, and both short and long sleep durations were associated with increased blood pressure levels.

Over the past few years, many studies on sleep and blood pressure have been published, reporting conflicting results in both children and adults (17–26). A population-based cross-sectional study recruited 19,407 adults aged 18–79 years, and they observed that there were no significant associations between sleep duration and hypertension in the general population (20). Moreover, Morita N et al. conducted a study on 102 Japanese students with an average age of 11.9 ± 1.8 years and found that there was no relationship between sleep and blood pressure (33). In contrast, a meta-analysis of six prospective cohort studies examining the relationship between sleep duration and the risk of hypertension showed that short sleep duration was associated

TABLE 3 Threshold effect analysis for the relationship between the sleep duration and blood pressure.

Models	SBP-Z		DBP-Z	
	Adjusted β (95% CI)	*P*-value	Adjusted β (95% CI)	*P*-value
Model I				
One line slope	−0.07 (−0.13, −0.01)	0.038	−0.05 (−0.10, −0.01)	0.035
Model II				
Turning point	10		8	
<10 slope 1	−0.10 (−0.17, −0.03)	0.004	−0.61 (−0.83, −0.39)	<0.001
>10 slope 2	0.34 (0.04, 0.64)	0.025	0.02 (0.04, 0.01)	0.048
LRT test	0.006		<0.001	

Model I, linear analysis; Model II, non-linear analysis. LRT test, Logarithmic likelihood ratio test. (*p*-value < 0.05 means Model II is significantly different from Model I, which indicates a non-linear relationship); Adjustment variables: age, sex, height, weight, IGF-1, TG and TC. SBP-Z, systolic blood pressure *z* scores; DBP-Z, diastolic blood pressure *z* scores; IGF-1, insulin like growth factor-1; TG, triglyceride; TC, total cholesterol. *P* < 0.05 is considered to be statistically significant.

TABLE 4 Threshold effect analysis for the relationship between the sleep duration and MAP-Z.

Models	MAP-Z	
	Adjusted β (95%CI)	*P*-value
Model I		
One line slope	−0.05 (−0.10, −0.01)	0.021
Model II		
Turning point	8	
<10 slope 1	−0.43 (−0.64, −0.22)	<0.001
>10 slope 2	0.03 (0.06, 0.01)	0.046
LRT test	<0.001	

Model I, linear analysis; Model II, non-linear analysis. LRT test, Logarithmic likelihood ratio test. (*p*-value < 0.05 means Model II is significantly different from Model I, which indicates a non-linear relationship); Adjustment variables: age, sex, height, weight, IGF-1, TG and TC. MAP-Z, mean arterial pressure *z* scores; IGF-1, insulin like growth factor-1; TG, triglyceride; TC, total cholesterol. *P* < 0.05 is considered to be statistically significant.

with an increased risk of hypertension (34). The results of our study are consistent with these studies. In this study, linear regression was used to find a negative association between sleep duration and blood pressure, and short sleep duration was related to high blood pressure levels.

Interestingly, smoothing curve fitting was applied, and it was found that there was a nonlinear relationship between sleep duration and blood pressure. We further performed piecewise linear regression to find the inflection point of 8 or 10 h. More specifically, when sleep duration was less than 8 or 10 h, there was a negative association between sleep duration and blood pressure, indicating that short sleep duration was related to a high blood pressure level. However, when sleep duration was more than 8 or 10 h, sleep duration was positively related to blood pressure. With increasing sleep duration, the blood pressure level increases significantly. This finding suggests that the optimal sleep duration in children with short stature was 8–10 h, and sleep durations either too short or too long can have a negative effect on blood pressure. This is consistent with the sleep duration recommended by the National Sleep Foundation (34). It is well established that shorter sleep duration is associated with elevated blood pressure levels (35); however, longer sleep duration was also associated with increased blood pressure. In the Sleep and Heart Health Study, an analysis of data from 5,910 participants aged 40 to 100 years (2,813 men and 3,097 women) found that sleeping nine hours or more was associated with a 30% increased risk of high blood pressure compared with sleeping seven to eight hours (36). In addition, consistent with our findings, Grandner M et al. assessed the relationship between sleep duration and blood pressure using combined data from the 2007–2017 National Health Interview Survey (NHIS) and 2013 Behavioural Risk Factor Surveillance System (BRFSS) from adults 18 years and older and reported that both short and long sleep durations are associated with increased hypertension risk (37).

Regarding the relationship between long sleep duration and blood pressure, the results of the study are also controversial (37–39). In addition to the reports that long sleep duration is related to high blood pressure (37), some studies have not found that long sleep duration is related to high blood pressure (38, 39). However, studies on the relationship between sleep duration and blood pressure in children with short stature are limited. This study reported that there is a nonlinear relationship between sleep duration and blood pressure, and sleep durations that are either too short or too long will increase blood pressure.

The underlying mechanisms by which sleep duration may contribute to increased blood pressure are complex and unclear. Some studies have suggested that short sleep duration may increase blood pressure by increasing sympathetic nervous system activity or by disrupting circadian rhythms and autonomic nervous responses (40, 41). In addition, short sleep periods may stimulate fatigue, irritability and stress, which increases the risk of elevated blood pressure (34). To date, no clear mechanism has been found to explain the relationship between long sleep duration and elevated blood pressure. However, some studies suggest that factors such as sleep disruption and depression may explain a link between long sleep and mortality (42, 43).

According to the hypertension guidelines, higher SBP and DBP are associated with an increased risk of CVD when they are considered separately. However, higher SBP is consistently associated with an increased risk of CVD after adjusting or stratifying DBP. In contrast, the association between DBP and CVD risk was not consistent after adjusting or stratifying SBP. In addition, mean arterial pressure can also predict the risk of CVD (44). Therefore, we analysed the relationship between sleep duration and blood pressure, including SBP-Z, DBP-Z and MAP-Z. The inflection point of the nonlinear relationship between sleep duration and SBP-Z is 10 h, and the inflection point of DBP-Z and MAP-Z is 8 h.

Several limitations of the present study are worth discussing. First, considering the cross-sectional nature of the data, it is impossible to establish a causal relationship between sleep duration and blood pressure. Second, sleep duration was based on subjective reports by parents or the participants. Although electroencephalogram (EEG) measurements of sleep duration are considered more accurate than subjective assessments, the results of subjective self-reporting correlate with those obtained by EEG methods (45). Finally, the population in the present study was composed of Chinese children and adolescents with short stature, and there was a nonlinear relationship between sleep duration and blood pressure. Different findings may be observed in other ethnic groups or disease populations, which is worthy of further study.

In conclusion, in the present study, a nonlinear relationship between sleep duration and blood pressure in children with short stature was observed. The findings suggest that the optimal sleep duration in children with short stature was 8–10 h, and sleep durations either too short or too long sleep durations were associated with increased blood pressure levels. Further studies are still needed to explore the potential biological mechanism of the association between sleep duration and blood pressure.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by Affiliated Hospital of Jining Medical University. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

QZ: Writing – original draft. MH: Data curation, Writing – review & editing. MZ: Methodology, Supervision, Writing – review

& editing. YC: Formal analysis, Investigation, Writing – review & editing. BB: Conceptualization, Supervision, Writing – review & editing.

Funding

The authors declare financial support was received for the research, authorship, and/or publication of this article.

This work was supported by the Natural Science Foundation of Shandong Province (no. ZR2022MH284).

Acknowledgments

The authors thank all the staff members in our institution.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Falkner B. The childhood role in development of primary hypertension. *Am J Hypertens*. (2018) 31:762–9. doi: 10.1093/ajh/hpy058

2. Chen X, Wang Y. Tracking of blood pressure from childhood to adulthood: a systematic review and meta-regression analysis. *Circulation*. (2008) 117:3171–80. doi: 10.1161/CIRCULATIONAHA.107.730366

3. Daniels SR. What is the prevalence of childhood hypertension? It depends on the definition. *JAMA Pediatr*. (2018) 172:519–20. doi: 10.1001/jamapediatrics.2018.0375

4. Taghizadeh S, Abbasalizad-Farhangi M, Pourali F, Asghari-Jafarabadi M. Predictors of childhood high blood pressure among overweight and obese children and adolescents according to the lifestyle-scoring algorithm using data from Iranian health care reform plan. *Clin Nutr Res*. (2021) 10:243–56. doi: 10.7762/cnr.2021.10.3.243

5. Muhihi AJ, Njelekela MA, Mpembeni R, Muhihi BG, Anaeli A, Chillo O, et al. Elevated blood pressure among primary school children in Dar es Salaam, Tanzania: prevalence and risk factors. *BMC Pediatr*. (2018) 18:54. doi: 10.1186/s12887-018-1052-8

6. Wang L, Song L, Liu B, Zhang L, Wu M, Cao Z, et al. Trends and Status of the prevalence of elevated blood pressure in children and adolescents in China: a systematic review and meta-analysis. *Curr Hypertens Rep*. (2019) 21:88. doi: 10.1007/s11906-019-0992-1

7. Fujita Y, Kouda K, Nakamura H, Nishio N, Takeuchi H, Iki M. Relationship between height and blood pressure in Japanese schoolchildren. *Pediatr Int*. (2010) 52:689–93. doi: 10.1111/j.1442-200 X.2010.03093.x

8. Stabouli S, Antza C, Chrysaidou K, Kotsis V. The challenge of simplifying blood pressure screening in children and adolescents. *J Clin Hypertens (Greenwich)*. (2020) 22:876–8. doi: 10.1111/jch.13858

9. Korczak DJ, Cleverley K, Birken CS, Pignatiello T, Mahmud FH, McCrindle BW. Cardiovascular disease risk factors among children and adolescents with depression. *Front Psychiatry*. (2021) 12:702737. doi: 10.3389/fpsyt.2021.702737

10. Chen WL, Tain YL, Chen HE, Hsu CN. Cardiovascular disease risk in children with chronic kidney disease: impact of apolipoprotein C-II and apolipoprotein C-III. *Front Pediatr*. (2021) 9:706323. doi: 10.3389/fped.2021.706323

11. Thompson M, Dana T, Bougatsos C, Blazina I, Norris SL. Screening for hypertension in children and adolescents to prevent cardiovascular disease. *Pediatrics*. (2013) 131:490–525. doi: 10.1542/peds.2012-3523

12. Akdag B, Fenkci S, Degirmencioglu S, Rota S, Sermez Y, Camdeviren H. Determination of risk factors for hypertension through the classification tree method. *Adv Ther*. (2006) 23:885–92. doi: 10.1007/BF02850210

13. Honaker SM, Meltzer LJ. Sleep in pediatric primary care: a review of the literature. *Sleep Med Rev*. (2016) 25:31–9. doi: 10.1016/j.smrv.2015.01.004

14. Fobian AD, Elliott L, Louie T. A systematic review of sleep, hypertension, and cardiovascular risk in children and adolescents. *Curr Hypertens Rep*. (2018) 20:42. doi: 10.1007/s119068-0841-7

15. Sun J, Wang M, Yang L, Zhao M, Bovet P, Xi B. Sleep duration and cardiovascular risk factors in children and adolescents: a systematic review. *Sleep Med Rev*. (2020) 53:101338. doi: 10.1016/j.smrv.2020.101338

16. Jiang W, Hu C, Li F, Hua X, Zhang X. Association between sleep duration and high blood pressure in adolescents: a systematic review and meta-analysis. *Ann Hum Biol*. (2018) 45:457–62. doi: 10.1080/03014460.2018.1535661

17. Sasaki-Otomaru A, Yamasue K, Tochikubo O, Saito K, Inamori M. Association of home blood pressure with sleep and physical and mental activity, assessed via a wristwatch-type pulsimeter with accelerometer in adults. *Clin Exp Hypertens*. (2020) 42:131–8. doi: 10.1080/10641963.2019.1590382

18. Lo K, Woo B, Wong M, Tam W. Subjective sleep quality, blood pressure, and hypertension: a meta-analysis. *J Clin Hypertens (Greenwich)*. (2018) 20:592–605. doi: 10.1111/jch.13220

19. Sparano S, Lauria F, Ahrens W, Fraterman A, Thumann B, Iacoviello L, et al. Sleep duration and blood pressure in children: analysis of the pan-European IDEFICS cohort. *J Clin Hypertens (Greenwich)*. (2019) 21:572–8. doi: 10.1111/jch.13520

20. Li M, Yan S, Jiang S, Ma X, Gao T, Li B. Relationship between sleep duration and hypertension in northeast China: a cross-sectional study. *BMJ Open*. (2019) 9:e23916. doi: 10.1136/bmjopen-2018-023916

21. Najafian J, Nouri F, Mohammadifard N. Association between sleep duration and hypertension: isfahan healthy heart program, Iran. *ARYA Atheroscler*. (2019) 15:22–6. doi: 10.22122/arya.v15i1.1657

22. Zhang H, Zhao X, Li Y, Mao Z, Huo W, Jiang J, et al. Night sleep duration and sleep initiation time with hypertension in Chinese rural population: the Henan rural cohort. *Eur J Public Health*. (2020) 30:164–70. doi: 10.1093/eurpub/ckz142

23. Quan S, Combs D, Parthasarathy S. Impact of sleep duration and weekend oversleep on body weight and blood pressure in adolescents. *Southwest J Pulm Crit Care*. (2018) 16:31–41. doi: 10.13175/swjpcc150-17

24. Aggarwal B, Makarem N, Shah R, Emin M, Wei Y, St-Onge MP, et al. Effects of inadequate sleep on blood pressure and endothelial inflammation in women: findings from the American heart association go red for women strategically focused research network. *J Am Heart Assoc*. (2018) 7:e008590. doi: 10.1161/JAHA.118.008590

25. Paciencia I, Araujo J, Ramos E. Sleep duration and blood pressure: a longitudinal analysis from early to late adolescence. *J Sleep Res*. (2016) 25:702–8. doi: 10.1111/jsr.12433

26. Satoh H, Nishihira J, Wada T, Fujii S, Tsutui H. The relation between habitual sleep duration and blood pressure values in Japanese male subjects. *Environ Health Prev Med*. (2013) 18:215–20. doi: 10.1007/s12199-012-0309-3

27. Zhao Q, Zhang M, Chu Y, Sun H, Pan H, Ban B. A retrospective analysis of patients with short stature in eastern China between 2013 and 2019. *Biomed Res Int*. (2021) 2021:6640026. doi: 10.1155/2021/6640026

28. Li H, Ji CY, Zong XN, Zhang YQ. Height and weight standardized growth charts for Chinese children and adolescents aged 0–18 years. *Chinese J Pediatr*. (2009) 47:487–92. doi: 10.3760/cma.j.issn.0578-1310.2009.07.003

29. Li H, Ji CY, Zong XN, Zhang YQ. Body mass index growth curves for Chinese children and adolescents aged 0–18 years. *Chinese J Pediatr*. (2009) 47:493–8. doi: 10.3760/cma.j.issn.0578-1310.2009.07.004

30. Meng LH, Xi B. The usage guidance of blood pressure reference in the fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and it's SPSS program. *Chin J Prev Med*. (2017) 51:957–60. doi: 10.3760/cma.j.issn.0253-9624

31. Wright CM, Ahmed L, Dunger DB, Preece MA, Cole TJ, Butler G. Can we characterise growth in puberty more accurately? Validation of a new puberty phase specific (PPS) growth chart. *Arch Dis Child*. (2012) 97:A100. doi: 10.1136/archdischild-2012-301885.236

32. Isojima T, Shimatsu A, Yokoya S, Chihara K, Tanaka T, Hizuka N, et al. Standardized centile curves and reference intervals of serum insulin-like growth factor-I (IGFI) levels in a normal Japanese population using the LMS method. *Endocr J*. (2012) 59:771–80. doi: 10.1507/endocrj.ej12-0110

33. Morita N, Kambayashi I, Okuda T, Oda S, Takada S, Nakajima T, et al. Inverse relationship between sleep duration and cardio-ankle vascular Index in children. *J Atheroscler Thromb*. (2017) 24:819–26. doi: 10.5551/jat.36517

34. Hirshkowitz M, Whiton K, Albert SM, Alessi C, Bruni O, DonCarlos L, et al. National sleep foundation's sleep time duration recommendations: methodology and results summary. *Sleep Health*. (2015) 1:40–3. doi: 10.1016/j.sleh.2014.12.010

35. Meng L, Zheng Y, Hui R. The relationship of sleep duration and insomnia to risk of hypertension incidence: a meta-analysis of prospective cohort studies. *Hypertens Res*. (2013) 36:985–95. doi: 10.1038/hr.2013.70

36. Gottlieb DJ, Redline S, Nieto FJ, Baldwin CM, Newman AB, Resnick HE, et al. Association of usual sleep duration with hypertension: the sleep heart health study. *Sleep*. (2006) 29:1009–14. doi: 10.1093/sleep/29.8.1009

37. Grandner M, Mullington JM, Hashmi SD, Redeker NS, Watson NF, Morgenthaler TI. Sleep duration and hypertension: analysis of >700,000 adults by age and sex. *J Clin Sleep Med*. (2018) 14:1031–9. doi: 10.5664/jcsm.7176

38. Deng HB, Tam T, Zee BC, Chung RY, Su X, Jin L, et al. Short sleep duration increases metabolic impact in healthy adults: a population-based cohort study. *Sleep*. (2017) 40:10. doi: 10.1093/sleep/zsx130

39. Clark AJ, Salo P, Lange T, Jennum P, Virtanen M, Pentti J, et al. Onset of impaired sleep and cardiovascular disease risk factors: a longitudinal study. *Sleep*. (2016) 39:1709–18. doi: 10.5665/sleep.6098

40. Gangwisch JE. Epidemiological evidence for the links between sleep, circadian rhythms and metabolism. *Obes Rev*. (2009) 10:37–45. doi: 10.1111/j.1467-789X.2009.00663.x

41. van Leeuwen W, Sallinen M, Virkkala J, Lindholm H, Hirvonen A, Hublin C, et al. Physiological and autonomic stress responses after prolonged sleep restriction and subsequent recovery sleep in healthy young men. *Sleep Biol Rhythms*. (2018) 16:45–54. doi: 10.1007/s41105-017-0122-x

42. Patel SR, Malhotra A, Gottlieb DJ, White DP, Hu FB. Correlates of long sleep duration. *Sleep*. (2006) 29:881–9. doi: 10.1093/sleep/29.7.881

43. Grandner MA, Drummond SP. Who are the long sleepers? Towards an understanding of the mortality rela tionship. *Sleep Med Rev*. (2007) 11:341–60. doi: 10.1016/j.smrv.2007.03.010

44. Whelton PK, Carey RM, Aronow WS, Casey DJ, Collins KJ, Dennison HC, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American college of cardiology/American heart association task force on clinical practice guidelines. *Hypertension*. (2018) 71:e13–115. doi: 10.1161/HYP.0000000000000065

45. Lewis SA. Subjective estimates of sleep: an EEG evaluation. *Br J Psychol*. (1969) 60:203–8. doi: 10.1111/j.2044-8295.1969.tb01193.x

frontiers | Frontiers in Pediatrics

TYPE Original Research
PUBLISHED 05 December 2023
DOI 10.3389/fped.2023.1294823

OPEN ACCESS

EDITED BY
Shikai Yu,
Tongji University, China

REVIEWED BY
Xiaohui Li,
Children's Hospital of Capital Institute of Pediatrics, China
Kai-Sheng Hsieh,
China Medical University, Taiwan

*CORRESPONDENCE
Jae Yoon Na
✉ hypedheart@hanyang.ac.kr

RECEIVED 15 September 2023
ACCEPTED 16 November 2023
PUBLISHED 05 December 2023

CITATION
Cha JH, Hwang JK, Choi Y-J and Na JY (2023) The risk of pediatric cardiovascular diseases in offspring born to mothers with systemic lupus erythematosus: a nationwide study.
Front. Pediatr. 11:1294823.
doi: 10.3389/fped.2023.1294823

The risk of pediatric cardiovascular diseases in offspring born to mothers with systemic lupus erythematosus: a nationwide study

Jong Ho Cha[1], Jae Kyoon Hwang[2], Young-Jin Choi[2,3] and Jae Yoon Na[1,3]*

[1]Department of Pediatrics, Hanyang University Hospital, Seoul, Republic of Korea, [2]Department of Pediatrics, Hanyang University Guri Hospital, Guri, Republic of Korea, [3]Department of Pediatrics, Hanyang University College of Medicine, Seoul, Republic of Korea

Background: Systemic lupus erythematosus (SLE), a common autoimmune disease predominantly affecting women, has been linked to various complications during pregnancy. The transfer of anti-Ro/SSA antibodies from SLE-affected mothers to their offspring can lead to neonatal lupus and cardiac issues. This study investigated the association between maternal SLE and the risk of pediatric cardiovascular disorders.
Methods: The study utilized South Korea's National Health Insurance Service (NHIS) database, covering 3,505,737 children born between 2007 and 2017 and tracked until 2020. Maternal SLE cases were identified using the World Health Organization's International Classification of Diseases Tenth revision (ICD-10) codes and linked with delivery records. Cardiologic disorders were categorized into congenital heart disease (CHD), arrhythmic disorders, and acquired heart disease. Propensity score matching with 1:4 ratios was applied to the set control group.
Results: Among 3,505,737 children, 0.7% (n = 23,330) were born to mothers with SLE. The incidence of preterm birth was significantly higher in the maternal SLE group (5.9% vs. 3.0%). Compared with the control group, children born to mothers with SLE exhibited a significantly elevated risk of overall CHDs (5.5%, adjusted odds ratio [aOR] 1.21; 95% confidence interval [CI] 1.14–1.29), including atrial septal defect (1.18; 1.09–1.28) and patent ductus arteriosus (1.15; 1.03–1.30). In addition, a notably higher risk was observed in arrhythmic disorders (complete atrioventricular block 7.20; 2.41–21.49) and acquired cardiac disorders, including cardiomyopathy (1.40; 1.17–1.68) and mucocutaneous lymph node syndrome (MCLS) (1.27; 1.15–1.43).
Conclusions: Maternal SLE is associated with congenital and acquired cardiac disorders in offspring, including structural, arrhythmic, and MCLS. This study highlights the need for continuous cardiovascular monitoring from the prenatal stage to preadolescence in these children due to multifactorial influences involving maternal autoantibodies, genetic predisposition, and environmental factors.

KEYWORDS

systematic lupus erythematosus, nationwide study, congenital heart disease, neonatal lupus erythematosus, mucocutaneous lymph node syndrome

1. Introduction

Systematic lupus erythematosus (SLE) is one of the most common autoimmune diseases that affect multi-system abnormalities (1). It predominantly affects women, with up to a 9-fold difference in incidence during reproductive ages (2). Previous studies demonstrated that SLE causes a variety of complications in mothers, such as pre-eclampsia, preterm birth, and fetal demise (3). Although fetal loss has been improved due to clinical protocols and prenatal monitoring, it is still an important issue in SLE, and health surveillance of the surviving infants should be maintained (4).

The passive transfer of anti-Ro/SSA autoantibodies from an SLE-affected mother to her offspring is known to increase several clinical conditions, such as neonatal lupus rash and hepatic and central nervous system involvement (5, 6). Canadian (7) and Chinese (8) studies have shown that offspring born from mothers with SLE were more likely to have adverse neonatal outcomes, such as neonatal intensive care unit admission, preterm birth, and patent ductus arteriosus (PDA). In particular, cardiac findings are notable, and the most serious complication is third-degree atrioventricular (AV) block, affecting approximately 2% of exposed pregnancies (9). Cutaneous and hematologic abnormalities are usually known to subside by 6–8 months of age with the resolution of maternal antibodies (10, 11). Conversely, it is known that neonatal SLE is related to various cardiovascular abnormalities, including arrhythmias, structural abnormalities, and cardiomyopathies (12). Given that these adverse conditions could result in permanent damage, the risk of cardiovascular abnormalities should be assessed (13).

Until now, previous studies regarding pregnancy-induced outcomes of SLE have been confined to maternal perspectives (14, 15) or addressed adverse outcomes in the neonatal period with a relatively small sample size of children (3, 7, 8). Thus, the cardiovascular outcomes of offspring born to mothers with SLE should be investigated. Herein, using nationwide health claims data from 2007 to 2017, we evaluated the association of maternal SLE with pediatric cardiovascular disorders, including congenital and acquired disorders.

2. Methods

2.1. Data source and study population

We obtained data on children born between 2007 and 2017 and followed their medical claims data until 2020 in the National Health Insurance Service (NHIS) database. In South Korea, more than 97% of the population are registered and covered by national medical insurance. The NHIS collects medical claims data and has made them available to use for research purposes since 2007. Diagnoses data are registered with the World Health Organization's International Classification of Diseases Tenth revision (ICD-10).

We extracted prenatal records by linking the data of the individuals (children) with the data of their respective mothers. For the extraction, we only linked mothers when a delivery record was registered in the NHIS database and the date of delivery was defined as the date of the birth. Maternal SLE was defined as an individual who visited an inpatient or outpatient clinic on more than one occasion and was assigned the ICD-10 code "M32" prior to delivery. We included 3,505,737 children registered in the NHIS database in the study. We excluded 138,549 individuals without baseline demographic information. Among the population, 23,330 children were born to mothers diagnosed with SLE. The study was approved by the Institutional Review Board of Hanyang University Guri Hospital (IRB No. GURI 2023-02-026). The requirement for informed consent was waived because public data from the NHIS were used (NHIS-2023-1-396). The reporting of this study conforms to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (online **Supplementary Table 1**).

2.2. Cardiologic manifestations and clinical variables

We categorized pediatric cardiologic disorders as congenital heart disease (CHD), arrhythmic disorders, and other acquired cardiologic disorders [e.g., cardiomyopathy (CMP) and mucocutaneous lymph node syndrome (MCLS)]. Moreover, we investigated neonatal lupus and death as outcomes. Each outcome was defined as more than two outpatient or inpatient visits with respective ICD-10 diagnostic codes.

As maternal characteristics, we selected cesarean section, intrauterine growth retardation (IUGR), pregnancy induced hypertension (PIH), gestational diabetes mellitus, chronic kidney disorders, and maternal CHD as variables of interests. Maternal CHD was defined as a mother who was assigned a diagnostic CHD code (Q2) during the observation period. Growing evidence suggests that genetic predisposition plays a crucial role in the pathogenesis of CHD; therefore, maternal CHD should be taken into account as a matching variable (16).

2.3. Statistical analysis

The demographic characteristics of the participants were calculated with weighted percentages and compared with the standardized mean difference (SMD). The propensity score was calculated using variables including birth year, sex, socioeconomic status, residence, preterm birth, and maternal CHDs. Additionally, differences in maternal characteristics and cardiac manifestations between two groups were compared using a chi-square test and featured with weighted percentages and a p value. Although SLE increasing the risk of preterm birth was previously known, we included preterm birth in the propensity score variables as it significantly increases the risk of CHD (15). The nearest available matching based on the estimated propensity score was performed with 1:4 ratios. Then, logistic regression analysis was used to estimate the odds ratio (OR) with a 95% confidence interval (CI) of CHD risk of children with maternal SLE. Statistical significance was determined using two-sided tests, with a p value of less than 0.05 considered significant. Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) and R version 4.2.1 (www.R-project.org).

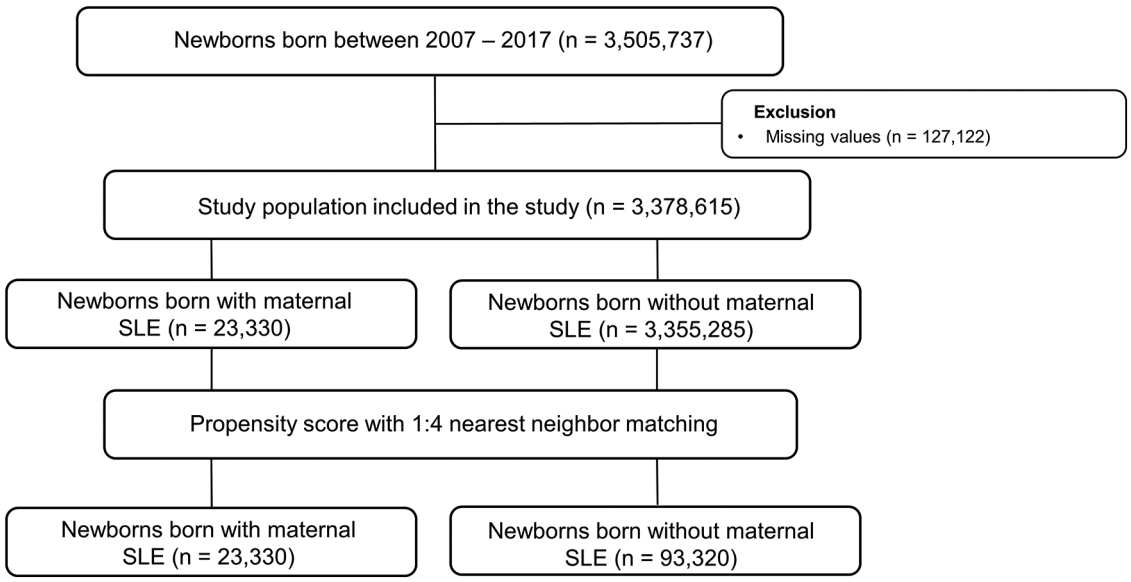


FIGURE 1
Selection flow of the population included in the analysis. SLE, systematic lupus erythematosus.

3. Results

We included 3,505,737 children registered in the national health insurance database in the study (Figure 1). We excluded 127,122 individuals without baseline demographic information. Among the population, 23,330 children were born from mothers diagnosed with SLE. The baseline demographic findings of the study population are shown in Table 1. Before matching, offspring born from mothers with SLE had a significantly higher incidence of preterm birth and maternal congenital heart disease (SMD > 0.1). After propensity score matching, the SMD between children with and without maternal SLE was lower than 0.1 in all variables, such as birth year, sex, socioeconomic status, residence, preterm birth, and maternal CHDs. The incidences of preterm birth and maternal CHD were 5.9% and 13.4%, respectively.

TABLE 1 Baseline characteristics of the pediatric population included in the study before and after propensity score matching.

	Children without maternal SLE (before matching) (*N* = 3,355,285)	Children without maternal SLE (after matching) (*N* = 93,320)	Children with maternal SLE (*N* = 23,330)	SMD (before matching)	SMD[c] (after matching)
Birth year				0.08	<0.001
2007–2010	816,412 (26.4)	24,776 (29.1)	6,194 (29.1)		
2011–2014	1,369,433 (44.3)	37,972 (44.5)	9,493 (44.5)		
2015–2017	906,788 (29.3)	22,504 (26.4)	5,626 (26.4)		
Sex				<0.01	<0.01
Boys	1,719,456 (51.2)	47,993 (51.4)	12,019 (51.5)		
Girls	1,635,829 (48.8)	45,327 (48.6)	11,311 (48.5)		
SES[a]				0.07	<0.001
Q1 (lowest)	356,999 (10.6)	9,551 (10.2)	2,387 (10.2)		
Q2	755,787 (22.5)	19,340 (20.7)	4,825 (20.7)		
Q3	1,349,712 (40.2)	36,857 (39.5)	9,225 (39.5)		
Q4 (highest)	892,787 (26.6)	27,572 (29.5)	6,893 (29.5)		
Residence[b]				0.14	<0.001
City	1,498,983 (44.7)	48,260 (51.7)	12,065 (51.7)		
Rural	1,856,302 (55.3)	45,060 (48.3)	11,265 (48.3)		
Preterm birth	101,472 (3.0)	5,544 (5.9)	1,386 (5.9)	0.14	<0.001
Maternal CHD	218,812 (6.5)	12,496 (13.4)	3,124 (13.4)	0.23	0.02

Data are expressed as numbers (weighted %).
SLE, systematic lupus erythematosus; SMD, standardized mean difference; SES, socioeconomic status; Q, quartile; CHD, congenital heart disease.
[a]Based on the amount of health insurance premiums. Income status was categorized into quartiles.
[b]City area was defined as Seoul and six major metropolitan cities (Busan, Incheon, Gwangju, Daegu, Daejeon, and Ulsan).
[c]Propensity score matching with birth year, sex, SES, residence, preterm birth, and maternal CHD.

TABLE 2 Prenatal and obstetric characteristics of the population included in the study.

	Children without maternal SLE (before matching) (*N* = 3,355,285)		Children without maternal SLE (after matching) (*N* = 93,320)		Children with maternal SLE (*N* = 23,330)		SMD (before matching)	SMD[a] (after matching)
	N	Weighted %	*N*	Weighted %	*N*	Weighted %		
Maternal characteristics								
Cesarean section	1,220,053	36.4	34,125	36.6	9,228	39.6	0.07	0.06
IUGR	107,949	3.2	3,362	3.6	1,088	4.7	0.07	0.05
PIH	49,271	1.5	1,802	1.9	749	3.2	0.12	0.08
Gestational diabetes mellitus	1,377,325	41.0	37,792	40.5	9,206	39.5	0.03	0.02
Chronic kidney disorders	12,793	0.4	1,802	1.9	557	2.4	0.17	0.16

Data are expressed as numbers (weighted %).
SLE, systematic lupus erythematosus; SMD, standardized mean difference; IUGR, intrauterine growth retardation; PIH, pregnancy induced hypertension.
[a]Propensity score matching with birth year, sex, SES, residence, preterm birth, and maternal CHD.

Table 2 summarizes the comparisons between maternal and cardiologic manifestations between two groups. For maternal characteristics, mothers with SLE had a higher incidence of cesarean section, IUGR, PIH, and chronic kidney disorders. However, these differences were not statistically significant.

For CHD, children of mothers with SLE had a significantly higher incidence of ventricular septal defect (VSD), atrial septal defect (ASD), PDA, and all CHDs. For arrhythmic disorders, 15 cases of AV block were identified in children of mothers with SLE, which was significantly higher than in the control group (six cases, $p < 0.05$). Additionally, the incidence of other arrhythmias was higher than in the control group (0.7% vs. 0.5%). However, the differences in the incidences of cardiac arrest, other block, atrial flutter, and tachyarrhythmia were not significant. The incidences of neonatal lupus and childhood mortality in the SLE mother group were 0.5% and 0.2%, respectively, which were higher than those in the control group. A description of the number of cases of CHD in children of mothers with SLE is summarized in Supplementary Table 2.

Children of mothers with SLE had a significantly higher risk of overall CHD (OR 1.23; 95% CI 1.15–1.31), as well as VSD, ASD, and PDA. Additionally, the risk of AV block was the highest [10.01 (3.88–25.79)], followed by other arrhythmias [1.37 (1.14–1.64)]. For acquired cardiac disorders, there was a higher risk of CMP [12.16 (8.34–17.73)] and MCLS [1.29 (1.17–1.43)]. Finally, the enhanced risk of neonatal lupus [12.16 (8.34–17.73)] and pediatric mortality [1.48 (1.17–1.87)] was also investigated (Figure 2).

4. Discussion

This nationwide study demonstrated that offspring born from mothers with SLE had a significantly higher risk of congenital

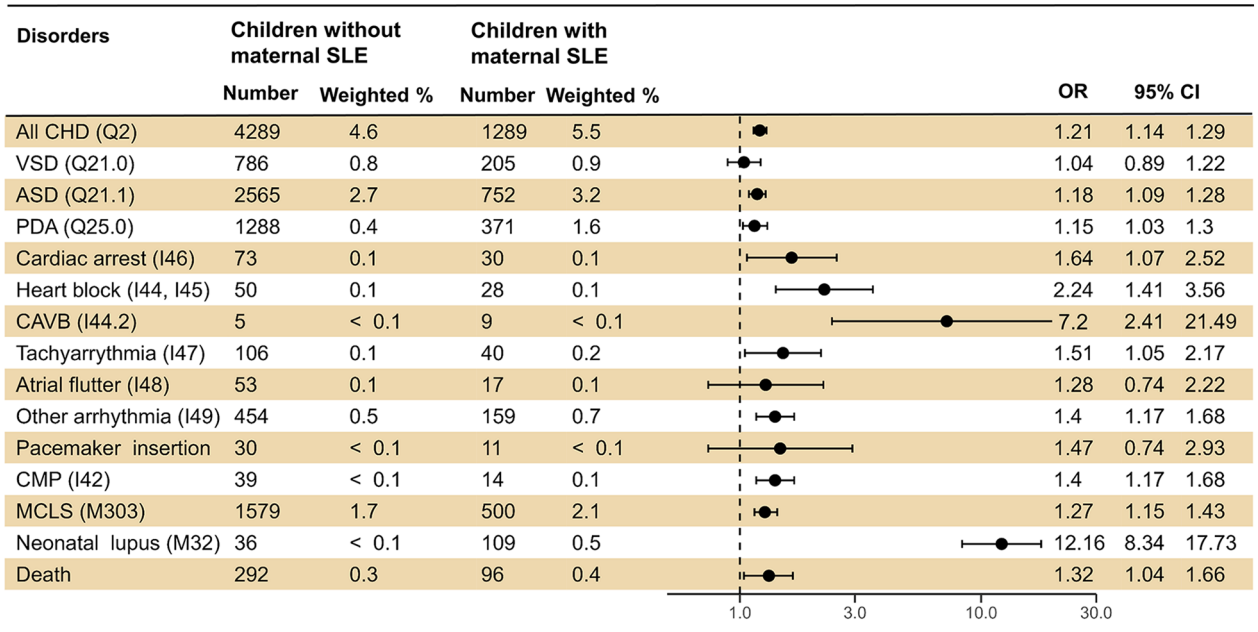


FIGURE 2
Logistic regression analysis presenting the risk of cardiovascular diseases in offspring born to mothers with SLE. SLE, systematic lupus erythematosus; OR, odds ratio; CI, confidence interval; CHD, congenital heart disease; VSD, ventricular septal defect; ASD, atrial septal defect; PDA, patent ductus arteriosus; AV, atrioventricular; CMP, cardiomyopathy; MCLS, mucocutaneous lymph node syndrome.

and acquired pediatric cardiologic disorders. In detail, maternal SLE was associated with congenital structural heart disorders. By contrast, the association with arrhythmic disorders was confined to AV block. Additionally, maternal SLE was associated with elevated risks of MCLS, CMP, and pediatric mortality.

To our knowledge, this is the first study to use nationwide data to assess the risk of cardiovascular disorders in offspring of mothers with SLE. It is already well-documented that SLE is strongly associated with pregnancy outcomes, and in our study, SLE was associated with the incidence of complications such as cesarean section, IUGR, PIH, and preterm birth. We did not include maternal comorbidities in the propensity score variables, except for maternal CHDs, as the association of these variables with pediatric cardiovascular disorder is unclear (17).

The incidence of overall CHD in offspring of SLE mothers was 5.5%, which was higher than previous reports (18, 19). There was an increased risk of preterm birth in the maternal SLE group, which can be interpreted as a key factor for the increased risk of CHD. However, according to our risk, the risk of CHD was still evident even after controlling for preterm birth. Further studies investigating whether SLE autoantibodies contribute to the pathogenesis of CHD should be undertaken. Rather, it could be the overdiagnosis bias, given that mothers with SLE are more likely to undergo a preemptive cardiologic work up during pregnancy. In addition, children born from mothers diagnosed with SLE may have been overdiagnosed with CHDs due to repeated echocardiograms, such as patent foramen ovale/ASD and PDA that can resolve spontaneously later in life.

Among arrhythmic disorders, we identified nine cases of third-degree AV block, with an estimated incidence of 1 per 5,000 live births, which was higher than in a previous study (20). The risk of third-degree AV block was 10-fold higher in the SLE mother group. Although we could not investigate the status of maternal autoantibodies due to methodological limitations, our results support the notion that the majority of pediatric third-degree AV block cases are due to maternal autoantibodies (21). We found that offspring born to mothers with SLE also have a prominent risk of first- and second-grade AV block. The initial manifestation of AV block could be either first or second degree, and those whose features usually spontaneously resolve within the first month of life (22, 23). This implies that the inflammatory reaction caused by maternal autoantibodies is mild and reversible (24). Neonatal lupus erythematosus is known to be closely associated with a variety of arrhythmic disorders (13). Our results showed that these adverse effects were limited to AV block, premature beat, ectopic beats, sinus arrhythmia, and long QT disorders.

Notably, we underline that the offspring born from SLE mothers had significantly higher risk of CMP and MCLS. According to previous studies, 15%–20% of affected children with third degree AV block could develop into more prominent myocardial disease, progressing to CMP (21, 25). Given that the incidence of CMP was higher than that of AV block, we assume that additional mechanism could underlie. The mechanism of cardiac damage resulting from maternal autoantibodies is still unclear, but the most known hypothesis is that maternal autoantibodies interfere with macrophage-mediated clearance of apoptotic cardiocytes by releasing pro-inflammatory cytokines and inducing inflammatory reactions, with subsequent cardiac inflammation and scarring (26–28). Nevertheless, we could not ascertain that maternal autoantibodies solely affected the pathogenesis of the CMP since pediatric CMP could result from many underlying cardiovascular conditions, not only maternal rheumatic disorders, but from coronary artery abnormalities, tachyarrhythmia, and secondary to underlying conditions (29).

There have been two studies with large sample sizes regarding the impact of maternal autoimmune disorders on MCLS, with conflicting results. Chu et al. (30) investigated 7,178 children and showed that SLE did not have an adverse effect on MCLS. However, when a broader range of autoimmune diseases, such as Sjogren's and rheumatoid arthritis, were included, maternal immune diseases were significantly associated. Meanwhile, a cohort study in Canada, with a follow-up for 12 years, stated that maternal rheumatic disorders had a 1.84-fold increase in MCLS in offspring; in particular, a higher risk was expected until 5 years of age (OR: 2.06, 95% CI: 1.77–2.41) (31). Unlike previous studies, we only included children who were born to mothers diagnosed with SLE, and considered maternal CHDs in the variables. It is known that transplacental autoantibodies disappear within the first 12 months. Thus, an inflammatory cascade known to be the pathogenesis of arrhythmic disorders would not explain the relationship with MCLS.

MCLS is a systemic vasculitis that affects small- and medium-sized arteries with elevated cytokine levels (32). Growing evidence suggests that immune complexes play a crucial role in the pathogenesis of MCLS (33). In addition, according to a genome-wide association study, autoimmune disease (e.g., SLE and rheumatoid arthritis) and MCLS share common candidate genes (e.g., BLK and CD40) (34). Although we could not verify the causality of the relationship, the genetic predisposition could affect the pathogenesis of MCLS, which would require clinical attention in febrile or infectious cases.

The strength of our study lies in the large sample size of nationwide health claims data, presenting pediatric cardiovascular diseases of offspring born to mothers with SLE. In contrast to previous studies that focused on the prenatal and neonatal health outcomes of childhood, we investigated overall pediatric cardiovascular disorders up until the pre-adolescent period. However, this study has several limitations due to methodological issues. First, we could not investigate the clinical information (e.g., maternal age, SLE flare, onset of maternal SLE, and duration of SLE) and laboratory findings (e.g., antibody status) of mothers. Such clinical symptoms and laboratory findings could not be obtained from our database, which is based on ICD-10 codes. The autoantibody profile is highly variable in SLE groups and could present different clinical manifestations of offspring (24). Approximately one half of pregnant SLE patients experience flare ups and should be considered a serious risk factor. Additionally, genetic predisposition to CHD was not identifiable due to the characteristics of our data. Further studies based on the nationwide data with genetic information should be carried out. Second, for children, we could not investigate the echocardiography and

echocardiogram findings for the diagnosis of cardiovascular disorders. Although we defined outcomes using diagnoses confirmed by pediatricians, the objective clinical findings would be helpful in assessing cardiovascular outcomes in children. Finally, as we obtained maternal data by linking ICD-10 codes regarding delivery, we could not identify abortion and stillbirth cases of mothers with SLE. To evaluate the CHD risk, results from fetal echocardiography should be investigated in further studies.

In conclusion, using nationwide registry health claims data, this study investigated the risk of pediatric cardiovascular disorders in offspring born to mothers with SLE. In addition to the significant risk of complete AV block, maternal SLE was significantly associated with overall CHD, CMP, acquired cardiovascular disorders, such as MCLS, and even mortality. We suspect these associations to be multifactorial etiology, with the combined effects of maternal autoantibodies, genetic predisposition, and environmental factors, which needs to be confirmed in further studies. We underline that offspring born to mothers with SLE should undergo regular surveillance of their cardiovascular systems from the prenatal period through to pre-adolescence.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The study was approved by the Institutional Review Board of Hanyang University Guri Hospital (IRB No. GURI 2023-02-026). The requirement for informed consent was waived because public data from the NHIS were used (NHIS-2023-1-396).

Author contributions

JC: Conceptualization, Data curation, Formal analysis, Methodology, Visualization, Writing – original draft. JH: Methodology, Writing – review & editing. YC: Data curation, Funding acquisition, Project administration, Visualization, Writing – review & editing. JN: Conceptualization, Funding acquisition, Methodology, Project administration, Writing – review & editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article.

This study was supported by Hanyang University (HY-202300000001146). The funding organization had no role in the design and conduct of the study.

Acknowledgments

This study used the National Health Insurance Service database (No. NHIS-2023-1-396). The interpretations and conclusions reported herein do not represent those of the National Health Insurance Service. The authors would like to thank Soorak Ryu, the Biostatistical Consulting and Research Lab, and the Medical Research Collaborating Center for their assistance with data analysis.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2023.1294823/full#supplementary-material

References

1. Yu KH, See LC, Kuo CF, Chou IJ, Chou MJ. Prevalence and incidence in patients with autoimmune rheumatic diseases: a nationwide population-based study in Taiwan. *Arthritis Care Res (Hoboken)*. (2013) 65:244–50. doi: 10.1002/acr.21820

2. Weckerle CE, Niewold TB. The unexplained female predominance of systemic lupus erythematosus: clues from genetic and cytokine studies. *Clin Rev Allergy Immunol*. (2011) 40:42–9. doi: 10.1007/s12016-009-8192-4

3. Bundhun PK, Soogund MZS, Huang F. Impact of systemic lupus erythematosus on maternal and fetal outcomes following pregnancy: a meta-analysis of studies published between years 2001–2016. *J Autoimmun*. (2017) 79:17–27. doi: 10.1016/j.jaut.2017.02.009

4. Clark CA, Spitzer KA, Laskin CA. Decrease in pregnancy loss rates in patients with systemic lupus erythematosus over a 40-year period. *J Rheumatol*. (2005) 32:1709–12.

5. Brucato A, Cimaz R, Caporali R, Ramoni V, Buyon J. Pregnancy outcomes in patients with autoimmune diseases and anti-ro/SSA antibodies. *Clin Rev Allergy Immunol*. (2011) 40:27–41. doi: 10.1007/s12016-009-8190-6

6. Izmirly PM, Saxena A, Kim MY, Wang D, Sahl SK, Llanos C, et al. Maternal and fetal factors associated with mortality and morbidity in a multi–racial/ethnic registry of anti-SSA/ro–associated cardiac neonatal lupus. *Circulation*. (2011) 124:1927–35. doi: 10.1161/CIRCULATIONAHA.111.033894

7. Nili F, McLeod L, O'Connell C, Sutton E, McMillan D. Maternal and neonatal outcomes in pregnancies complicated by systemic lupus erythematosus: a population-based study. *J Obstet Gynaecol Can*. (2013) 35:323–8. doi: 10.1016/S1701-2163(15)30959-2

8. Wu J, Ma J, Bao C, Di W, Zhang W-H. Pregnancy outcomes among Chinese women with and without systemic lupus erythematosus: a retrospective cohort study. *BMJ Open*. (2018) 8:e020909. doi: 10.1136/bmjopen-2017-020909

9. Lateef A, Petri M. Systemic lupus erythematosus and pregnancy. *Rheum Dis Clin*. (2017) 43:215–26. doi: 10.1016/j.rdc.2016.12.009

10. Prendiville JS, Cabral DA, Poskitt KJ, Au S, Sargent MA. Central nervous system involvement in neonatal lupus erythematosus. *Pediatr Dermatol*. (2003) 20:60–7. doi: 10.1046/j.1525-1470.2003.03014.x

11. Zuppa AA, Riccardi R, Frezza S, Gallini F, Luciano RMP, Alighieri G, et al. Neonatal lupus: follow-up in infants with anti-SSA/ro antibodies and review of the literature. *Autoimmun Rev*. (2017) 16:427–32. doi: 10.1016/j.autrev.2017.02.010

12. Vanoni F, Lava SA, Fossali EF, Cavalli R, Simonetti GD, Bianchetti MG, et al. Neonatal systemic lupus erythematosus syndrome: a comprehensive review. *Clin Rev Allergy Immunol*. (2017) 53:469–76. doi: 10.1007/s12016-017-8653-0

13. Hornberger L, Al Rajaa N. Spectrum of cardiac involvement in neonatal lupus. *Scand J Immunol*. (2010) 72:189–97. doi: 10.1111/j.1365-3083.2010.02437.x

14. Joo YB, Kim K-J, Park K-S, Park Y-J. Pregnancy rates and perinatal outcomes in women with systemic lupus erythematosus: data from the Korean national health claims database. *Clin Rheumatol*. (2021) 40:2243–50. doi: 10.1007/s10067-020-05496-4

15. Park J-S, Chung MK, Lim H, Lee J, Lee CH. Risk of pregnancy complications and low birth weight offsprings in Korean women with rheumatic diseases: a nationwide population-based study. *J Korean Med Sci*. (2022) 37(2):e18. doi: 10.3346/jkms.2022.37.e18

16. Zaidi S, Brueckner M. Genetics and genomics of congenital heart disease. *Circ Res*. (2017) 120:923–40. doi: 10.1161/CIRCRESAHA.116.309140

17. Leybovitz-Haleluya N, Wainstock T, Landau D, Sheiner E. Maternal gestational diabetes mellitus and the risk of subsequent pediatric cardiovascular diseases of the offspring: a population-based cohort study with up to 18 years of follow up. *Acta Diabetol*. (2018) 55:1037–42. doi: 10.1007/s00592-018-1176-1

18. Costedoat-Chalumeau N, Amoura Z, Lupoglazoff JM, Thi Huong DL, Denjoy I, Vauthier D, et al. Outcome of pregnancies in patients with anti-SSA/ro antibodies: a study of 165 pregnancies, with special focus on electrocardiographic variations in the children and comparison with a control group. *Arthritis Rheum*. (2004) 50:3187–94. doi: 10.1002/art.20554

19. Solomon DG. Birth order, gender and recurrence rate in autoantibody-associated congenital heart block: implications for pathogenesis and family counseling. *Lupus*. (2003) 12:646. doi: 10.1191/0961203303lu425xx

20. Cioffi GM, Gasperetti A, Tersalvi G, Schiavone M, Compagnucci P, Sozzi FB, et al. Etiology and device therapy in complete atrioventricular block in pediatric and young adult population: contemporary review and new perspectives. *J Cardiovasc Electrophysiol*. (2021) 32:3082–94. doi: 10.1111/jce.15255

21. Jaeggi ET, Hamilton RM, Silverman ED, Zamora SA, Hornberger LK. Outcome of children with fetal, neonatal or childhood diagnosis of isolated congenital atrioventricular block: a single institution's experience of 30 years. *J Am Coll Cardiol*. (2002) 39:130–7. doi: 10.1016/S0735-1097(01)01697-7

22. Bergman G, Wahren-Herlenius M, Sonesson SE. Diagnostic precision of Doppler flow echocardiography in fetuses at risk for atrioventricular block. *Ultrasound Obstet Gynecol*. (2010) 36:561–6. doi: 10.1002/uog.7532

23. Rein A, Mevorach D, Perles Z, Gavri S, Nadjari M, Nir A, et al. Early diagnosis and treatment of atrioventricular block in the fetus exposed to maternal anti-SSA/Ro-SSB/La antibodies: a prospective, observational, fetal kinetocardiogram–based study. *Circulation*. (2009) 119:1867–72. doi: 10.1161/CIRCULATIONAHA.108.773143

24. Salomonsson S, Dzikaite V, Zeffer E, Eliasson H, Ambrosi A, Bergman G, et al. A population-based investigation of the autoantibody profile in mothers of children with atrioventricular block. *Scand J Immunol*. (2011) 74:511–7. doi: 10.1111/j.1365-3083.2011.02610.x

25. Moak JP, Barron KS, Hougen TJ, Wiles HB, Balaji S, Sreeram N, et al. Congenital heart block: development of late-onset cardiomyopathy, a previously underappreciated sequela. *J Am Coll Cardiol*. (2001) 37:238–42. doi: 10.1016/S0735-1097(00)01048-2

26. Buyon JP, Clancy RM, Friedman DM. Cardiac manifestations of neonatal lupus erythematosus: guidelines to management, integrating clues from the bench and bedside. *Nat Rev Rheumatol*. (2009) 5:139–48. doi: 10.1038/ncprheum1018

27. Izmirly PM, Kim MY, Llanos C, Le PU, Guerra MM, Askanase AD, et al. Evaluation of the risk of anti-SSA/Ro-SSB/La antibody-associated cardiac manifestations of neonatal lupus in fetuses of mothers with systemic lupus erythematosus exposed to hydroxychloroquine. *Ann Rheum Dis*. (2010) 69:1827–30. doi: 10.1136/ard.2009.119263

28. Clancy RM, Alvarez D, Komissarova E, Barrat FJ, Swartz J, Buyon JP. Ro60-associated single-stranded RNA links inflammation with fetal cardiac fibrosis via ligation of TLRs: a novel pathway to autoimmune-associated heart block. *J Immunol*. (2010) 184:2148–55. doi: 10.4049/jimmunol.0902248

29. Lee TM, Hsu DT, Kantor P, Towbin JA, Ware SM, Colan SD, et al. Pediatric cardiomyopathies. *Circ Res*. (2017) 121:855–73. doi: 10.1161/CIRCRESAHA.116.309386

30. Chu H-W, Lin C-H, Lin M-C, Hsu Y-C. Increased risk of Kawasaki disease in infants born of mothers with immune disorders. *Front Pediatr*. (2021) 9:659598. doi: 10.3389/fped.2021.659598

31. Belkaibech S, Potter BJ, Kang H, Lee GE, Bilodeau-Bertrand M, Auger N. Maternal autoimmune disorders and risk of Kawasaki disease in offspring. *J Pediatr*. (2020) 222:240–243.e1. doi: 10.1016/j.jpeds.2020.02.016

32. Kawasaki T. Acute febrile mucocutaneous syndrome with lymphoid involvement with specific desquamation of the fingers and toes in children. *Arerugi*. (1967) 16:178–222.

33. Sakurai Y. Autoimmune aspects of Kawasaki disease. *J Investig Allergol Clin Immunol*. (2019) 29:251–61. doi: 10.18176/jiaci.0300

34. Onouchi Y. Identification of novel Kawasaki disease susceptibility genes by genome-wide association studies. *Kawasaki Dis*. (2017):23–9. doi: 10.1007/978-4-431-56039-5_4

frontiers | Frontiers in Cardiovascular Medicine

TYPE Review
PUBLISHED 04 January 2024
DOI 10.3389/fcvm.2023.1277041

OPEN ACCESS

EDITED BY
Shikai Yu,
Tongji University, China

REVIEWED BY
Stefan Kurath-Koller,
Medical University Graz, Austria
Rachele Adorisio,
Bambino Gesù Children's Hospital (IRCCS), Italy
Gabrielle Norrish,
Great Ormond Street Hospital Children's Charity, United Kingdom
Xiaohui Li,
Children's Hospital of Capital Institute of Pediatrics, China

*CORRESPONDENCE
Omar Baqal
✉ ojbaqal@gmail.com

†These authors have contributed equally to this work and share first authorship

RECEIVED 13 August 2023
ACCEPTED 14 December 2023
PUBLISHED 04 January 2024

CITATION
Shafqat A, Shaik A, Koritala S, Mushtaq A, Sabbah BN, Nahid Elshaer A and Baqal O (2024) Contemporary review on pediatric hypertrophic cardiomyopathy: insights into detection and management.
Front. Cardiovasc. Med. 10:1277041.
doi: 10.3389/fcvm.2023.1277041

Contemporary review on pediatric hypertrophic cardiomyopathy: insights into detection and management

Areez Shafqat[1†], Abdullah Shaik[1,2†], Snygdha Koritala[3], Ali Mushtaq[1,4], Belal Nedal Sabbah[1], Ahmed Nahid Elshaer[1,5] and Omar Baqal[1,6*]

[1]College of Medicine, Alfaisal University, Riyadh, Saudi Arabia, [2]Department of Internal Medicine, Ascension St. John Hospital, Detroit, MI, United States, [3]Dr. Pinnamaneni Siddhartha Institute of Medical Sciences & Research Foundation, Gannavaram, India, [4]Department of Internal Medicine, Cleveland Clinic Foundation, Cleveland, OH, United States, [5]Department of Internal Medicine, Creighton University School of Medicine, Omaha, NE, United States, [6]Department of Internal Medicine, Mayo Clinic, Phoenix, AZ, United States

Hypertrophic cardiomyopathy is the most common genetic cardiac disorder and is defined by the presence of left ventricular (LV) hypertrophy in the absence of a condition capable of producing such a magnitude of hypertrophy. Over the past decade, guidelines on the screening, diagnostic, and management protocols of pediatric primary (i.e., sarcomeric) HCM have undergone significant revisions. Important revisions include changes to the appropriate screening age, the role of cardiac MRI (CMR) in HCM diagnosis, and the introduction of individualized pediatric SCD risk assessment models like HCM Risk-kids and PRIMaCY. This review explores open uncertainties in pediatric HCM that merit further attention, such as the divergent American and European recommendations on CMR use in HCM screening and diagnosis, the need for incorporating key genetic and imaging parameters into HCM-Risk Kids and PRIMaCY, the best method of quantifying myocardial fibrosis and its prognostic utility in SCD prediction for pediatric HCM, devising appropriate genotype- and phenotype-based exercise recommendations, and use of heart failure medications that can reverse cardiac remodeling in pediatric HCM.

KEYWORDS

hypertrophic cardiomyopathy, cardiac MRI, sudden cardiac death, myocardial fibrosis, exercise, late gadolinium enhanced (LGE)

1 Introduction

Hypertrophic cardiomyopathy (HCM) is the most common genetic heart disease, with a prevalence of 0.2% and an incidence of approximately 1 per 500 adults (1). These figures are likely underestimated due to the large number of asymptomatic cases; the actual prevalence of the disease is much higher when genetic testing and contemporary imaging techniques are applied (1). The pathogenesis of adult HCM is linked to autosomal dominant mutations in various genes that encode sarcomeric proteins, most frequently beta myosin heavy chain 7 (MHY7) and myosin-binding protein C3 (MYBPC3) (2). The clinical course of HCM is highly variable, ranging from asymptomatic to life-threatening complications such as sudden cardiac death (SCD), left

ventricular outflow tract obstruction (LVOTO), heart failure with reduced ejection fraction (HFrEF), and atrial fibrillation with associated embolic events (3).

Compared to adults, pediatric HCM is an evolving field due to relatively limited data on epidemiology, etiologies, screening, diagnostic protocols, and management strategies. Epidemiological data from the United States indicate that HCM is substantially less common in children than adults, with an estimated prevalence of 1.2/1,000,000 and an annual incidence rate of 1.3/100,000 (4–6). Furthermore, the penetrance of child relatives of HCM patients is low during childhood and adolescence (7).

Pediatric HCM can be classified based on etiology into primary and secondary (8). Primary HCM can be due to sarcomeric mutations or can be idiopathic, which may be due to currently unidentified sarcomeric mutations or non-sarcomeric variants (9). Primary HCM is sometimes called familial HCM because of its typical autosomal dominant pattern of inheritance. The clinical outcomes of familial HCM due to sarcomeric mutations or idiopathic HCM are very similar, hence the two are often grouped as primary familial HCM (8). Primary HCM is typically asymptomatic through the first years of life, appearing during late childhood or adolescence, and exhibits an annual mortality rate of ~1%, which is not significantly different from adult HCM. On the other hand, secondary HCM due to glycogen storage diseases, lysosomal storage diseases, syndromic cases, fatty acid oxidation disorders, and endocrine disorders like acromegaly typically manifests during infancy and is associated with a high mortality rate (10–12).

This review focuses on primary familial HCM, either with an identified pathogenic/likely pathogenic (P/LP) sarcomeric genetic variant or idiopathic. We survey the existing literature on the screening and diagnostic approaches for childhood-onset HCM and SCD risk assessment in such cases and highlight open questions in these areas.

2 HCM diagnosis and risk assessment

2.1 Cardiac MRI in HCM diagnosis

The diagnostic criterion for HCM in children is different than in adults. Left ventricular (LV) thickness children is adjusted for body size and growth, with a thickness >2 standard deviations (SD) above the mean after adjustment considered diagnostic for HCM (13–15), Some flexibility can be employed in the SD criterion when there is a high pretest probability of HCM like a strong family history or a positive cascade genetic test (16). Transthoracic echocardiography (TTE) is the primary imaging modality for diagnosing HCM but has limitations like poor acoustic windows and an overestimation of wall thickness on oblique sections (17–24).

Cardiac MRI (CMR) better distinguishes between the epicardial and endocardial layers to offer detailed information about LV systolic and diastolic function, LVOTO severity, atrial enlargement, and mitral regurgitation (17). CMR is also effective in detecting LV aneurysms, mural thrombi, and papillary muscle abnormalities in patients with sarcomeric HCM (13, 16). Existing data in adults with suspected HCM have showed that CMR leads to a clear HCM diagnosis in 44.7% of patients, indicated an alternative diagnosis in 5.3% of patients, and demonstrated no significant hypertrophy was found in 20.4% of patients, thereby refuting TTE findings (25). It will be important to determine whether these findings translate to pediatric HCM patients. Nevertheless, recommendations on when CMR is indicated for diagnosis vary. The 2014 and 2023 ESC guidelines recommend conducting CMR all HCM patients at initial evaluation to establish a baseline (13, 15), while the 2020 AHA/ACC recommends reserving CMR for cases where TTE findings are inconclusive (16). The 2023 ESC guidelines recommend considering CMR every 2–5 years to monitor disease progression on a case-by-case basis (class IIa recommendation) (15).

Given that phenotypic manifestations of HCM in children are more subtle than in adults, the question arises whether all children with suspected or diagnosed HCM should undergo CMR, as many of the aforementioned manifestations may be missed by TTE. Hence, studies evaluating the diagnostic yield and prognostic value of CMR, especially when TTE is negative or inconclusive, are needed in pediatric HCM patients. CMR can visualize subtle morphological changes in HCM genotype-positive individuals who do not have LV hypertrophy, a situation that often arises in children. These changes include narrow blood-filled myocardial crypts (i.e., deep, blood-filled invaginations within the LV myocardium), elongated mitral leaflets, and expanded extracellular space (23, 26–28). Lorenzini et al. showed that 32% of sarcomeric mutation carriers (median age 14.2 years) who were HCM phenotype-negative at first evaluation on TTE fulfilled diagnostic criteria of HCM on CMR (29). Furthermore, younger age at HCM diagnosis and sarcomeric mutations are predictive of long-term adverse outcomes including heart failure, atrial fibrillation, and ventricular arrhythmias (30). These findings strongly support the ESC guidelines that CMR be conducted in all genotype-positive children (15). However, there is currently insufficient evidence on the benefit of CMR in aiding the diagnosis of familial HCM without a genetic diagnosis (class IIb recommendation) (15).

Different HCM genotypes can differentially affect cardiac anatomy and physiology, manifesting as different degrees of myocardial perfusion alterations, fibrosis, and diastolic dysfunction. Increasing consideration of these changes as part of the HCM spectrum may result in a broadening of what defines HCM beyond simply LV hypertrophy (9). We posit that CMR would become key in this context by providing a more comprehensive description of the cardiac anatomy (Figure 1). CMR itself is a tool to explore the genotype-phenotype association, exemplified by the use of different CMR techniques to associate differet genotypes (e.g., sarcomeric vs. non-sarcomeric) with divergent findings on myocardial oxygenation (31). The translational potential of genotype-phenotype studies is illustrated by the results of the randomized, double-blinded, placebo-controlled trial showing that mavacampten—a first-in-class drug targeting cardiac myosin ATPase tailored to the pathophysiology of sarcomeric HCM—significantly improved exercise capacity, LVOTO, NYHA functional class, and health status in patients with hypertrophic obstructive cardiomyopathy (HOCM) (32).

FIGURE 1
Proposed future directions in the field of pediatric HCM.

2.2 Sudden cardiac death risk assessment

Risk factors for SCD vary between adults and pediatrics, which are reflected in different recommendations on SCD risk assessment in both groups. Approaches for SCD risk assessment in adults include the six-parameter risk score recommended by the 2011 AHA/ACC guidelines, the HCM Risk-SCD score recommended by the 2014 and 2023 ESC guidelines, and the enhanced 2020 AHA/ACC SCD risk assessment approach (14, 33, 34). For children, the 2020 AHA/ACC guidelines recommend ICD placement with HCM children who have ≥1 major risk factor for SCD, including a family history of SCD, massive LVH ≥30 mm in any LV segment, syncope, LV apical aneurysm, and LV systolic dysfunction. However, these risk factors were largely derived from studies conducted on adult patients (16). The phenotypic characteristics of HCM in children differ from those in adults (see above), hence the applicability of adult risk factors in pediatric cases may be limited (35–37). The need for devising SCD assessment approaches tailored to pediatric HCM is underscored by the higher risk of SCD in children (0.8%–2%) than in adults (<0.8%) (38, 39). Furthermore, children are ∼36% more likely to experience arrhythmic events compared to adults (38, 39). Children ICD recipients face a lifetime of device-related complications, including lead fracture/failure, infective endocarditis, or the need for lead repositioning, for which there are currently no preventative approaches (39).

Unique risk factors for SCD in the pediatric population include LV posterior wall diameter, left atrial diameter, and LVOTO, which are not risk factors for SCD in adult HCM (40). Conversely, family history of SCD and abnormal blood pressure response to exercise are not significant risk factors for SCD in HCM children (41). The evidence behind age as a risk factor for SCD in children is weak, hence it is not incorporated in current risk prediction models (discussed below) (42). A meta-analysis by Norrish et al. reported that SCD risk factors with sufficient evidence for use in pediatric HCM patients include previous ventricular tachycardia/ventricular fibrillation, unexplained syncope, non-sustained ventricular tachycardia, and extreme LVH (37). Subsequent studies identified left ventricular posterior wall diameter, left ventricular outflow tract gradient, and, myocardial fibrosis as additional risk factors (40, 43). Furthermore, although the meta-analysis by Norrish et al. did not find an abnormal blood pressure response to exercise to be a significant predictor of SCD (37), a recent study evaluating a cohort of 630 primary HCM pediatric HCM patients <18 years demonstrated that abnormal exercise stress test results were present in ∼28% of patients, with exercise stress test-induced ischemia being independently associated with lower SCD-free survival (HR, 3.32; 95% CI, 1.27–8.70) (44). It is important to note that the meta-analysis by Norrish et al. was based on a limited number of studies which were limited in terms of their patient selection, sample size, and follow-up times. Therefore, our understanding of the risk factors for SCD in pediatric HCM patients continues to evolve through robustly designed multi-center studies.

Two models exist that enable individualized SCD risk assessment in pediatric HCM (Table 1). Norrish et al. developed a risk prediction model for SCD in children called HCM Risk-Kids. This model achieved a c-statistic—which is a measure of the discriminative ability of a risk prediction model—of 0.69, with 1 patient being saved for every 10 ICD implantations in patients with a ≥6% 5-year risk of SCD (35). HCM Risk-Kids has been externally validated on a cohort of 421 HCM patients aged 1–16, with the 5-year SCD risk cut-off of ≥6% identifying 73.9% of SCD events with a c-statistic of 0.70 (45). Miron et al. developed another individualized SCD prediction model, PRIMaCY, which achieved a c-statistic of ∼70% in predicting 5-year SCD risk (40). No study has directly compared the performance of HCM-Risk kids and PRIMaCY in predicting the risk of SCD. These models were recently incorporated into the 2023 ESC cardiomyopathy guidelines, which recommended the use of either of these two models for HCM patients <16 years old (15).

Although these models have transformed pediatric HCM clinical practice, some notable limitations must be contended with (46). Most glaringly, important predictors of future adverse outcomes like electrocardiography parameters, CMR-based features, measures of myocardial fibrosis, and genetic factors like the presence of sarcomeric mutations have not been included (Figure 1). The importance of myocardial fibrosis and genetic factors is discussed below. Another critique raised by Maron et al. is concern over the derivation of HCM Risk-Kids from the HCM Risk-SCD score, which the authors found to lack sensitivity (47). However, the HCM Risk-SCD score has been externally validated in other multi-institutional studies and meta-analyses (48, 49). Although it is no longer the case that pediatric risk factors for SCD need to be derived from adult studies, the criteria by which variables were selected for the HCM Risk-Kids model was that they needed to be examined in at least two or

TABLE 1 Comparison of the individualized SCI prediction models for pediatric HCM.

Characteristics	HCM-risk kids	PRIMaCY
Age range for use	≥1 years and ≤16 years	≤18 years
Predictor variables used **(Differences bolded)**	1. Unexplained syncope. 2. **Maximal left-ventricular wall thickness.** 3. Left atrial diameter. 4. Left ventricular outflow tract gradient. 5. Non-sustained ventricular tachycardia	1. **Age at diagnosis.** 2. **Interventricular septal thickness.** 3. **Left ventricular posterior wall thickness.** 4. Left atrial diameter. 5. Left-ventricular outflow tract gradient. 6. Non-sustained ventricular tachycardia 7. Unexplained syncope
Internal validation c-statistic	0.69 (95% CI = 0.66–0.72	0.75 (CI not provided)
External validation c-statistic	0.714 (95% 0.58–0.85)	0.71 (CI not provided)
Model website	https://hcmriskkids.org/	https://primacycalculator.com/
Future directions	• Incorporate CMR-based assessments of cardiac structure and function • Incorporate measures of myocardial fibrosis • Evaluate if incorporating EKG findings improve SCD prediction by these models • Update models according to future data on adverse outcome risk based on genetic basis of HCM	

more studies employing univariate or multivariate analyses. Employing only predictors established in multivariate analyses, although more robust, was not possible because of the limited data on pediatric HCM.

These findings highlight the transformative impact of individualized pediatric SCD assessment models but also raise suggestions on how to improve them. Future studies expanding our knowledge of the genotype-phenotype association in HCM may reveal important caveats about the genetic basis of SCD risk that need to be reflected in these models.

2.3 Myocardial fibrosis in SCD risk assessment

Myocardial fibrosis can be an indicator of myocardial ischemia, LV diastolic dysfunction, and future risk of atrial fibrillation and SCD (50). Late-gadolinium enhancement (LGE) is the most widely used tool to quantitatively measure myocardial fibrosis. Studies have demonstrated that LGE improves the stratification of adult HCM patients at low-to-intermediate risk of SCD when added to the 2011 AHA/ACC algorithm and HCM-Risk SCD (16, 51, 52). Consequently, the enhanced AHA/ACC SCD risk assessment approach incorporates LGE and LV apical aneurysm detected by CMR to the 2011 AHA/ACC six-parameter prediction score and is currently the most sensitive SCD risk assessment method for adult HCM patients (~95%) (16, 34). Integrating artificial intelligence (AI) into CMR-LGE, a multi-center study on 1,229 HCM patients (mean age 52 years) showed that radiomic features—i.e., using computational algorithms to extract quantitative features from medical images—of myocardial scars on LGE-CMR added incremental prognostic value to HCM Risk-SCD and AHA/ACC SCD risk assessment protocols for adults (53). The 2023 ESC guidelines maintained the recommendation of utilizing HCM Risk-SCD as the first-line tool in SCD risk assessment in adult HCM patients, but state that the presence of extensive LGE (≥15%) in patients classified as low-risk can inform decision-making on prophylactic ICD implantation (15).

HCM Risk-Kids and PRIMaCY are yet to incorporate LGE into their risk prediction (26, 33, 34, 54). Low levels of myocardial fibrosis with LGE (>2% of LV mass) are common in children with HCM and the introduction of LGE significantly improves the predictive accuracy of the HCM Risk-Kids prediction model (55, 56). A recent study on a cohort of 166 pediatric HCM patients with a mean age of 10.4 years demonstrated the prognostic value of LGE in determining major cardiac events (i.e., sustained VT, resuscitated cardiac arrest, SCD, end-stage heart failure, heart transplant, and appropriate ICD intervention) (57). This study showed that the optimal cutoff LGE extent for predicting events was ≥2% (57). The predictive accuracy—evaluated by the median time-dependent area under the curve (AUC)—of LGE extent (0.88, 95% CI 0.86–0.89) significantly outperformed that of syncope (0.63, 95% CI 0.61–0.66, $p < 0.0001$) and nonsustained ventricular tachycardia (0.52, 95% CI 0.50–0.53, $p < 0.0001$), both of which have been included in the individualized pediatric SCD predictive models (57). Although this study utilized a composite primary endpoint not composed of just SCD or its equivalent event (i.e., sustained VT, resuscitated cardiac arrest, or appropriate ICD intervention) but also end-stage heart failure and heart transplantation, these results advocate for the introduction of LGE in the SCD risk assessment for pediatric HCM (Figure 1).

The influence of genetic background such as the presence of sarcomeric mutations on the decision to perform LGE is an area of active interest. LGE may be less prevalent in pediatric HCM (46%) compared to adults (~60%), particularly in sarcomeric mutation carriers without overt left ventricular hypertrophy (58). However, some pediatric patients demonstrate progression of LGE extent over time, although age at diagnosis or time elapsed since diagnosis was not predictive of LGE increase, indicating a potential genetic basis for the progression of myocardial fibrosis in HCM (58). These results highlight the need for further

exploration of genotype-phenotype associations with respect to myocardial fibrosis development and progression, which may enhance the decision-making process of when to opt for LGE based on patient genotype.

There is no universally accepted/agreed-upon method of quantifying myocardial fibrosis. LGE may not be the most sensitive method for detecting fibrosis. Alternative approaches like T1 mapping or calculation of extracellular volume (ECV) fraction may be more sensitive for assessing diffuse interstitial fibrosis (59). For example, left atrial enlargement and diastolic dysfunction can be present in childhood-onset HCM without LVH, which may be due to diffuse interstitial fibrosis that is undetectable by LGE (58, 60). In adult HCM patients, T1 mapping and ECV fraction measurements have been associated with major cardiac events like SCD in patients without LGE, even in those determined low-risk by the enhanced AHA/ACC strategy and HCM Risk-SCD (61, 62). Studies exploring what the added prognostic value of T1 mapping over LGE is in predicting SCD risk and other adverse cardiac events in pediatric primary HCM are needed (Figure 1). These alternate approaches may also constitute avenues to explore the genotype-phenotype association of HCM, as one study applied radiomics analysis to T1 mapping to study the genotype-phenotype associations of sarcomeric (MYH8 and MYPBC3) HCM patients with respect to myocardial fibrosis (63).

3 Appropriate screening age for children

Genetic evaluation of relatives of HCM patients requires a systematic approach including a comprehensive family history to assess for early-onset HCM and family history of SCD, a comprehensive phenotypic (i.e., clinical) and genetic evaluation of the proband to confirm phenotype-positivity and guide cascade genetic testing, referral for genetic counseling, and genotype- and phenotype-directed guidance on potential therapies like ICD, medications, and lifestyle modifications (64).

The 2011 AHA/ACC guidelines recommended screening first-degree child relatives with a positive HCM family history at the age of 12 years, with earlier screening recommended in children with a family history of SCD, participation in intense physical activities, and an early growth spurt (14). The 2014 ESC guidelines recommended initiating screening in first-degree child relatives with an unknown genetic history after the age of 10 years with screening intervals of 1–2 years between the ages of 10–20 and every 2–5 years thereafter (13).

Studies in the years following these guidelines challenged the notion that sarcomeric mutations and clinically significant adverse events in children with familial HCM are rare. Approximately 43%–63% of pediatric HCM cases are associated with sarcomeric mutations, and sarcomeric childhood-onset HCM is linked increased risk of heart failure and a composite clinical outcome of life-threatening ventricular arrhythmias, atrial fibrillation, stroke, and death (38, 65, 66). Childhood-onset HCM also exhibits a steeper increase in LV wall thickness and higher median event rate than adults, associated with a greater likelihood of developing life-threatening ventricular arrhythmias and interventions such as heart transplantation or ventricular assist device implantation (38, 67). Furthermore, a significant proportion of HCM phenotype-positive children and those with major adverse cardiac events were below the recommended screening age of 10 years, with around 69% of these children meeting the 2011 AHA/ACC and 2014 ESC criteria for early screening (67, 68).

Considering these findings, the updated 2020 AHA/ACC guidelines recommended clinical and/or genetic screening first-degree children relatives of genotype-positive patients irrespective of age. All children and adolescents with a family history of early-onset HCM are also advised to undergo screening regardless of age (16). Echoing the trend of basing screening decisions off proband genetic testing results rather than a cut-off age, the 2023 ESC cardiomyopathy guidelines recommended that if a P/LP genetic variant is identified, cascade genetic testing should be performed in first-degree relatives irrespective of age. Genotype-positive relatives should undergo clinical evaluation by EKG, multimodality imaging (echocardiography and CMR), and long-term follow-up, while relatives without the disease-causing variant are discharged from further follow-up but counseled to seek re-assessment if they develop symptoms (15). The value of genetic testing at a young age is further indicated by a study showing that a younger age at HCM diagnosis and sarcomeric mutations are predictive of long-term adverse outcomes including heart failure, atrial fibrillation, and ventricular arrhythmias (30). In favor of discharging genotype-negative patients, Nielsen et al. showed that first-degree relatives of an index HCM patient with no P/LP variant have a low frequency of diagnosis at initial evaluation and risk of developing the condition during 5 years of follow-up, and, if diagnosed, are at low risk of SCD (69). On the other hand, even sarcomeric variants of undetermined significance (VUS) have been shown to correlate with adverse outcomes (30), hence child relatives of the index VUS HCM patient should be offered serial clinical evaluations because of age-related penetrance (15). Finally, if no P/LP variant is identified in the proband or if genetic testing is not performed, then clinical evaluation with EKG and multi-modality imaging should be performed in first-degree relatives (class I recommendation) (15).

A puzzling HCM patient population that requires further improvement in their management is genotype-positive phenotype-negative patients. More precision is needed when ascertaining their risk of phenotypic conversion, which is affected by the specific underlying genetic mutation and possibly by gender. A retrospective study following 285 phenotype-negative sarcomeric mutation carriers demonstrated that 46% of individuals develop HCM over 15 years of follow-up (29). Male sex and an abnormal EKG were independently associated with higher penetrance. Furthermore, the *TNNI3* sarcomeric protein variants had the lowest penetrance (29). Hence, future updates must account for individual differences in risk of phenotypic conversion, perhaps reflected as a stronger emphasis on the use of CMR and myocardial fibrosis assessment in high-risk groups (Figure 1).

Early genetic screening of children is not without its challenges (Table 2). It may not be feasible to screen every first-degree child relative of the index HCM patient. Many families also choose not to undergo genetic testing, limiting the identification of P/LP

TABLE 2 Potential benefits and harms of early screening for HCM in children.

Benefits	Harms
Decrease in uncertainty regarding HCM status	Increased anxiety about the child's future
Anticipating future care enhances patient management through informed decision-making	Alteration of one's self-image and stigma associated with cardiovascular disease
Early detection and management with possible improved prognosis	Lack of confidence around exercise/ physical activity can negatively impact quality of life
Overall reduced healthcare costs by reducing the need for advanced, lifelong therapies for complications	Increased insurance costs and accessibility limitations

variants and cascade genetic testing in relatives (70). Clinical and imaging evaluation of children should take place in these circumstances. The financial and psychological cost of universal screening need also be considered, especially because significant LV hypertrophy and adverse events like SCD—although more common than previously thought—are still exceedingly rare before 10 years of age (70). The psychological aspects of an HCM diagnosis are increasingly recognized, such as anxiety among the child and especially parents, a difficult transition to higher levels of education and from pediatric to adult care, and the social stigma associated with cardiovascular disease and its consequences on confidence and anxiety, especially around exercise. Support from a trained professional like a clinical psychologist has been shown to significantly mitigate quality of life impairment in children who receive an HCM diagnosis (71, 72). On the other hand, genetic and clinical screening to identify potentially affected child relatives of the affected HCM individual does not seem to impair quality of life (72). Lastly, universal early screening could promote the potentially unnecessary prescription of medical treatment, lifestyle changes particularly surrounding exercise, and prophylactic implantation of ICDs. A paradigm shift towards individualized risk assessment and shared decision-making is emphasized because indiscriminate screening in an era where judicious resource allocation is crucial does not seem feasible.

To address many of these challenges, we need to understand the link between specific genotypic variants, phenotypic HCM manifestations, and associated risks of adverse events (9). Genetic studies on the penetrance of different P/LP variants, most of which are currently unknown (15), are required to inform screening decisions (Figure 1). Further research may expand the definition of HCM beyond LV hypertrophy since different genotypes can differentially affect various aspects of cardiac structure and function and thus may be detected differently during screening (9).

4 Management of pediatric HCM

4.1 Exercise recommendations

HCM was originally described in the context of SCD and was popularized as the most common cause of SCD in professional athletes (73). Also, exercise can theoretically trigger hypertrophy of the myocardium, which may exacerbate LVOTO. Consequently, management strategies have historically strictly advised against any form of exercise other than low-intensity training, stemming from the fear of triggering a ventricular arrhythmia and SCD (13, 14). Subsequent studies began to highlight the negative psychological and long-term medical outcomes HCM patients may be predisposed to because of this restriction on their lives. Furthermore, a substantive percentage of HCM patients nowadays are largely asymptomatic and exhibit a normal life expectancy. It thus becomes important to explore more deeply the types of physical activity that HCM patients can carry out, especially during childhood and adolescence given its enormous benefits on physical and social development in this phase.

Recent studies have begun to show that exercise training during childhood and adolescence is associated with favorable indices of diastolic function independent of LVH (74). This is consistent with data on adult HCM patients, where a sedentary lifestyle is associated with obesity and adverse cardiovascular outcomes on the one hand and exercise is correlated with improved exercise capacity and cardiovascular and quality-of-life outcomes on the other (75–83). Recent studies also indicate that even vigorous exercise in genotype-positive HCM patients across most age groups including children and adolescents does not increase the risk of a primary endpoint of death, resuscitated SCD, arrhythmic syncope, and appropriate shock from an ICD (76). Furthermore, endurance exercise in athletes with HCM is associated with an enlarged LV cavity size and amelioration of outflow obstruction (84). Consequently, the recent North American and European guidelines adopt somewhat of a more liberal approach and encourage low-to-moderate intensity for all HCM genotype-positive individuals, even those exhibiting the phenotype (15, 16). Competitive and high-intensity sport is still approached with caution and is allowed for phenotype-negative and low-risk pediatric and adult phenotype-positive individuals after extensive initial assessment and re-assessments to check for phenotypic progression (15). For future studies, in line with the emphasis on genotype-phenotype associations and tailored management strategies, it will be important to distinguish exercise recommendations for different genotypes and for pediatric patients in different risk categories of the individualized SCD risk models.

4.2 Medications

Therapy for heart failure does not distinguish between specific etiologies and can be grouped into medical therapy, resynchronization therapy, ventricle assist devices, and transplantation. Different medications indicated for the treatment of HFrEF include angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARBs), angiotensin receptor neprilysin inhibitors (ARNI), beta blockers, mineralocorticoid receptor antagonists, and sodium-glucose cotransporter-2 (SGLT2) inhibitors (85, 86). These medications are also indicated in end-stage HCM with LV systolic dysfunction (86).

The role of these medications in early-stage HCM, which often is the case in pediatric patients, is not well understood. The multicenter,

randomized, double blind, placebo controlled, phase 2 VANISH clinical trial of 178 participants including both adults and children with early-stage HCM showed that valsartan treatment for 2 years improved cardiac structure and function, indicated by an integrated *z*-score of LV wall thickness, mass, and volume, left atrial volume, doppler systolic and diastolic velocities, and serum levels of hs-troponin T and pro-BNP (87). In contrast, the INHERIT clinical trial did not show a statistically significant benefit to losartan use in decreasing LV mass in middle-aged patients with overt HCM compared to placebo (88). The INHERIT trial utilized CMR and cardiac CT to measure the primary outcome of LV mass, while secondary outcomes included LV fibrosis, maximum LV wall thickness, left atrial volume, and plasma levels of NT-pro-BNP. Therefore, different outcome measurements may have contributed to the conflicting results of the VANISH and INHERIT studies. However, a recent analysis showed that utilizing the VANISH composite *z*-score in the INHERIT cohort still did not result in a statistical benefit to losartan use (89).

It is plausible that ACEi/ARB may be beneficial in reversing cardiac remodeling in early-phase disease but this effect is lost upon progression to overt HCM (90). However, the recent multicenter, double-blind, placebo-controlled VANISH randomized clinical trial of 34 sarcomeric HCM patients (mean age of 16 years) showed no statistical benefit to valsartan use in patients with early subclinical HCM with no LVH using the aforementioned integrated *z*-score approach (91). However, this study was underpowered to detect a statistically significant benefit due to a small sample size, short follow-up duration (~2 years), and slow phenotypic progression in both the valsartan and placebo group. Larger scale studies with longer follow-up durations are required to conclusively assess the clinical benefit of valsartan on cardiac remodeling in early phase HCM. It will also be important to determine if the underlying genotype influences treatment response in the early phase.

5 Conclusions

Tremendous advancements have been made in the screening protocols, timely diagnosis, and management of pediatric HCM, a historically understudied field. The recent ESC cardiomyopathy guideline update embraced the individualized pediatric SCD prediction models, but the incorporation of key imaging and genetic parameters into these models is awaited. Other important knowledge gaps notably include gaining a better understanding of the genotype-phenotype association, the best technique to detect myocardial fibrosis, and defining the potential role of AI as clinical decision support systems in screening and as algorithms like LGE-CMR radiomics approaches. Addressing these challenges will undoubtedly contribute to improving the care of these patients and thereby alleviate a significant healthcare burden in terms of morbidity, mortality, and health expenditures.

Author contributions

AS: Conceptualization, Writing – original draft, Writing – review & editing. AbS: Conceptualization, Writing – original draft, Writing –review & editing. SK: Conceptualization, Writing – original draft. AM: Writing – review & editing. ANE: Writing – review & editing. BS: Writing – original draft. OB: Conceptualization, Supervision, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Semsarian C, Ingles J, Maron MS, Maron BJ. New perspectives on the prevalence of hypertrophic cardiomyopathy. *J Am Coll Cardiol.* (2015) 65(12):1249–54. doi: 10.1016/j.jacc.2015.01.019

2. Ingles J, Burns C, Bagnall RD, Lam L, Yeates L, Sarina T, et al. Nonfamilial hypertrophic cardiomyopathy: prevalence, natural history, and clinical implications. *Circ Cardiovasc Genet.* (2017) 10(2):e001620. doi: 10.1161/CIRCGENETICS.116.001620

3. Clinical course and management of hypertrophic cardiomyopathy. *N Engl J Med.* (2018) 379(20):1976–7. doi: 10.1056/NEJMc1812159

4. Ommen SR, Semsarian C. Hypertrophic cardiomyopathy: a practical approach to guideline directed management. *Lancet.* (2021) 398(10316):2102–8. doi: 10.1016/S0140-6736(21)01205-8

5. Lipshultz SE, Sleeper LA, Towbin JA, Lowe AM, Orav EJ, Cox GF, et al. The incidence of pediatric cardiomyopathy in two regions of the United States. *N Engl J Med.* (2003) 348(17):1647–55. doi: 10.1056/NEJMoa021715

6. Nandi D, Hayes EA, Wang Y, Jerrell JM. Epidemiology of pediatric hypertrophic cardiomyopathy in a 10-year medicaid cohort. *Pediatr Cardiol.* (2021) 42(1):210–4. doi: 10.1007/s00246-020-02472-2

7. Jensen MK, Havndrup O, Christiansen M, Andersen PS, Diness B, Axelsson A, et al. Penetrance of hypertrophic cardiomyopathy in children and adolescents: a 12-year follow-up study of clinical screening and predictive genetic testing. *Circulation.* (2013) 127(1):48–54. doi: 10.1161/CIRCULATIONAHA.111.090514

8. Lipshultz SE, Law YM, Asante-Korang A, Austin ED, Dipchand AI, Everitt MD, et al. Cardiomyopathy in children: classification and diagnosis: a scientific statement from the American heart association. *Circulation*. (2019) 140(1):e9–68. doi: 10.1161/CIR.0000000000000682

9. Nguyen MB, Mital S, Mertens L, Jeewa A, Friedberg MK, Aguet J, et al. Pediatric hypertrophic cardiomyopathy: exploring the genotype-phenotype association. *J Am Heart Assoc*. (2022) 11(5):e024220. doi: 10.1161/JAHA.121.024220

10. Norrish G, Field E, Kaski JP. Childhood hypertrophic cardiomyopathy: a disease of the cardiac sarcomere. *Front Pediatr*. (2021) 9:708679. doi: 10.3389/fped.2021.708679

11. Colan SD, Lipshultz SE, Lowe AM, Sleeper LA, Messere J, Cox GF, et al. Epidemiology and cause-specific outcome of hypertrophic cardiomyopathy in children: findings from the pediatric cardiomyopathy registry. *Circulation*. (2007) 115(6):773–81. doi: 10.1161/CIRCULATIONAHA.106.621185

12. Marian AJ, Braunwald E. Hypertrophic cardiomyopathy: genetics, pathogenesis, clinical manifestations, diagnosis, and therapy. *Circ Res*. (2017) 121(7):749–70. doi: 10.1161/CIRCRESAHA.117.311059

13. Elliott PM, Anastasakis A, Borger MA, Borggrefe M, Cecchi F, Charron P, et al. 2014 ESC guidelines on diagnosis and management of hypertrophic cardiomyopathy: the task force for the diagnosis and management of hypertrophic cardiomyopathy of the European society of cardiology (ESC). *Eur Heart J*. (2014) 35(39):2733–79. doi: 10.1093/eurheartj/ehu284

14. Gersh BJ, Maron BJ, Bonow RO, Dearani JA, Fifer MA, Link MS, et al. 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: executive summary. *Circulation*. (2011) 124(24):2761–96. doi: 10.1161/CIR.0b013e318223e230

15. Arbelo E, Protonotarios A, Gimeno JR, Arbustini E, Barriales-Villa R, Basso C, et al. 2023 ESC guidelines for the management of cardiomyopathies: developed by the task force on the management of cardiomyopathies of the European society of cardiology (ESC). *Eur Heart J*. (2023) 44(37):3503–626. doi: 10.1093/eurheartj/ehad194

16. Ommen SR, Mital S, Burke MA, Day SM, Deswal A, Elliott P, et al. 2020 AHA/ACC guideline for the diagnosis and treatment of patients with hypertrophic cardiomyopathy: a report of the American college of cardiology/American heart association joint committee on clinical practice guidelines. *Circulation*. (2020) 142(25):e558–631. doi: 10.1161/CIR.0000000000000937

17. Rickers C, Wilke NM, Jerosch-Herold M, Casey SA, Panse P, Panse N, et al. Utility of cardiac magnetic resonance imaging in the diagnosis of hypertrophic cardiomyopathy. *Circulation*. (2005) 112(6):855–61. doi: 10.1161/CIRCULATIONAHA.104.507723

18. Corona-Villalobos CP, Sorensen LL, Pozios I, Chu L, Eng J, Abraham MR, et al. Left ventricular wall thickness in patients with hypertrophic cardiomyopathy: a comparison between cardiac magnetic resonance imaging and echocardiography. *Int J Cardiovasc Imaging*. (2016) 32(6):945–54. doi: 10.1007/s10554-016-0858-4

19. Moon JC, Fisher NG, McKenna WJ, Pennell DJ. Detection of apical hypertrophic cardiomyopathy by cardiovascular magnetic resonance in patients with non-diagnostic echocardiography. *Heart*. (2004) 90(6):645–9. doi: 10.1136/hrt.2003.014969

20. Maron MS, Maron BJ, Harrigan C, Buros J, Gibson CM, Olivotto I, et al. Hypertrophic cardiomyopathy phenotype revisited after 50 years with cardiovascular magnetic resonance. *J Am Coll Cardiol*. (2009) 54(3):220–8. doi: 10.1016/j.jacc.2009.05.006

21. Hindieh W, Weissler-Snir A, Hammer H, Adler A, Rakowski H, Chan RH. Discrepant measurements of maximal left ventricular wall thickness between cardiac magnetic resonance imaging and echocardiography in patients with hypertrophic cardiomyopathy. *Circ Cardiovasc Imaging*. (2017) 10(8):e006309. doi: 10.1161/CIRCIMAGING.117.006309

22. Bois JP, Geske JB, Foley TA, Ommen SR, Pellikka PA. Comparison of maximal wall thickness in hypertrophic cardiomyopathy differs between magnetic resonance imaging and transthoracic echocardiography. *Am J Cardiol*. (2017) 119(4):643–50. doi: 10.1016/j.amjcard.2016.11.010

23. Maron MS, Rowin EJ, Maron BJ. How to image hypertrophic cardiomyopathy. *Circ Cardiovasc Imaging*. (2017) 10(7):e005372. doi: 10.1161/CIRCIMAGING.116.005372

24. O'Brien C, Britton I, Karur GR, Iwanochko RM, Morel CF, Nguyen ET, et al. Left ventricular mass and wall thickness measurements using echocardiography and cardiac MRI in patients with fabry disease: clinical significance of discrepant findings. *Radiol Cardiothorac Imaging*. (2020) 2(3):e190149. doi: 10.1148/ryct.2020190149

25. Śpiewak M, Kłopotowski M, Ojrzyńska N, Petryka-Mazurkiewicz J, Miłosz-Wieczorek B, Mazurkiewicz Ł, et al. Impact of cardiac magnetic resonance on the diagnosis of hypertrophic cardiomyopathy—a 10-year experience with over 1000 patients. *Eur Radiol*. (2021) 31(3):1194–205. doi: 10.1007/s00330-020-07207-8

26. Maron Barry J, Desai Milind Y, Nishimura Rick A, Spirito P, Rakowski H, Towbin Jeffrey A, et al. Management of hypertrophic cardiomyopathy. *J Am Coll Cardiol*. (2022) 79(4):390–414. doi: 10.1016/j.jacc.2021.11.021

27. Kebed KY, Al Adham RI, Bishu K, Askew JW, Klarich KW, Oh JK, et al. Evaluation of apical pouches in hypertrophic cardiomyopathy using cardiac MRI. *Int J Cardiovasc Imaging*. (2014) 30(3):591–7. doi: 10.1007/s10554-013-0355-y

28. Rowin EJ, Maron BJ, Maron MS. The hypertrophic cardiomyopathy phenotype viewed through the prism of multimodality imaging: clinical and etiologic implications. *JACC: Cardiovascular Imaging*. (2020) 13(9):2002–16. doi: 10.1016/j.jcmg.2019.09.020

29. Lorenzini M, Norrish G, Field E, Ochoa JP, Cicerchia M, Akhtar MM, et al. Penetrance of hypertrophic cardiomyopathy in sarcomere protein mutation carriers. *J Am Coll Cardiol*. (2020) 76(5):550–9. doi: 10.1016/j.jacc.2020.06.011

30. Ho CY, Day SM, Ashley EA, Michels M, Pereira AC, Jacoby D, et al. Genotype and lifetime burden of disease in hypertrophic cardiomyopathy: insights from the sarcomeric human cardiomyopathy registry (SHaRe). *Circulation*. (2018) 138(14):1387–98. doi: 10.1161/CIRCULATIONAHA.117.033200

31. Raman B, Tunnicliffe EM, Chan K, Ariga R, Hundertmark M, Ohuma EO, et al. Association between sarcomeric variants in hypertrophic cardiomyopathy and myocardial oxygenation: insights from a novel oxygen-sensitive cardiovascular magnetic resonance approach. *Circulation*. (2021) 144(20):1656–8. doi: 10.1161/CIRCULATIONAHA.121.054015

32. Olivotto I, Oreziak A, Barriales-Villa R, Abraham TP, Masri A, Garcia-Pavia P, et al. Mavacamten for treatment of symptomatic obstructive hypertrophic cardiomyopathy (EXPLORER-HCM): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. (2020) 396(10253):759–69. doi: 10.1016/S0140-6736(20)31792-X

33. O'Mahony C, Jichi F, Pavlou M, Monserrat L, Anastasakis A, Rapezzi C, et al. A novel clinical risk prediction model for sudden cardiac death in hypertrophic cardiomyopathy (HCM risk-SCD). *Eur Heart J*. (2014) 35(30):2010–20. doi: 10.1093/eurheartj/eht439

34. Maron MS, Rowin EJ, Wessler BS, Mooney PJ, Fatima A, Patel P, et al. Enhanced American college of cardiology/American heart association strategy for prevention of sudden cardiac death in high-risk patients with hypertrophic cardiomyopathy. *JAMA Cardiol*. (2019) 4(7):644–57. doi: 10.1001/jamacardio.2019.1391

35. Norrish G, Ding T, Field E, Ziólkowska L, Olivotto I, Limongelli G, et al. Development of a novel risk prediction model for sudden cardiac death in childhood hypertrophic cardiomyopathy (HCM risk-kids). *JAMA Cardiol*. (2019) 4(9):918–27. doi: 10.1001/jamacardio.2019.2861

36. Mathew J, Zahavich L, Lafreniere-Roula M, Wilson J, George K, Benson L, et al. Utility of genetics for risk stratification in pediatric hypertrophic cardiomyopathy. *Clin Genet*. (2018) 93(2):310–9. doi: 10.1111/cge.13157

37. Norrish G, Cantarutti N, Pissaridou E, Ridout DA, Limongelli G, Elliott PM, et al. Risk factors for sudden cardiac death in childhood hypertrophic cardiomyopathy: a systematic review and meta-analysis. *Eur J Prev Cardiol*. (2017) 24(11):1220–30. doi: 10.1177/2047487317702519

38. Marston NA, Han L, Olivotto I, Day SM, Ashley EA, Michels M, et al. Clinical characteristics and outcomes in childhood-onset hypertrophic cardiomyopathy. *Eur Heart J*. (2021) 42(20):1988–96. doi: 10.1093/eurheartj/ehab148

39. Norrish G, Kaski JP. The risk of sudden death in children with hypertrophic cardiomyopathy. *Heart Fail Clin*. (2022) 18(1):9–18. doi: 10.1016/j.hfc.2021.07.012

40. Miron A, Lafreniere-Roula M, Steve Fan CP, Armstrong KR, Dragulescu A, Papaz T, et al. A validated model for sudden cardiac death risk prediction in pediatric hypertrophic cardiomyopathy. *Circulation*. (2020) 142(3):217–29. doi: 10.1161/CIRCULATIONAHA.120.047235

41. Balaji S, DiLorenzo MP, Fish FA, Etheridge SP, Aziz PF, Russell MW, et al. Risk factors for lethal arrhythmic events in children and adolescents with hypertrophic cardiomyopathy and an implantable defibrillator: an international multicenter study. *Heart Rhythm*. (2019) 16(10):1462–7. doi: 10.1016/j.hrthm.2019.04.040

42. Norrish G, Cleary A, Field E, Cervi E, Boleti O, Ziółkowska L, et al. Clinical features and natural history of preadolescent nonsyndromic hypertrophic cardiomyopathy. *J Am Coll Cardiol*. (2022) 79(20):1986–97. doi: 10.1016/j.jacc.2022.03.347

43. Xia K, Sun D, Wang R, Zhang Y. Factors associated with the risk of cardiac death in children with hypertrophic cardiomyopathy: a systematic review and meta-analysis. *Heart Lung*. (2022) 52:26–36. doi: 10.1016/j.hrtlng.2021.11.006

44. Conway J, Min S, Villa C, Weintraub RG, Nakano S, Godown J, et al. The prevalence and association of exercise test abnormalities with sudden cardiac death and transplant-free survival in childhood hypertrophic cardiomyopathy. *Circulation*. (2023) 147(9):718–27. doi: 10.1161/CIRCULATIONAHA.122.062699

45. Norrish G, Qu C, Field E, Cervi E, Khraiche D, Klaassen S, et al. External validation of the HCM risk-kids model for predicting sudden cardiac death in childhood hypertrophic cardiomyopathy. *Eur J Prev Cardiol*. (2022) 29(4):678–86. doi: 10.1093/eurjpc/zwab181

46. Bianco F, Bucciarelli V. Hypertrophic cardiomyopathy risk scoring for sudden cardiac death in paediatrics, adolescents, and adults: stuck on the puzzle of clinical, imaging, and genetic features. *Eur J Prev Cardiol*. (2022) 29(4):675–7. doi: 10.1093/eurjpc/zwab199

47. Maron BJ, Casey SA, Chan RH, Garberich RF, Rowin EJ, Maron MS. Independent assessment of the European society of cardiology sudden death risk model for hypertrophic cardiomyopathy. *Am J Cardiol*. (2015) 116(5):757–64. doi: 10.1016/j.amjcard.2015.05.047

48. O'Mahony C, Akhtar MM, Anastasiou Z, Guttmann OP, Vriesendorp PA, Michels M, et al. Effectiveness of the 2014 European society of cardiology guideline

on sudden cardiac death in hypertrophic cardiomyopathy: a systematic review and meta-analysis. *Heart*. (2019) 105(8):623–31. doi: 10.1136/heartjnl-2018-313700

49. O'Mahony C, Jichi F, Ommen SR, Christiaans I, Arbustini E, Garcia-Pavia P, et al. International external validation study of the 2014 European society of cardiology guidelines on sudden cardiac death prevention in hypertrophic cardiomyopathy (EVIDENCE-HCM). *Circulation*. (2018) 137(10):1015–23. doi: 10.1161/CIRCULATIONAHA.117.030437

50. Sivalokanathan S, Zghaib T, Greenland GV, Vasquez N, Kudchadkar SM, Kontari E, et al. Hypertrophic cardiomyopathy patients with paroxysmal atrial fibrillation have a high burden of left atrial fibrosis by cardiac magnetic resonance imaging. *JACC Clin Electrophysiol*. (2019) 5(3):364–75. doi: 10.1016/j.jacep.2018.10.016

51. Weng Z, Yao J, Chan RH, He J, Yang X, Zhou Y, et al. Prognostic value of LGE-CMR in HCM: a meta-analysis. *JACC: Cardiovasc Imaging*. (2016) 9(12):1392–402. doi: 10.1016/j.jcmg.2016.02.031

52. Mentias A, Raeisi-Giglou P, Smedira NG, Feng K, Sato K, Wazni O, et al. Late gadolinium enhancement in patients with hypertrophic cardiomyopathy and preserved systolic function. *J Am Coll Cardiol*. (2018) 72(8):857–70. doi: 10.1016/j.jacc.2018.05.060

53. Fahmy AS, Rowin EJ, Jaafar N, Chan RH, Rodriguez J, Nakamori S, et al. Radiomics of late gadolinium enhancement reveals prognostic value of myocardial scar heterogeneity in hypertrophic cardiomyopathy. *JACC: Cardiovasc Imaging*. (2023):S1936-878X(23)00222-X. doi: 10.1016/j.jcmg.2023.05.003

54. Maron BJ, Rowin EJ, Maron MS. Evolution of risk stratification and sudden death prevention in hypertrophic cardiomyopathy: twenty years with the implantable cardioverter-defibrillator. *Heart Rhythm*. (2021) 18(6):1012–23. doi: 10.1016/j.hrthm.2021.01.019

55. Kirmani S, Woodard PK, Shi L, Hamza TH, Canter CE, Colan SD, et al. Cardiac imaging and biomarkers for assessing myocardial fibrosis in children with hypertrophic cardiomyopathy. *Am Heart J*. (2023) 264:153–62. doi: 10.1016/j.ahj.2023.06.005

56. Petryka-Mazurkiewicz J, Ziolkowska L, Kowalczyk-Domagala M, Mazurkiewicz L, Boruc A, Spiewak M, et al. LGE For risk stratification in primary prevention in children with HCM. *JACC: Cardiovasc Imaging*. (2020) 13(12):2684–6. doi: 10.1016/j.jcmg.2020.06.009

57. Ali LA, Marrone C, Martins DS, Khraiche D, Festa P, Martini N, et al. Prognostic factors in hypertrophic cardiomyopathy in children: an MRI based study. *Int J Cardiol*. (2022) 364:141–7. doi: 10.1016/j.ijcard.2022.06.043

58. Axelsson Raja A, Farhad H, Valente AM, Couce JP, Jefferies JL, Bundgaard H, et al. Prevalence and progression of late gadolinium enhancement in children and adolescents with hypertrophic cardiomyopathy. *Circulation*. (2018) 138(8):782–92. doi: 10.1161/CIRCULATIONAHA.117.032966

59. Haaf P, Garg P, Messroghli DR, Broadbent DA, Greenwood JP, Plein S. Cardiac T1 mapping and extracellular volume (ECV) in clinical practice: a comprehensive review. *J Cardiovasc Magn Reson*. (2016) 18(1):89. doi: 10.1186/s12968-016-0308-4

60. Hussain T, Dragulescu A, Benson L, Yoo S-J, Meng H, Windram J, et al. Quantification and significance of diffuse myocardial fibrosis and diastolic dysfunction in childhood hypertrophic cardiomyopathy. *Pediatr Cardiol*. (2015) 36(5):970–8. doi: 10.1007/s00246-015-1107-7

61. Xu J, Zhuang B, Sirajuddin A, Li S, Huang J, Yin G, et al. MRI T1 mapping in hypertrophic cardiomyopathy: evaluation in patients without late gadolinium enhancement and hemodynamic obstruction. *Radiology*. (2019) 294(2):275–86. doi: 10.1148/radiol.2019190651

62. Qin L, Min J, Chen C, Zhu L, Gu S, Zhou M, et al. Incremental values of T1 mapping in the prediction of sudden cardiac death risk in hypertrophic cardiomyopathy: a comparison with two guidelines. *Front Cardiovasc Med*. (2021) 8:661673. doi: 10.3389/fcvm.2021.661673

63. Wang J, Yang F, Liu W, Sun J, Han Y, Li D, et al. Radiomic analysis of native T1 mapping images discriminates between MYH7 and MYBPC3-related hypertrophic cardiomyopathy. *J Magn Reson Imaging*. (2020) 52(6):1714–21. doi: 10.1002/jmri.27209

64. Hershberger RE, Givertz MM, Ho CY, Judge DP, Kantor PF, McBride KL, et al. Genetic evaluation of cardiomyopathy-a heart failure society of America practice guideline. *J Card Fail*. (2018) 24(5):281–302. doi: 10.1016/j.cardfail.2018.03.004

65. Kaski JP, Syrris P, Esteban MT, Jenkins S, Pantazis A, Deanfield JE, et al. Prevalence of sarcomere protein gene mutations in preadolescent children with hypertrophic cardiomyopathy. *Circ Cardiovasc Genet*. (2009) 2(5):436–41. doi: 10.1161/CIRCGENETICS.108.821314

66. Kindel SJ, Miller EM, Gupta R, Cripe LH, Hinton RB, Spicer RL, et al. Pediatric cardiomyopathy: importance of genetic and metabolic evaluation. *J Card Fail*. (2012) 18(5):396–403. doi: 10.1016/j.cardfail.2012.01.017

67. Norrish G, Jager J, Field E, Quinn E, Fell H, Lord E, et al. Yield of clinical screening for hypertrophic cardiomyopathy in child first-degree relatives. *Circulation*. (2019) 140(3):184–92. doi: 10.1161/CIRCULATIONAHA.118.038846

68. Lafreniere-Roula M, Bolkier Y, Zahavich L, Mathew J, George K, Wilson J, et al. Family screening for hypertrophic cardiomyopathy: is it time to change practice guidelines? *Eur Heart J*. (2019) 40(45):3672–81. doi: 10.1093/eurheartj/ehz396

69. Nielsen SK, Hansen FG, Rasmussen TB, Fischer T, Lassen JF, Madsen T, et al. Patients with hypertrophic cardiomyopathy and normal genetic investigations have few affected relatives. *J Am Coll Cardiol*. (2023) 82(18):1751–61. doi: 10.1016/j.jacc.2023.08.041

70. Mital S, Ommen S. To screen or not to screen, that is the question. *Circulation*. (2019) 140(3):193–5. doi: 10.1161/CIRCULATIONAHA.119.041021

71. Spanaki A, O'Curry S, Winter-Beatty J, Mead-Regan S, Hawkins K, English J, et al. Psychosocial adjustment and quality of life in children undergoing screening in a specialist paediatric hypertrophic cardiomyopathy clinic. *Cardiol Young*. (2016) 26(5):961–7. doi: 10.1017/S1047951115001717

72. Bratt E-L, Östman-Smith I, Axelsson Å, Berntsson L. Quality of life in asymptomatic children and adolescents before and after diagnosis of hypertrophic cardiomyopathy through family screening. *J Clin Nurs*. (2013) 22(1–2):211–21. doi: 10.1111/j.1365-2702.2012.04108.x

73. Wasfy MM, Hutter AM, Weiner RB. Sudden cardiac death in athletes. *Methodist Debakey Cardiovasc J*. (2016) 12(2):76–80. doi: 10.14797/mdcj-12-2-76

74. Andreassen K, Dejgaard LA, Lie Ø, Fink TS, Lunde IG, Edvardsen T, et al. Exercise training during childhood and adolescence is associated with favorable diastolic function in hypertrophic cardiomyopathy. *Int J Cardiol*. (2022) 364:65–71. doi: 10.1016/j.ijcard.2022.06.042

75. Konhilas JP, Watson PA, Maass A, Boucek DM, Horn T, Stauffer BL, et al. Exercise can prevent and reverse the severity of hypertrophic cardiomyopathy. *Circ Res*. (2006) 98(4):540–8. doi: 10.1161/01.RES.0000205766.97556.00

76. Lampert R, Ackerman MJ, Marino BS, Burg M, Ainsworth B, Salberg L, et al. Vigorous exercise in patients with hypertrophic cardiomyopathy. *JAMA Cardiol*. (2023) 8(6):595–605. doi: 10.1001/jamacardio.2023.1042

77. Olivotto I, Maron BJ, Tomberli B, Appelbaum E, Salton C, Haas TS, et al. Obesity and its association to phenotype and clinical course in hypertrophic cardiomyopathy. *J Am Coll Cardiol*. (2013) 62(5):449–57. doi: 10.1016/j.jacc.2013.03.062

78. Joanna S, Jodie I, Anna T, Jillian P, Kylie B, Christopher S. Physical activity in hypertrophic cardiomyopathy: prevalence of inactivity and perceived barriers. *Open Heart*. (2016) 3(2):e000484. doi: 10.1136/openhrt-2016-000484

79. Fumagalli C, Maurizi N, Day SM, Ashley EA, Michels M, Colan SD, et al. Association of obesity with adverse long-term outcomes in hypertrophic cardiomyopathy. *JAMA Cardiol*. (2020) 5(1):65–72. doi: 10.1001/jamacardio.2019.4268

80. Saberi S, Wheeler M, Bragg-Gresham J, Hornsby W, Agarwal PP, Attili A, et al. Effect of moderate-intensity exercise training on peak oxygen consumption in patients with hypertrophic cardiomyopathy: a randomized clinical trial. *JAMA*. (2017) 317(13):1349–57. doi: 10.1001/jama.2017.2503

81. MacNamara JP, Dias KA, Hearon CM, Ivey E, Delgado VA, Saland S, et al. Randomized controlled trial of moderate- and high-intensity exercise training in patients with hypertrophic cardiomyopathy: effects on fitness and cardiovascular response to exercise. *J Am Heart Assoc*. (2023) 12(20):e031399. doi: 10.1161/JAHA.123.031399

82. Sabiha G, Sanjay S. Exercise prescription in individuals with hypertrophic cardiomyopathy: what clinicians need to know. *Heart*. (2022) 108(24):1930. doi: 10.1136/heartjnl-2021-319861

83. Reineck E, Rolston B, Bragg-Gresham JL, Salberg L, Baty L, Kumar S, et al. Physical activity and other health behaviors in adults with hypertrophic cardiomyopathy. *Am J Cardiol*. (2013) 111(7):1034–9. doi: 10.1016/j.amjcard.2012.12.018

84. Sheikh N, Papadakis M, Schnell F, Panoulas V, Malhotra A, Wilson M, et al. Clinical profile of athletes with hypertrophic cardiomyopathy. *Circ Cardiovasc Imaging*. (2015) 8(7):e003454. doi: 10.1161/CIRCIMAGING.114.003454

85. Tromp J, Ouwerkerk W, van Veldhuisen DJ, Hillege HL, Richards AM, van der Meer P, et al. A systematic review and network meta-analysis of pharmacological treatment of heart failure with reduced ejection fraction. *Heart Fail*. (2022) 10(2):73–84. doi: 10.1016/j.jchf.2021.09.004

86. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: developed by the task force for the diagnosis and treatment of acute and chronic heart failure of the European society of cardiology (ESC) with the special contribution of the heart failure association (HFA) of the ESC. *Eur Heart J*. (2021) 42(36):3599–726. doi: 10.1093/eurheartj/ehab368

87. Ho CY, Day SM, Axelsson A, Russell MW, Zahka K, Lever HM, et al. Valsartan in early-stage hypertrophic cardiomyopathy: a randomized phase 2 trial. *Nat Med*. (2021) 27(10):1818–24. doi: 10.1038/s41591-021-01505-4

88. Olivotto I, Ashley EA. INHERIT (INHibition of the renin angiotensin system in hypertrophic cardiomyopathy and the effect on hypertrophy-a randomised intervention trial with losartan). *Glob Cardiol Sci Pract*. (2015) 2015:7. doi: 10.5339/gcsp.2015.7

89. Severinsen T, Thune JJ, Gudmundsdottir HL, Vissing CR, Iversen K, Ho CY, et al. Angiotensin receptor blockers in patients with hypertrophic cardiomyopathy: a comparison of VANISH and INHERIT randomized trials. *Am Heart J*. (2023) 266:198–200. doi: 10.1016/j.ahj.2023.08.013

90. Teekakirikul P, Eminaga S, Toka O, Alcalai R, Wang L, Wakimoto H, et al. Cardiac fibrosis in mice with hypertrophic cardiomyopathy is mediated by non-myocyte proliferation and requires tgf-β. *J Clin Invest*. (2010) 120(10):3520–9. doi: 10.1172/JCI42028

91. Vissing CR, Axelsson Raja A, Day SM, Russell MW, Zahka K, Lever HM, et al. Cardiac remodeling in subclinical hypertrophic cardiomyopathy: the VANISH randomized clinical trial. *JAMA Cardiol*. (2023) 8(11):1083–8. doi: 10.1001/jamacardio.2023.2808

frontiers | Frontiers in Cardiovascular Medicine

TYPE Original Research
PUBLISHED 01 February 2024
DOI 10.3389/fcvm.2024.1247472

OPEN ACCESS

EDITED BY
Shikai Yu,
Tongji University, China

REVIEWED BY
Nicolau Beckmann,
Novartis Institutes for BioMedical Research, Switzerland
Paul Philipp Heinisch,
Technical University Munich, Germany

*CORRESPONDENCE
Jana Lücht
jana.luecht@dhzc-charite.de

†These authors have contributed equally to this work and share first authorship

RECEIVED 26 June 2023
ACCEPTED 19 January 2024
PUBLISHED 01 February 2024

CITATION
Lücht J, Seiler R, Herre AL, Brankova L, Fritsche-Guenther R, Kirwan J, Huscher D, Münzfeld H, Berger F, Photiadis J, Tong G and Schmitt KRL (2024) Promising results of a clinical feasibility study: CIRBP as a potential biomarker in pediatric cardiac surgery. Front. Cardiovasc. Med. 11:1247472. doi: 10.3389/fcvm.2024.1247472

Promising results of a clinical feasibility study: CIRBP as a potential biomarker in pediatric cardiac surgery

Jana Lücht[1,2*†], Raphael Seiler[1†], Alexa Leona Herre[1], Liliya Brankova[1], Raphaela Fritsche-Guenther[3], Jennifer Kirwan[3], Dörte Huscher[4,2], Hanna Münzfeld[5], Felix Berger[1], Joachim Photiadis[6], Giang Tong[1] and Katharina R. L. Schmitt[1]

[1]Department of Congenital Heart Disease/Pediatric Cardiology, Deutsches Herzzentrum der Charité – Medical Heart Center of Charité and German Heart Institute Berlin, Berlin, Germany, [2]Berlin Institute of Health at Charité – Universitätsmedizin Berlin, Berlin, Germany, [3]Metabolomics Platform, Berlin Institute of Health at Charité – Universitätsmedizin Berlin, Berlin, Germany, [4]Institute of Biometry and Clinical Epidemiology, Charité – Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany, [5]Department of Radiology, Charité – Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany, [6]Department of Congenital Heart Surgery and Pediatric Heart Surgery, Deutsches Herzzentrum der Charité – Medical Heart Center of Charité and German Heart Institute Berlin, Berlin, Germany

Objective: Cold-inducible RNA binding Protein (CIRBP) has been shown to be a potent inflammatory mediator and could serve as a novel biomarker for inflammation. Systemic inflammatory response syndrome (SIRS) and capillary leak syndrome (CLS) are frequent complications after pediatric cardiac surgery increasing morbidity, therefore early diagnosis and therapy is crucial. As CIRBP serum levels have not been analyzed in a pediatric population, we conducted a clinical feasibility establishing a customized magnetic bead panel analyzing CIRBP in pediatric patients undergoing cardiac surgery.

Methods: A prospective hypothesis generating observational clinical study was conducted at the German Heart Center Berlin during a period of 9 months starting in May 2020 (DRKS00020885, https://drks.de/search/de/trial/DRKS00020885). Serum samples were obtained before the cardiac operation, upon arrival at the pediatric intensive care unit, 6 and 24 h after the operation in patients up to 18 years of age with congenital heart disease (CHD). Customized multiplex magnetic bead-based immunoassay panels were developed to analyze CIRBP, Interleukin-1β (IL-1β), Interleukin-6 (IL-6), Interleukin-8 (IL-8), Interleukin-10 (IL-10), Monocyte chemotactic protein 1 (MCP-1), Syndecan-1 (SDC-1), Thrombomodulin (TM), Vascular endothelial growth factor (VEGF-A), Angiopoietin-2 (Ang-2), and Fibroblast growth factor 23 (FGF-23) in 25 µl serum using the Luminex MagPix® system.

Abbreviations

AKI, acute kidney injury; ALT, alanine transaminase; Ang-2, Angiopoietin-2; AST, aspartate transferase; CHD, congenital heart disease; CIRBP, cold-inducible RNA binding Protein; CK, creatinine kinase; CK-MB, creatinine kinase-myoglobin binding; CLS, capillary leak syndrome; CPB, cardiopulmonary bypass; CRP, C-reactive protein; DAMP, damage associated molecular pattern; FGF-23, Fibroblast growth factor 23; ICU, intensive care unit; IL-10, Interleukin-10; IL-1β, Interleukin-1β; IL-6, Interleukin-6; IL-8, Interleukin-8; KDIGO, Kidney Disease: Improving Global Outcomes; LDH, lactate dehydrogenase; LOD/Q, limit of detection/quantification; MCP-1, Monocyte chemotactic protein 1; MFI, mean fluorescent intensities; mRNA, messenger ribonucleic acid; PICU, pediatric intensive care unit; QC, quality control; RACHS-1, Risk Adjustment for Congenital Heart Surgery 1; RBM3, cold-shock proteins RNA-binding motif 3; S/T ratio, subcutaneous-thoracic ratio; SDC-1, Syndecan-1; SIRS, systemic inflammatory response syndrome; T0, timepoint of preoperative sample acquisition; T1, timepoint of the postoperative sample acquisition: directly after operation; T2, timepoint of the postoperative sample acquisition: 6 h after operation; T3, timepoint of the postoperative sample acquisition: 24 h after operation; TM, Thrombomodulin; VEGF-A, Vascular endothelial growth factor; VIS, vasoactive-inotropic score.

Results: 19 patients representing a broad range of CHD (10 male patients, median age 2 years, 9 female patients, median age 3 years) were included in the feasibility study. CIRBP was detectable in the whole patient cohort. Relative to individual baseline values, CIRBP concentrations increased 6 h after operation and returned to baseline levels over time. IL-6, IL-8, IL-10, and MCP-1 concentrations were significantly increased after operation and except for MCP-1 concentrations stayed upregulated over time. SDC-1, TM, Ang-2, as well as FGF-23 concentrations were also significantly increased, whereas VEGF-A concentration was significantly decreased after surgery.
Discussion: Using customized magnetic bead panels, we were able to detect CIRBP in a minimal serum volume (25 µl) in all enrolled patients. To our knowledge this is the first clinical study to assess CIRBP serum concentrations in a pediatric population.

KEYWORDS

pediatric cardiology, pediatric cardiac surgery, cold inducible RNA-binding protein (CIRBP), inflammation, endothelial dysfunction, biomarker, feasibility study

1 Introduction

Systemic inflammatory response syndrome (SIRS) is a frequent complication after cardiac surgery in children with congenital heart disease (CHD) caused by multiple factors including tissue injury due to surgical incision and the extracorporeal circuit during cardiopulmonary bypass (CPB) (1). During CPB the contact of blood to the synthetic surface of the extracorporeal circuit induces an early phase of systemic inflammation by activation of the complement system and release of proinflammatory cytokines (2). The late response is triggered by ischemia/reperfusion-induced injury leading to endotoxemia due to intestinal barrier changes. This stimulates systemic inflammation even further (2–4), causing and aggravating an impaired vascular endothelial barrier, which can lead to capillary leak syndrome (CLS) (2, 5). Postoperative morbidity is increased as SIRS and CLS are associated with a longer stay on the pediatric intensive care unit (PICU), prolonged mechanical ventilation, and higher demand for catecholamines (5–8).

To date, routinely assessed laboratory markers including C-reactive protein (CRP), Interleukin-6 (IL-6), lactate, and platelet count have been shown to be influenced by cardiac surgery, however they cannot be used to identify patients with SIRS (6). Different diagnostic approaches for CLS have been described including measurement of subcutaneous cytokines and hemoconcentration in infants with hypoplastic left heart syndrome undergoing Norwood stage 1 operation (9, 10). However, as we are currently lacking suitable biomarkers for identifying patients at risk of SIRS and CLS early on, diagnosis and therefore treatment of critically ill patients can be delayed.

CLS is primarily induced by endothelial dysfunction leading to a shift of intravascular fluid and protein to surrounding tissue and cavities, resulting in edema as well as intravasal volume and protein depletion. Vascular barrier and therefore, vascular permeability is controlled by two major components consisting of an inner, lumen facing layer consisting of endothelial glycocalyx and an outer layer, the endothelial cells (11). Furthermore, experimental studies have shown that the endothelial glycocalyx plays an important role in maintaining colloid osmotic gradient and preventing tissue edema (12, 13). Syndecan-1 (SDC-1) is a part of the endothelial glycocalyx that gets released upon glycocalyx degradation and has been described as a marker for glycocalyx shedding (14). Thrombomodulin (TM) is a transmembrane glycoprotein found in the vascular endothelium (15) and serves as a biomarker for endothelial injury as its release as soluble TM is initiated only by endothelial cell injury (16). Both the release of SDC-1 and elevated serum TM has been described in patients with SIRS/sepsis (17–19). Furthermore, Angiopoietin-2 (Ang-2) and vascular endothelial growth factor (VEGF-A) have been described as biomarkers for vascular leakage. Ang-2 is an endothelial growth factor that can be released upon endothelial activation (20). Both Angiopoietin-1 (Ang-1) and Ang-2 bind to the endothelial receptor tyrosine kinase (Tie2) (21). Whereas Ang-1 induces stabilization of the endothelial barrier, Ang-2 has been shown to induce inflammation and vascular leakage (22, 23). VEGF-A has been shown to play an important role in the induction of vascular permeability (24). VEGF-A is produced by neutrophils, macrophages, endothelial and smooth muscle cells, and stored in platelets (25–27). VEGF-A synthesis and release is induced by hypoxia, nitric oxide, coagulation, and bacterial endotoxins (25, 28–30). *In vivo* studies have shown that Ang-2 and VEGF-A are linked in the pathogenesis of vascular leakage as Ang-2 induced vascular barrier changes is synergistically driven by VEGF-A (31, 32). Ang-2 has been described as a biomarker for increased vascular permeability and poor outcome in both adults and children with SIRS and sepsis (33, 34). Additionally, SDC-1, Ang-2, and VEGF-A have also been studied in children after cardiac surgery (35–39).

Cold inducible RNA-binding protein (CIRBP) is a highly conserved 18-kDa nuclear protein belonging to the family of cold-shock proteins (40). It is expressed in various tissues (41) and upregulated upon stimuli including mild to moderate cold stress (28–34°C), ultraviolet radiation, and hypoxia (40, 42, 43). Extracellular CIRBP has been shown to act as a damage associated molecular pattern (DAMP) and has been reported as a novel biomarker for inflammation (44–46). By binding to toll-like receptor 4 (TLR4) and myeloid differentiation factor 2 (MD2) complex (44) as well as triggering receptor expressed on

myeloid cells-1 (TREM-1) (47) and Interleukin 6 receptor (IL-6R) (48), CIRBP activates the proinflammatory stress response. *In vitro* and *in vivo* studies have reported CIRBP as a potent mediator of inflammation due to its ability to promote both cytokines and the release of other DAMPs, whereas CIRBP blockage resulted in a significant reduction of inflammation as well as higher survival rates (44, 45).

As both experimental and clinical data have described CIRBP as a mediator of inflammation, it could serve as a potential biomarker for postoperative inflammatory reactions in our pediatric cohort. Furthermore, experimental studies have reported CIRBP to be involved in the pathogenesis of endothelial dysfunction (49). However, to our knowledge CIRBP has not been analyzed in children with CHD after cardiac surgery. Moreover, a potential correlation between sex and age dependency in the amount of CIRBP detectable in serum after cardiac surgery with CHD has not been investigated.

Therefore, we conducted a feasibility study using a customized magnetic bead panel to analyze CIRBP, pro- and anti-inflammatory cytokines, as well as previously described biomarkers for increased vascular permeability at defined time points before and after cardiac surgery.

2 Methods

2.1 Study design

This prospective observational feasibility study was conducted at the German Heart Center Berlin after approval by the Ethics Committee of Charité—Universitätsmedizin Berlin, Germany (decision EA2/180/19). The study was registered with the German register for clinical studies before patients' recruitment (registration number: DRKS00020885; https://drks.de/search/de/trial/DRKS00020885). Written consent was obtained from the parents of each patient before study inclusion. Patients younger than 18 years receiving a cardiac surgery at our center were enrolled. Exclusion criteria were as follows: gestational age ≤ 37 weeks, a known maternal alcohol or substance abuse during pregnancy, immunodeficiencies or immunosuppressive medication, syndromic diseases (e.g., Trisomy 21 and 18), and congenital kidney disease.

2.1.1 Preoperative, operative and postoperative management

19 Patients were enrolled over a period of 9 months starting in May 2020. Anesthesia was performed by standardized protocols using propofol (3–5 mg/kg), rocuronium (1 mg/kg) and sufentanil (1 µg/kg) for induction and propofol (5 mg/kg/h), remifentanil (1–3 µg/kg/min), and dexmedetomidine (0.25–1 µg/kg/h) for maintenance. All patients received a urinary catheter, a central venous line as well as a femoral or radial arterial cannula upon induction of anesthesia. Most patients received a single shot dexamethasone (0.15 −0.5 mg/kg) before cardiac surgery. Core temperature was measured during surgery and postoperatively on the intensive care unit via a rectal temperature probe.

Cardiac surgery was performed depending on the underlying anomaly. On-pump beating heart surgery was performed in 5 patients (26%) to prevent reperfusion injury, aortic cross-clamping was necessary in 14 patients (74%). CPB was performed using polyvinyl tubing, roller pumping (mast-mounted pump, Stöckert Instruments, München, Germany), and a hollow fiber membrane oxygenator (Capiox RX05, Terumo Corp., Tokyo, Japan). Priming of the extracorporeal circuit was achieved using a balanced electrolyte solution (Ionosteril, Fresenius Kabi, Bad Homburg, Germany), and heparin (500 IE/kg), as well as tranexamic acid (10–15 mg/kg at initiation of CPB and 1–3 mg/kg/h for maintenance) was administered. Flowrate was maintained at 3 L/m^2 body surface area during cardiopulmonary bypass. Upon weaning from cardiopulmonary bypass, protamine sulfate was administered according to remaining heparin effect (usually 10 mg/1,000 IE). After the operation, patients were transferred to our intensive care unit. For postoperative management of analgesia sufentanil (0.2–0.6 µg/kg/h) or morphine (30–60 µg/kg/h) or piritramide (0.1 mg/kg) plus additive metamizole (10 mg/kg) and paracetamol (10 mg/kg) were standardly administered. Dexmedetomidine (0.25–1 µg/kg/h) was given for postoperative adjuvant sedation.

2.1.2 Protocol of blood sample acquisition

Blood samples for biomarker analysis were obtained via the central venous line preoperatively after the induction of anesthesia (T0) as well as postoperatively upon arrival on the pediatric intensive care unit (PICU) (T1), and both 6 and 24 h after the operation (T2 and T3 respectively, Figure 1). We collected 1 ml blood for patients ≤15 kg and 2 ml of blood for patients >15 kg at each timepoint in Serum-Gel Microvette® 500 (20.1344 Sarstedt, Nümbrecht, Germany). Samples were centrifuged at $26 \times g$ for 10 min and frozen temporarily at −8°C until final storage at −80°C.

2.1.3 Study outcomes

The aim of this clinical feasibility study was to measure perioperative CIRBP serum levels as well as concentrations of cytokines and biomarkers for endothelial dysfunction in a very small sample volume (25 µl/sample) from children undergoing cardiac surgery. Clinical primary endpoints were defined as duration of mechanical ventilation, duration of the intensive care unit stay, as well as the level of inotropic support. Administered catecholamines were documented hourly from the time of T1 (arrival on PICU) up to 72 h after operation and both maximum and mean vasoactive inotropic scores were calculated according to *Gaies* et al. (50).

Secondary endpoints were defined as 30-day mortality, as well as postoperative complications such as infection, arrhythmia, acute kidney injury, and signs for capillary leakage. Acute kidney injury was defined according to the KDIGO guidelines (51). Serum creatinine was assessed preoperatively in a standardized preoperative blood collection (usually 1 day before the operation, including analysis of red and white blood cell count, platelet count, CRP, liver and kidney values, as well as blood clotting analysis) at the studied time points (Figure 1 Protocol of time points) up to 96 h after operation, as well as maximum creatinine value during the hospital stay. For assessment of CLS, we analyzed both positive fluid overload exceeding >10% bodyweight during

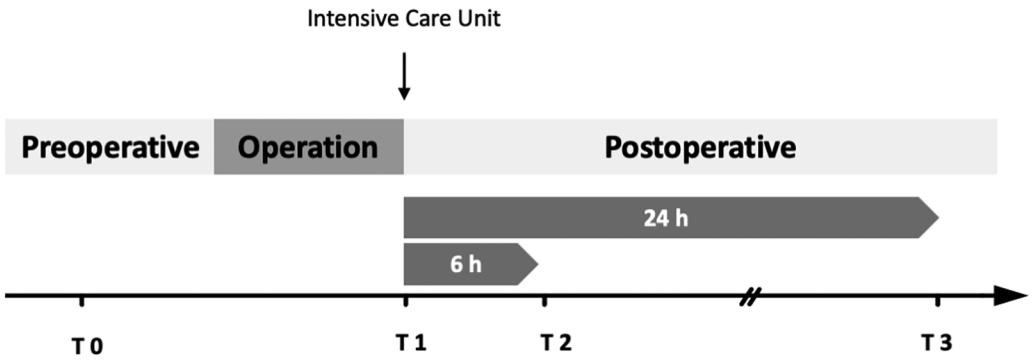


FIGURE 1
Protocol of time points for blood sample collection. T0 = Baseline, collection after induction of anesthesia via central venous line; T1 = collection upon arrival on the intensive care unit; T2 = 6 h after T1; T3 = 24 h after T1. Blood samples were obtained in Serum-Gel Microvette® 500, centrifuged at 26 × g for 10 min and stored at −80°C until analysis.

the first 72 h after operation and a subcutaneous-thoracic ratio (S/T) with a threshold of >12.6% calculated from a chest x-ray based on *Sonntag* et al., 24 to 72 h after operation (52). We utilized both tools as capillary leak syndrome is a frequently described complication after pediatric cardiac surgery, but we are currently lacking objective diagnostic criteria for this postoperative complication. Chest x-rays are part of postoperative diagnostics especially after extubation but are not performed routinely especially in pediatric patients. In our experience capillary leak syndrome is a clinical diagnosis. As fluid balance was assessed and analyzed postoperatively, we included this analysis. Chest-x-rays were analyzed by an experienced radiologist. x-rays were not included in the analysis if soft tissue was cut off. Fluid balance was documented for the first 72 h after operation (including the operation period) and fluid overload (FO) was calculated using the fluid balance method as follows (53):

$$\%FO = \frac{\text{Total fluid intake (ml)} - \text{Total fluid outtake (ml)}}{\text{pre} - \text{operative weight (kg)}} \times 100$$

Furthermore, the amount of blood products (erythrocytes, thrombocytes, fresh frozen plasma), clinical and laboratory chemical signs for infection and organ dysfunction (body temperature, CRP, leukocytes, urea, creatinine, aspartate transferase (AST), alanine transaminase (ALT), creatinine kinase (CK), creatinine kinase-myoglobin binding (CK-MB), lactate, and lactate dehydrogenase (LDH) and microbiological cultures were assessed.

For risk adjustment concerning in-hospital mortality we used the Risk Adjustment for Congenital Heart Surgery 1 (RACHS-1) consensus-based scoring system (54).

TABLE 1 List of analyzed serum biomarkers and assay IDs.

Protein	Assay ID
CIRBP	SPRCUS1273
IL-1β	SPRCUS1273
IL-6	SPRCUS1273
IL-8	SPRCUS1273
IL-10	SPRCUS1273
MCP-1	SPRCUS1273
FGF-23	SPRCUS1273
VEGF-A	SPRCUS1273
Ang-2	SPRCUS1355
SDC-1	SPRCUS1355
TM	SPRCUS1355

2.2 Magpix® bead-based analysis

Proteins were measured via MagPix® analysis (Merck/Millipore) using customized magnetic bead panels (Merck KGaA, Darmstadt, Germany) as listed in Table 1. Serum samples were defrosted and diluted according to manufacturer's recommendations. Briefly, for SPRCUS1273 neat samples were used, whereas samples were diluted at 1:8 for SPRCUS1355. For data acquisition, Xponent (Merck KGaA, Darmstadt, Germany, version 4.2) and Milliplex (Merck KGaA, Darmstadt, Germany, version 5.1.0.0) software were used. All samples showed a bead count of >100. Serum background was subtracted from the mean fluorescent intensities (MFI) and concentration (pg/mL) was determined using an 8-point calibration curve including matrix (best fit from Milliplex Analyst software was used). Single samples were measured. For determining the instrumental variance, pooled quality control (QC) samples were used as quality control ($n = 3$ analysed at the beginning, middle and end of the run). The biological variability was higher compared to the technical variability. One patient's sample at T3 was clotted in the well, consequently the assay SPRCUS1273 could not be run for this sample.

2.3 Statistical analysis

Numbers are presented as counts and percentages for categorical data and mean with standard deviation or median with range for continuous data. Data and respective tests were considered as a non-confirmatory, hypothesis-generating pilot study. The Wilcoxon test was used to compare post-surgery measurements with the pre-surgery biomarker value. No replacement of missing biomarker

values was applied for analysis. *P*-values of <0.05 were considered significant; adjustment for 3 parallel tests of the 3 post-surgery measurements compared to the pre-surgery measurement, in case of gender comparisons for the 4 parallel tested time points per biomarker was done with Bonferroni correction. Longitudinal analysis of biomarker data was conducted with linear mixed-effects models (R packages lmer4 and lmerTest) with splines of grade 3 for time including age, sex, and duration of surgery as covariables. Considering the complexity of the linear mixed-effects models regarding the available case numbers, effects with p-values < 0.1 were also considered as "significant" signals. IBM SPSS Statistics 28.0 and R version 4.0.2 was used for analysis.

TABLE 2 Demographic and clinical data.

	Sex	
	Male	Female
Number of patients: 19	10 (53%)	9 (47%)
Demographic data		
Median age (years), (range)	2 (0–15)	3 (0–18)
0–12 months	4 (40%)	3 (33%)
13–24 months	1 (10%)	
25 months – 12 years	3 (30%)	5 (56%)
>12 years	2 (20%)	1 (11%)
Diagnoses (number)		
	AS (1)	AI (1)
	ASD (1)	ASD (1)
	AVSD (2)	ccTGA, MA, PA (1)
	Ebstein's anomaly (1)	DORV, TGA, PS, VSD (1)
	CoA, AS, VSD (1)	HLHS (1)
	PA, VSD (1)	PAPVD (1)
	TA (1)	TOF (1)
	VSD (2)	TA (1)
		VSD, ASD (1)
Procedures (number)		
	Complex surgery (2)	Complex surgery (1)
	ASD closure (1)	Aortic valve replacement (1)
	Modified Fontan operation (1)	ASD closure (1)
	AVSD correction (1)	Modified Fontan operation (1)
	Pulmonary replacement (2)	Glenn Shunt (2)
	Ross operation (1)	PAPVD correction (1)
	VSD closure (2)	TOF repair (1)
		VSD closure (1)
Characteristics of operation and CPB (median; range)		
RACHS-1	2 (1–6)	2 (1–4)
Operation time (min)	343 (135–777)	331 (177–754)
CPB-time (min)	180 (60–480)	180 (60–480)
Aortic cross-clamp time (min)	45 (0–259)	67 (0–266)
Perfusion time (min)	133 (60–467)	162 (56–480)
Re-perfusion time (min)	22 (0–184)	13 (0–178)

AS, Aortic stenosis; AI, Aortic insufficiency; ASD, Atrial septal defect; AVSD, Atrioventricular septal defect; CoA, Coarctation; (cc)TGA,(congenital corrected) transposition of the great arteries; DORV, Double outlet right ventricle; HLHS, Hypoplastic left heart syndrome; MA, Mitral atresia; PA, Pulmonary atresia; PAPVD, Partial anomalous pulmonary venous connection; PS, Pulmonary stenosis; TA, Tricuspid atresia; TOF, Tetralogy of Fallot; VSD, Ventricuklar septal defect; RACHS-1, Risk Adjustment for Congenital Heart Surgery 1; CPB, cardiopulmonary bypass.

3 Results

For this pilot study, we enrolled 19 patients consisting of 10 males and 9 females. The median age was 2.9 years ranging from 0 to 18 years. Our cohort did not include neonatal patients. Demographic and data on diagnoses and procedures are summarized in Table 2. The study cohort represented a broad range of patients with congenital heart disease concerning both age and complexity of anomalies treated at our center. All patients survived until hospital discharge. On-pump beating cardiac surgery was performed in 5 patients (2 pulmonary valve replacements, 2 Glenn-anastomosis, and 1 modified-Fontan procedure). Aortic cross-clamping was necessary in 14 patients. In 6 patients systemic mild-moderate hypothermia (32–35.9°C) and in 5 patients moderate deep hypothermia (<30°C–31.9°C, with the lowest temperature 28°C) was applied, whereas 8 patients were kept at normothermia during CPB.

Duration of mechanical ventilation and maximum as well as mean vasoactive-inotropic score (VIS) was comparable in both male and female patients. However, duration of stay on the PICU was longer in male compared to female patients (median 31 h and 9 h, respectively as summarized in Table 3). Acute kidney injury as defined by KDIGO criteria, infections, and arrhythmia presented frequent complications in our patient cohort (Table 3) (51). One patient showed respiratory failure, hemodynamic instability, and increased demand for volume and catecholamines after modified Fontan procedure and was re-intubated during the first 24 h after initial surgery (55, 56). After catheterization on the first postoperative

TABLE 3 Perioperative characteristics.

	Sex	
	Male	Female
Number of patients: 19	10 (53%)	9 (47%)
Mechanical ventilation (h)	9.7 (5.5–270)	7.6 (4.9–339)
Length of PICU stay (h)	30.8 (7.2–463)	8.75 (7.2–890)
VIS mean (median; range)		
1–24 h	0.68 (0.01–13.02)	0.30 (0–7.2)
25–48 h	0 (0–6.7)	0 (0–4.57)
49–72 h	0 (0–5.1)	0 (0–1.97)
1–72 h	0.33 (0–7.6)	0.19 (0–4.61)
VIS max (median; range)		
1–24 h	3.3 (0.2–26.02)	3.46 (0–12.89)
25–48 h	0 (0–11.8)	0 (0–6.29)
49–72 h	0 (0–16.4)	0 (0–2.91)
1–72 h	3.33 (0.2–26.02)	3.46 (0–12.89)
Complications (number)		
Infection	1	3
Arrhythmia	2	0
Acute kidney injury	3 (30%)	2 (22%)
Postoperative S/T-ratio >12.6% up to 72 h (range in %)	1 (14.1)	2 (13.7–16.8)
Fluid overload > 10% (range)		
24 h	6 (2–16)	4 (−1–16)
48 h	0 (−9 - 4)	0 (−7 - 3)
72 h	0 (−7 - 0)	0 (−6 - 3)
Cardiac arrest	0	0

PICU, Pediatric intensive care unit; VIS, Vasoactive-inotropic Score; Max, maximum; S/T-ratio, Subcutaneous-thoracic ratio.

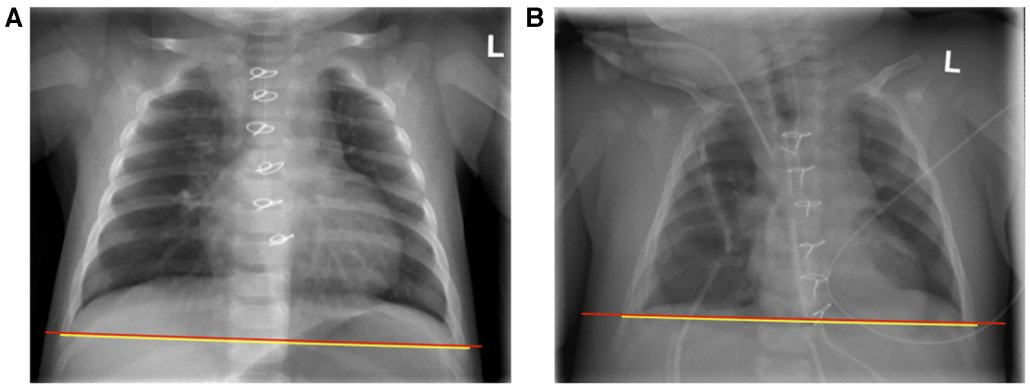


FIGURE 2
Example of chest x-ray analysis for assessment of subcutaneous-thoracic (S/T) ratio according to *sonntag* et al. (52) (**A**) Pre- and (**B**) postoperative x-rays of a patient with an S/T-ratio 16.8.

day, the patient received a re-thoracotomy and takedown of the Fontan-procedure. Another patient showed an atrioventricular block III° postoperatively and received a transvenous pacemaker 10 days after initial cardiac surgery. S/T-ratio and fluid overload were assessed as criteria for CLS. In 7 patients S/T ratio was not analyzable due to a cut off soft tissue on the x-ray. 3 patients showed an S/T-ratio >12.6% during the first 72 h after CPB (an exemplary chest x-ray analysis is shown in Figure 2). During the first 24 h after operation both male and female patients presented a median fluid overload of 16% (Table 3). None of the enrolled patients died during hospitalization, 30-day mortality was 0% in both male and female patients. One patient with univentricular heart physiology was released after initial shunt operation and 6 weeks later readmitted to another hospital due to gastroenteritis. Two days after readmission the patient had an in-hospital cardiac arrest most likely due to shunt thrombosis, was transferred to our hospital under resuscitation conditions, where we ended the treatment due to the poor prognosis.

3.1 Analysis of biomarkers

We collected blood and urine samples at the respective timepoints for all patients (Figure 1. Protocol of timepoints). The study protocol included blood and urine sample collection at the same timepoints. The urine samples were used to discover new urinary biomarker for early detection of acute kidney injury using proteomics analysis. However, not in all 19 patients included in the feasibility study urine samples could be collected during all timepoints. Furthermore, as this manuscript focuses on the feasibility of the customized magnetic bead panels, data on proteomic analysis will be published separately. For 15 patients, blood samples were obtained at all timepoints. In 3 patients T3 was not obtained as patient care on PICU did not allow sample acquisition at that timepoint, and one patient needed a re-thoracotomy at this timepoint.

Our first objective—the reliable measurement of protein concentrations in the serum of children in the clinical setting—was achieved. In short, the analyzed biomarkers could be detected using the customized magnetic bead panels. For IL-6, IL-8, MCP1, and FGF-23 a value above the limit of detection/quantification (LOD/Q) could be quantified in all samples. For CIRBP $n = 9$ samples showed values below the LOD/Q, while for IL-1β $n = 10$ sample values were below the LOD/Q. For IL-10 and VEGF-A one sample each was below LOD/Q.

3.1.1 Cytokines analyzed

IL-6, IL-8, MCP-1, and IL-10 all showed low baseline serum concentrations at induction of anesthesia (T0; Figure 3). In comparison to baseline values, both pro-inflammatory cytokines IL-6 and IL-8 were significantly increased at all postoperative timepoints (T1, IL-6 $p < 0.001$, IL-8 $p < 0.001$; T2, IL-6 $p < 0.001$, IL-8 $p < 0.001$; T3, IL-6 $p = 0.002$, IL-8 $p = 0.002$). Furthermore, IL-10 serum concentration was significantly increased at all postoperative timepoints (T1, $p < 0.001$; T2, $p < 0.001$; T3, $p = 0.007$). MCP-1 serum concentration was significantly higher directly after surgery (T1, $p = 0.025$,). Individual differences between baseline and the three postoperative time points are displayed in Figure 4, for all cytokines analyzed.

IL-1β baseline levels were generally higher than other analyzed cytokines, and serum concentrations showed a non-significant increase directly after surgery (T1). Overall, no significant increase in IL-1β serum concentration was observed (Figures 3, 4).

Furthermore, we examined the course of serum biomarkers concentrations with linear mixed-effects models adjusted for age, sex, and duration of surgery (Figure 5). IL-1β, IL-10, and MCP-1 serum concentrations increased directly after surgery and decreased at 6 and 24 h after operation (T2 and T3) upon returning to baseline levels. Whereas IL-6 showed a persistent increased concentration directly after operation, IL-8 peaked at T2 (6 h after operation) and returned to baseline level over time. Furthermore, linear mixed-effect models for the course of IL-1β serum concentration revealed the interaction of female sex and time as potentially significant (β(SE) = 14.3(7.7), $p = 0.071$; Table 4), indicating a more pronounced time course for female sex. Interestingly, we observed a tendency in increased IL-1β serum concentrations at all analyzed timepoints in male compared to female patients, however, this difference was not statistically significant (Figure 6).

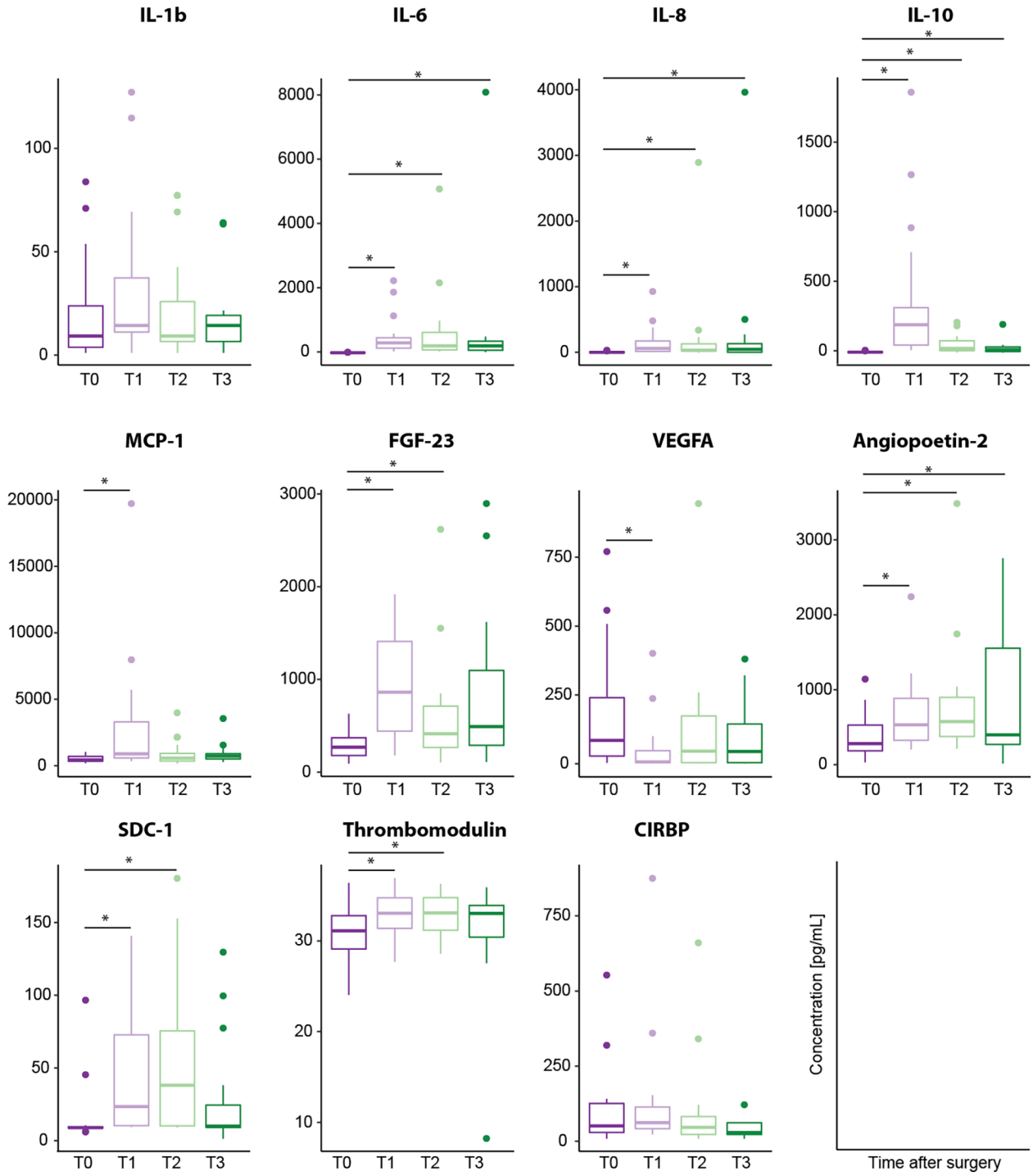


FIGURE 3
Biomarker serum concentration [pg/ml] analyzed using customized magnetic bead panels. Timepoints of blood sample collection: T0 = baseline, at anesthesia induction; T1 = arrival on the intensive care unit; T2 = 6 h after T1; T3 = 24 h after T1. Dots represent statistical outliers. Statistical analysis was performed using the Wilcoxon test; *p*-values were adjusted for 3 parallel tests (all post-operative measurements vs. baseline) and $*p < 0.05$ was considered statistically significant.

3.1.2 Biomarkers for endothelial dysfunction

Serum concentrations of SDC-1, Ang-2, and TM increased significantly after operation. SDC-1 serum concentration was low at induction of anesthesia and showed a significant increase both directly (T1, $p < 0.001$) and 6 h after surgery (T2, $p = 0.002$) in comparison to baseline (T0) (Figures 3A,B). Furthermore, TM serum levels increased directly after surgery (T1, $p = 0.042$) and 6 h (T2, $p = 0.047$) compared to baseline values (Figures 3, 4) with serum concentrations undulating around 30 pg/ml (Figure 3A). Ang-2 serum concentrations

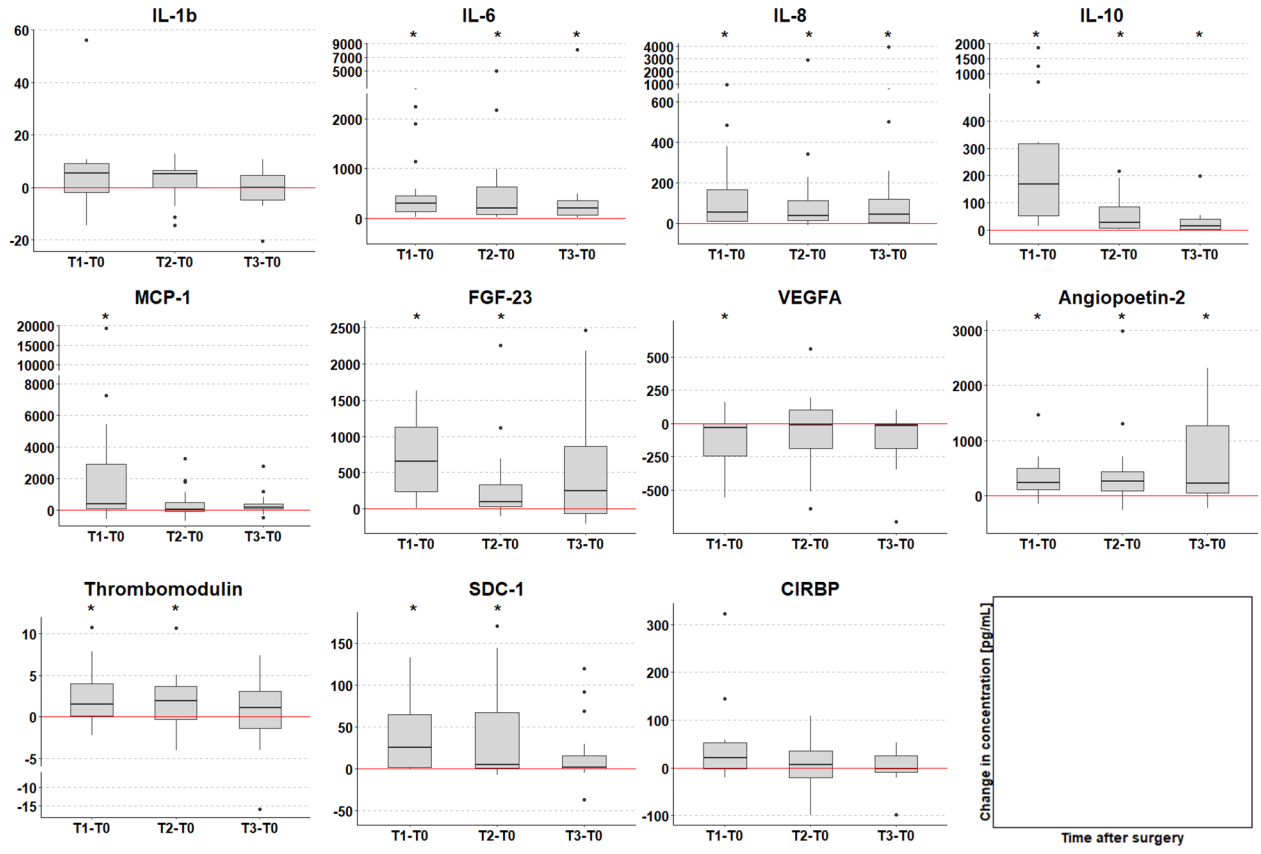


FIGURE 4
Change in biomarker serum concentration [pg/ml] compared to T0 (time of anesthesia induction). Timepoints of post-surgery blood sample collection: T1 = arrival on the intensive care unit (median 8 h after T0); T2 = 6 h after T1; T3 = 24 h after T1. The red line at 0 indicates no change, positive values increase and negative values decrease compared to T0. Dots represent statistical outliers. *p*-values were adjusted for 3 parallel tests; stars indicate significant changes ($p < 0.05$).

increased significantly at all postoperative timepoints (T1, $p = 0.002$; T2, $p = 0.004$; T3, $p = 0.016$, Figures 3, 4).

VEGFA showed a different dynamic with a significant decrease in serum levels directly after surgery (T1, $p = 0.039$) in comparison to baseline (Figures 3, 4).

Analyzing the course of biomarker serum concentrations, SDC-1 increases postoperatively, showing a peak at 6 h after operation, whereas both TM and Ang-2 serum concentration increase over time (Figure 5). Furthermore, modelling the course of SDC-1 and TM serum concentrations, we found age and/or the interaction of time with age, female sex, or duration of surgery to show statistical significance (all $p < 0.1$, Table 4). For TM serum concentrations indicating stronger fluctuation with higher age and increasing duration of surgery flattened by female sex. For SDC-1 suggesting a generally lower level with increasing age and stronger fluctuation with increasing duration of surgery flattened by female sex. The course of Ang-2 serum concentration also seems to be influenced by age and duration of surgery but not by female sex (Table 4).

3.1.3 Fibroblast growth factor (FGF-23)

Fibroblast growth factor FGF-23 has been previously described as a biomarker for acute kidney injury (AKI) after pediatric cardiac surgery (57–60). As we plan to analyze potential biomarkers for acute kidney injury in our clinical trial, we included FGF-23 in our customized magnetic bead panel. FGF-23 concentration significantly increased directly after operation as compared to preoperative serum levels (T1, $p < 0.001$), and remained significantly higher until 6 h after operation (T2 $p = 0.007$, Figures 3, 4).

Analyzing the course of serum concentration with linear mixed-effect models, FGF-23 peaked directly after surgery, decreased 6 h after surgery, and increased again 24 h after surgery (Figure 5). Potential variables of interest influencing the course of FGF-23 serum concentration was duration of surgery ($p < 0.1$, Table 4), tending to increase fluctuation.

3.1.4 CIRBP Serum concentration

CIRBP was detectable at all investigated timepoints. Serum concentration increased postoperatively although not statistically relevant (Figure 3). In comparison to baseline, CIRBP showed an increase at T1 then returning to baseline levels over time (Figures 4, 5). In the longitudinal model we found a signal that duration of surgery had a significant influence on the course of CIRBP serum concentration ($p < 0.1$, Table 4). There was no significant sex related difference in CIRBP serum concentrations (Figure 6).

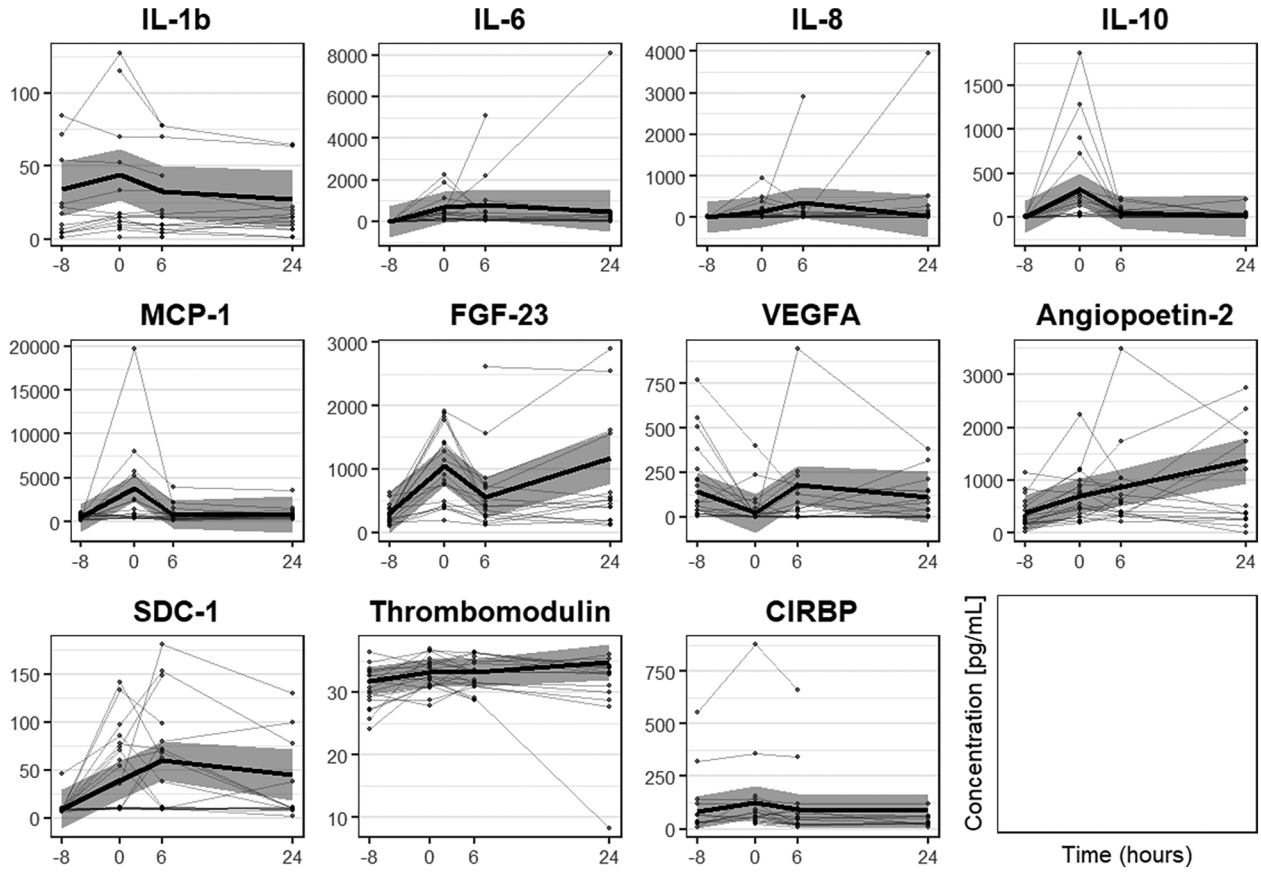


FIGURE 5
Course of biomarker serum concentration [pg/ml] analyzed with linear mixed-effects models adjusted for age, sex and duration of surgery. The model estimation is shown as bold black line with 95% confidence interval. Dots with connecting lines represent individual courses of biomarker serum concentrations for single patients. Timepoints of blood sample collection: T0 = at anesthesia induction (median 8 h before T1); T1 = arrival on the intensive care unit (=0 h); T2 = 6 h after T1; T3 = 24 h after T1.

As CIRBP is known to be upregulated by mild to moderate hypothermia (28–34°C) (40, 42), we analyzed CIRBP serum concentrations in patients treated with hypothermia during CPB. However, we did not detect significant differences in CIRBP serum levels between patients undergoing normothermic, mild-moderate hypothermic, or moderate deep hypothermic CPB.

4 Discussion

As both systemic inflammatory reactions and CLS are frequent complications after cardiac surgery in children with CHD, early diagnosis and treatment of patients at risk remain challenges in postoperative clinical management. This feasibility study was conducted to evaluate customized multiplex magnetic bead panels for the analysis of proinflammatory cytokines, previously described biomarkers for vascular leakage, acute kidney injury, and CIRBP in pediatric patients undergoing cardiac surgery at our center. CIRBP has been previously described as an inflammatory mediator and its serum or plasma concentration has been analyzed in adults after septic or hemorrhagic shock as well as after cardiac surgery. To our knowledge this is the first study to analyze serum concentrations of CIRBP in children with CHD before, during, and after cardiac surgery.

Peripheral blood concentrations of CIRBP have so far been analyzed using western-blot analysis and Enzyme-linked Immunoabsorbant Assay. As far as we know, CIRBP has not been analyzed using a customized magnetic bead panel and furthermore has not been detected in a pediatric cohort. Merck/Millipore established the customized magnetic bead panel and validated the measurements for our feasibility study using our serum samples. Using this technique, we were able to detect CIRBP as well as the other biomarkers including cytokines (IL-1β, IL-6, IL-8, MCP-1, and IL-10), markers for endothelial dysfunction (SDC-1, TM, Ang-2, and VEGF), and FGF-23 as a marker for kidney injury in a minimal serum sample volume (25 µl) in all enrolled patients. As blood sample volume is an important restriction in pediatric clinical studies, the ability to detect multiple analytes in a minimal serum volume is an important goal. Especially as we plan to enroll patients of different ages including neonates, infants, and toddlers up to adolescents with CHD for a larger follow-up clinical trial, the successful quantification of all analyzed biomarkers using the customized magnetic panel is an important achievement of this feasibility study.

10.3389/fcvm.2024.1247472

TABLE 4 Estimates of the linear mixed-effects models for the course of biomarkers over the 4 time points of measurement adjusted for age, sex and duration of surgery, and respective interaction terms with time. For significant parameters the *p*-value is shown in bold fond. Timepoints of blood sample collection in the model were: −8 h (T0) = at anesthesia induction; 0 h (T1) = arrival on the intensive care unit; 6 h (T2) = 6 h after T1; 24 h (T3) = 24 h after T1.

	IL1b		IL6		IL8		IL10		MCP1		FGF23	
	ß (SE)	*p*	ß (SE)	*p*	ß (SE)	*P*	ß (SE)	*p*	ß (SE)	*p*	ß (SE)	*p*
(Intercept)	37.1 (18.2)	0.054	3.3 (708.1)	0.996	11.9 (365.6)	0.974	15.9 (182)	0.931	558.5 (1,522.7)	0.715	319.8 (313.0)	0.313
Age	1.3 (1.3)	0.334	−0.1 (52.4)	0.999	0.0 (27.1)	0.999	−0.4 (12.7)	0.974	−23.9 (112.7)	0.833	−3 (23.2)	0.897
Time	−23.5 (20.5)	0.262	1,137 (2,146.5)	0.599	482.6 (1,155.3)	0.678	−829.7 (524.1)	0.121	−5,159 (4,630)	0.271	−1,516.5 (798.2)	0.065
Time²	−18.9 (18.2)	0.306	−111.8 (1,589.2)	0.944	88.5 (857.7)	0.918	338.6 (409.3)	0.413	1,604.6 (3,428.6)	0.642	−288.9 (587.6)	0.626
Time³	−14.8 (11.3)	0.202	−120.2 (1,025.3)	0.907	411.9 (548.2)	0.456	−335.4 (250.9)	0.188	−2,270.8 (2,210.7)	0.310	−769.5 (386.4)	0.053
Female sex	−23.1 (13.5)	0.103	−1.0 (539.9)	0.998	−1.6 (278.8)	0.995	−5.5 (133)	0.967	69 (1,161)	0.953	−56.7 (238.6)	0.813
Duration of surgery	−1.6 (2.4)	0.531	0.0 (98.9)	1.000	0.1 (51.1)	0.998	−0.7 (24.1)	0.978	5.5 (212.8)	0.979	1.8 (43.7)	0.967
Age *time	−0.9 (1.3)	0.476	14.4 (152)	0.925	−35.9 (82)	0.663	15.8 (37.1)	0.674	311.3 (327.9)	0.348	1.8 (56.2)	0.974
Age * time²	0.8 (1.2)	0.489	−102.9 (115.2)	0.377	−33.4 (62.2)	0.594	−6.6 (28.4)	0.816	−216.5 (248.5)	0.389	−23.6 (42.5)	0.583
Age * time³	−0.8 (0.6)	0.221	−65.2 (70.2)	0.358	6.3 (37.8)	0.868	4.1 (17.1)	0.812	136.2 (151.4)	0.373	−2.5 (26.1)	0.924
Female sex * time	18.0 (14.2)	0.212	−318.5 (1,578.9)	0.841	−865.1 (851.6)	0.314	−243.4 (385.5)	0.531	3,240.2 (3,406.3)	0.347	186.2 (584.7)	0.752
Female sex * time²	2.6 (13)	0.844	−254.6 (1,203)	0.833	138.1 (648.6)	0.832	133.9 (299.9)	0.658	−1,380.4 (2,595.3)	0.598	−137.7 (445.9)	0.759
Female sex * time³	14.3 (7.7)	0.071	744.6 (784.5)	0.348	392.6 (422)	0.356	−76.2 (191.7)	0.693	1,451.1 (1,692.2)	0.396	−431.1 (291.8)	0.147
Duration of surgery * time	1.2 (2.9)	0.679	−103.4 (313.4)	0.743	44.2 (168.3)	0.794	49.6 (76.4)	0.519	−274.1 (676)	0.687	110 (117.1)	0.353
Duration of surgery * time²	3.0 (2.1)	0.173	322.7 (229.3)	0.167	67.7 (123.7)	0.587	−2.3 (56.6)	0.967	440.3 (494.7)	0.378	274.4 (84.8)	0.002
Duration of surgery * time³	0.7 (1.6)	0.685	92.1 (167.2)	0.584	−74.6 (88.2)	0.401	15.3 (40.5)	0.707	−92.7 (360.2)	0.798	187.6 (64.7)	0.006

cont.	VEGFA		Ang-2		TM		SDC1		CIRBP	
	ß (SE)	*p*	ß (SE)	*p*	ß (SE)	*p*	ß (SE)	*p*	ß (SE)	
(Intercept)	168.7 (105.5)	0.116	195.7 (330.1)	0.557	74.6 (103.6)	0.481	10.3 (19.6)	0.602	33.2 (2.1)	**<0.001**
Age	−16.2 (7.8)	**0.043**	−20.4 (24.4)	0.409	−3.6 (8.1)	0.660	−0.3 (1.5)	0.819	−0.3 (0.2)	0.093
Time	686.5 (297.7)	**0.026**	−364.4 (775.7)	0.641	−117.5 (82)	0.163	−34.3 (52.6)	0.518	−0.8 (5.2)	0.882
Time²	−52.8 (219.7)	0.811	152.7 (597.4)	0.800	−63.2 (69.3)	0.369	−45.3 (40.5)	0.270	1.2 (4.0)	0.772
Time³	272.8 (143.2)	0.063	−365.6 (376.5)	0.337	−58.2 (48.1)	0.236	−28 (25.4)	0.277	−3.5 (2.5)	0.177
Female sex	86.8 (80.4)	0.286	−67 (251.7)	0.791	91.5 (80.3)	0.270	3.3 (15.0)	0.825	−2.1 (1.6)	0.197
Duration of surgery	8.6 (14.7)	0.562	47.8 (46.1)	0.307	−4.0 (14.4)	0.784	0.1 (2.7)	0.970	0 (0.3)	0.924
Age *time	6.3 (21.3)	0.770	112.5 (57.4)	0.057	2.3 (6.1)	0.703	7.1 (3.9)	0.074	0.3 (0.4)	0.386
Age * time²	17.9 (16)	0.270	11.7 (44.0)	0.791	0.3 (7.2)	0.966	1.7 (3.0)	0.580	0.2 (0.3)	0.524
Age * time³	3.6 (9.9)	0.720	−45.4 (26.6)	0.096	2.6 (3.4)	0.457	5.8 (1.8)	**0.002**	−0.2 (0.2)	0.272
Female sex * time	−448.5 (223.4)	0.051	−296.4 (591.5)	0.619	−20.9 (63.8)	0.746	−57 (40.1)	0.163	0.5 (4.0)	0.906
Female sex * time²	−182.5 (168)	0.283	−279.5 (458.1)	0.545	22.3 (60.7)	0.716	−8.1 (31.0)	0.795	0.2 (3.1)	0.955
Female sex * time³	−158.8 (110.5)	0.158	−498.5 (300.4)	0.104	−10.8 (34.5)	0.756	−36.4 (20.2)	0.079	−4.9 (2.0)	**0.020**
Duration of surgery * time	−68.7 (43.7)	0.123	46.3 (108.4)	0.672	9.2 (12.7)	0.474	10.1 (7.4)	0.177	−0.1 (0.7)	0.921
Duration of surgery * time²	−22.3 (31.7)	0.485	145.5 (85.2)	0.095	16.5 (9.4)	0.089	18.4 (5.8)	**0.003**	0.2 (0.6)	0.673
Duration of surgery * time³	−36.7 (23.8)	0.129	231.7 (60.7)	**<0.001**	3.8 (7.6)	0.619	3.8 (4.1)	0.351	1.1 (0.4)	**0.011**

4.1 Cytokines

We analyzed pro-inflammatory cytokines IL-1β, IL-6, and IL-8 serum concentrations in our cohort. Both IL-6 and IL-8 levels were increased directly after operation and remained increased during all analyzed postoperative timepoints compared to baseline values (Figures 3, 4). Analysis of the course of biomarker serum concentrations over time using linear mixed-effects models, IL-6 remained upregulated during all postoperative timepoints, whereas IL-8 showed a peak at 6 h and decreased 24 h after surgery (Figure 5). We did not see a significant regulation of IL-1β during the analyzed timepoints compared to baseline levels (Figures 3, 4), however linear mixed-effects models showed IL-1β increasing directly after operation and returning to baseline levels over time (Figure 5). The regulation of both IL-6 and IL-8 concentrations after CPB are consistent with previous clinical studies analyzing cytokine concentrations in children and infants after cardiac surgery (61–67). *Allan* et al. analyzed various cytokine plasma concentration in infants (median age 37 days) undergoing cardiac surgery at similar timepoints up to 24 h after CPB. Although this study concentrated on one age group, they detected similar dynamics of cytokine regulation with both IL-6 and IL-8 being upregulated directly after cardiac surgery (61). Furthermore, we recently analyzed cold-shock proteins as well as

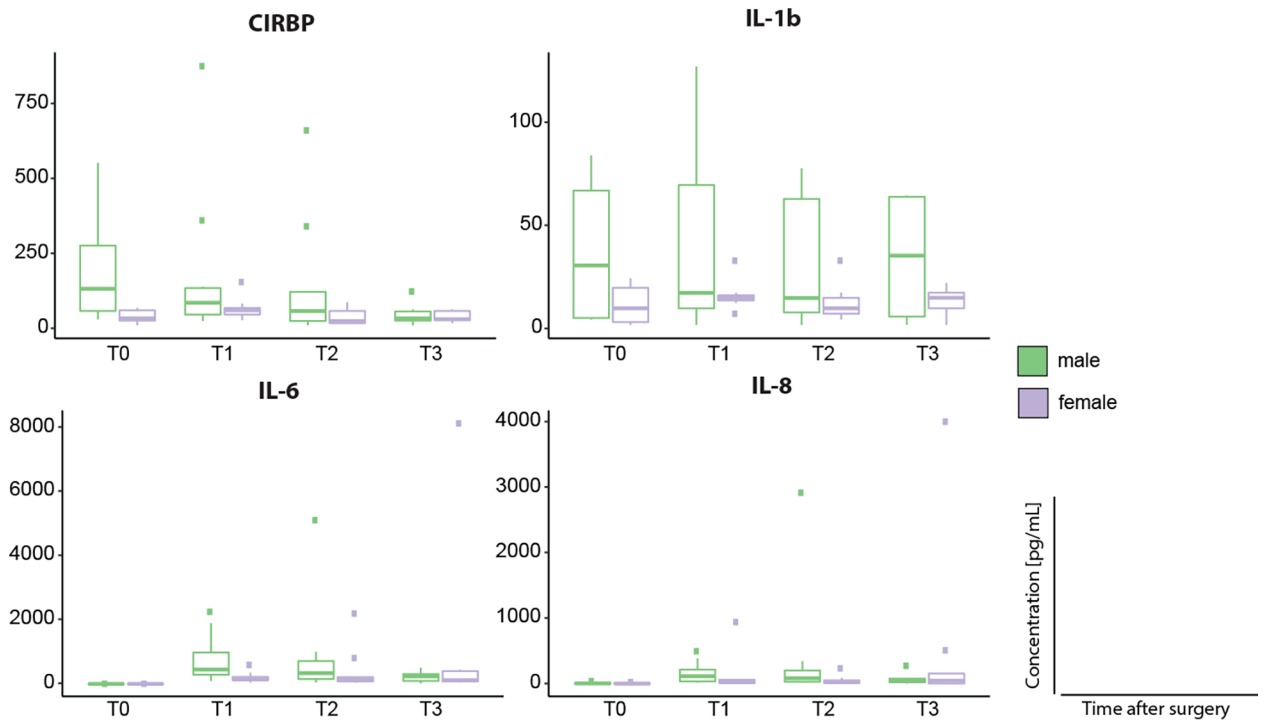


FIGURE 6
Sex associated differences of CIRBP, IL-1β, IL-6 and IL-8 serum concentrations [pg/ml]. Timepoints of blood sample collection: T0 = baseline, at anesthesia induction; T1 = arrival on the intensive care unit; T2 = 6 h after T1; T3 = 24 h after T1. Dots represent statistical outliers.Statistical analysis was performed using the Mann-Whitney test; *p*-values were adjusted for 4 parallel tests for each biomarker; none of the differences, also due to small case numbers, were statistically significant.

cytokines in dry blood spot samples of 23 patients with CHD of varying ages and diagnoses (median age 19 years) undergoing CPB and hypothermia. Both IL-6 and IL-8 were significantly increased after CPB and stayed elevated up to 24 h after surgery (62). However, in our previously published patient cohort we also detected a significant increase in IL-1β 24 h after CPB (62), which we did not see in our feasibility study. However, postoperative regulation of IL-1β has been controversial in clinical studies so far. Whereas no significant regulation of IL-1β has been reported in neither infants nor children after CPB (61, 66), there have been reports that IL-1β levels are significantly elevated in direct response to CPB in infants (63). As the median patient age was significantly higher in our last cohort the differing secretion dynamics might be due to age difference. Nevertheless, larger patients' cohorts are needed to further investigate a possible age dependency.

Analysis with linear mixed-effects models showed time and female sex as potential variables of interests in IL-1β serum concentration course (Table 4). Furthermore, we detected a trend in increased IL-1β serum concentrations at all timepoints in female patients (Figure 6) However, as we conducted a hypothesis-generating, non-confirmatory clinical study these signals need to be evaluated in future studies.

Furthermore, we analyzed the chemokine MCP-1 as well as the anti-inflammatory cytokine IL-10. Analyzing the course of serum concentration over time using linear mixed-effects models suggests MCP-1 and IL-10 to have a similar regulation dynamic. Both cytokines were upregulated directly after cardiac surgery and decreased back to baseline levels over time (Figure 4). This observed regulation is consistent with the results of various clinical studies analyzing infants and children after CPB (61, 64–66). We previously described an increase in both MCP-1 and IL-10 directly after CPB and decrease to baseline levels 24 h after surgery (62). However, other studies focusing on infants after pediatric cardiac surgery report different regulation of IL-10. *Gu* et al. detected an increase of IL-10 concentration directly after CPB showing a peak at 12 h after surgery before decreasing (63). While *Trotter* et al. showed that IL-10 levels remained elevated up to 7 days after CPB (67). As we did not analyze cytokine concentrations 12 h after CPB, we might have missed a potential further increase of IL-10 in our patient cohort. Nevertheless, a possible age-dependency needs to be investigated further.

4.2 Biomarker for endothelial dysfunction

SDC-1, Ang-2, and TM serum concentrations increased after operation. Both SDC-1 and TM increased both directly as well as 6 h after operation, whereas Ang-2 was upregulated during all postoperative timepoints as compared to baseline (Figures 3, 4). *In vivo* studies have shown that ischemia/reperfusion-induced injury leads to glycocalyx shedding and a significant increase in SDC-1

release (68). Various clinical studies have reported that SDC-1 concentration increases after cardiac surgery in both adults and pediatric patients (14, 38, 39, 69). *Bruegger* et al. analyzed SDC-1 in infants undergoing CPB with both beating heart aortic clamping and deep hypothermic circulatory arrest. They report a significant upregulation of serum SDC-1 concentration directly after CPB with SDC-1 remaining upregulated until intensive care unit (ICU) admission (39). In adults undergoing coronary artery bypass grafting with or without the use of CPB, SCD-1 was significantly upregulated during surgery and normalized during the first 24 h after surgery (69). However, previous clinical studies analyzing SDC-1 after pediatric cardiac surgery analyzed SDC-1 levels up to 2 h after surgery (38, 39). To our knowledge, this is the first report of SDC-1 levels 24 h after CPB in children. Analysis of the course of biomarker serum concentrations reveals a differing dynamic of the analyzed biomarkers for endothelial dysfunction as SDC-1 peaks at 6 h after operation whereas both Ang-1 and TM concentrations increase during the analyzed postoperative timepoints (Figure 5).

Changes in TM concentration after pediatric cardiac surgery have not been studied so far. TM has been shown to be associated with poor outcome in both children and adults suffering from sepsis (18, 19). In septic adults, TM serum concentration correlated with the risk of development of disseminated intravascular coagulation, multiple organ failure, or death during ICU stay (18, 19). TM enables thrombin-mediated activation of protein C playing a part in coagulation, fibrinolysis, and inflammation (70, 71). As it is released upon inflammation and endothelial cell damage (72), it remains an interesting potential biomarker for SIRS and CLS and its' regulation after pediatric cardiac surgery warrants further investigation.

Whereas Ang-2 levels increased after CPB, we report a significant decrease of VEGF-A directly after CPB and a slight increase during later timepoints although not statistically significant (Figures 3, 4). *Giuliano* et al. analyzed both Ang-2 and VEGF-A plasma concentrations in children undergoing CPB (median age 5 months) at the same timepoints as in our study (prior to operation, 0, 6 and 24 h after CPB). Ang-2 was significantly elevated 6 h after CPB and remained upregulated until 24 h after CPB. VEGF-A concentrations, however, were not significantly regulated after CPB (35).

SDC-1 has been associated with severe acute kidney injury as well as prolonged duration of stay on the intensive care unit as well as hospital stay after pediatric CPB (38). Ang-2 concentration at 6 h after CPB has been reported to show a correlation with CPB time and surgery complexity as assessed via RACHS-1. Furthermore, Ang-2 concentration was associated with the duration of stay on the ICU (35). VEGF concentration has been shown to be elevated after CPB in neonates and was associated with postoperative capillary leak syndrome (36). Elevated preoperative as well as postoperative VEGF-A concentrations have been associated with cyanotic congenital heart disease (36, 37).

Analysis with linear mixed-effects models revealed age, female sex, and duration of surgery as potential variables to influence both SDC-1 and TM course of serum concentrations over time, whereas Ang-2 concentration seems to be influenced by age and duration of surgery (Table 4). To our knowledge this has not been reported so far, however our study cohort represents a small and heterogenous group both in relation to age and cardiac defect. Additionally, there was no neonatal patient included in our study cohort. Therefore, both associations with cardiac anomalies as well as age and adverse clinical outcome need to be investigated further.

4.3 Fibroblast growth factor (FGF-23)

FGF-23 has been associated with AKI after CPB in children (59, 60). FGF23 is an osteocyte-derived hormone playing an important role in phosphate and vitamin D homeostasis (73). Serum FGF23 has been shown to be increased in both early stages of chronic kidney disease (74) as well as in early stages of acute kidney injury (75, 76). Preoperative FGF23 serum concentration was associated with AKI development after CPB suggesting FGF23 as a suitable screening marker for AKI (60). Additionally, FGF23 has also been described to be associated with inflammatory processes in experimental studies (77). We report a significant increase at both directly as well as 6 h after surgery in our patient cohort (Figures 3, 4). AKI occurred in 5 patients (26%, 22% in female and 30% in male patients). In accordance with AKI, FGF-23 serum concentrations seem to be influenced by the duration of surgery (Table 4). We report that FGF23 serum concentrations could be measured adequately using our customized panel.

4.4 CIRBP

CIRBP has been reported as a key player in the innate inflammatory response. Both *in vitro* and *in vivo* studies have shown that CIRBP enhances inflammation by inducing proinflammatory cytokines and DAMPs release (44). CIRBP antiserum as well as blockage of its receptors have been shown to reduce systemic inflammation, organ dysfunction, and mortality in *in vivo* sepsis and hemorrhagic shock model (44, 47). We could detect CIRBP in all patients, with increasing serum concentration after cardiac surgery (Figures 3, 4). Furthermore, linear mixed-effects models revealed duration of surgery having a potential influence on CIRBP serum concentrations (Table 4). However, as the purpose of this feasibility study was to establish the validity of our customized magnetic bead panel in order to analyze multiple analytes using only a small sample volume, the question of the present study is related to the measurability of biomarkers in the setting of CPB in children. Due to the size of our cohort, the potential value and significance of CIRBP as a biomarker was not assessed in this study. Nevertheless, the stable course for 17 out of 19 patients could raise the question if for the 2 patients with higher initial values and different progression the post-surgery recovery was divergent from the rest of the group. This has to be investigated in a larger sample. Following the positive results of this feasibility study, we further conducted a larger trial including 108 patients and are in the process of analyzing the results. To

our knowledge this is the first study analyzing CIRPB in a pediatric population. So far, CIRBP has been detected in peripheral blood of patients suffering from septic and hemorrhagic shock (44, 46) with high CIRBP concentrations correlating with a poor survival rate (46). Furthermore, CIRBP has been detected in adult patients after cardiac surgery with CPB showing a correlation between duration of CPB and postoperative lung dysfunction (78). Whereas serum CIRBP was detectable in all patients suffering from hemorrhagic shock with a mean blood collection time of 43 h after onset of shock, CIRBP could not be detected in the control group (44). *Zhou et al.* report elevated plasma levels of CIRBP in septic patients and suggests CIRBP as an independent predictor for sepsis mortality as non survivors showed significantly higher CIRBP levels compared to survivors (46). *Chen* et al. analyzed CIRBP plasma concentration using Enzyme-linked immunosorbent-Assay in 31 adult patients (median age 60 years; 17 male, 14 female) undergoing cardiovascular surgery at 1 day before surgery, as well as 6 h, and 1, 3, and 5 days after surgery. They observed a significant increase in serum CIRBP 6 h after CPB that returned to baseline levels 5 days after surgery. CIRBP plasma levels were upregulated up to 1,300pg/ml postoperatively. Furthermore, they also observed a correlation between increased CIRBP concentrations with increasing CPB duration (78).

Interestingly, hypothermia did not have an influence on CIRBP concentration in serum. We recently investigated the gene expression of both cold-shock proteins RNA-binding motif 3 (RBM3) and CIRBP in patients treated with targeted-temperature management (33°C for 24 h) after cardiac arrest. CIRBP mRNA expression showed a tendency of upregulation after 24 h of cooling and decreased significantly during the following 48 h, whereas RBM3 was significantly elevated after 24 h of cooling (79). *Chen* et al. also did not observe a significant regulation of CIRBP due to hypothermia during CPB (mean temperature during CPB 31.6 ± 1.4°C) (78). However, the number of patients treated with hypothermia in our study was small and varied in temperatures between 28 and 32.1°C. Therefore, potential effects due to hypothermic treatment might not have been detected. Furthermore, we did not analyze the effect of body temperature after CPB on CIRBP concentration. As both slow rewarming after hypothermia during CPB and hyperthermia/fever could occur after pediatric cardiac operation, the possible effect of body temperature following CPB on CIRBP serum concentration needs to be analyzed in larger patients cohorts. In the following clinical study, we plan on assessing temperature along with other vital parameters up to 72 h after cardiac operation to investigate possible correlations.

4.5 Sex-associated differences

It is known that there are sex dependent differences concerning the incidence of specific cardiac defects in CHD. Transposition of the great arteries and left-sided obstructions occur more often in males, whereas atrial septal defects and Ebstein's anomalies are reported to be more frequent in female patients (80). Moreover, retrospective analyses report that male patients are more likely to undergo complex high-risk cardiac surgery (81). This aspect might influence early postoperative morbidity and potentially biomarker concentration. However, data on sex associated differences regarding postoperative mortality is to date inconsistent (82, 83). *Trotter* et al. investigated sex related differences in postoperative cytokine levels in 18 infants and children after CPB. All patients showed significant increases in IL-8 and IL-10 after surgery, however IL-10 plasma concentration was reported significantly higher in female patients (67). We did not observe a sex dependent regulation in IL-10 concentrations, but we did observe a non-significant trend in higher IL-1β at all respective timepoints in male patients (Figure 6). To our knowledge, a correlation between gender and CIRBP expression and secretion has not been investigated so far. We did not detect sex related differences in CIRBP serum concentrations (Figure 6). *Trotter* et al. reported a significant increase in the sex steroid progesterone in both male and female patients after CPB, but observed that only male patients developed multiple organ dysfunction (67). Considering the relatively small number of patients in their study and differences in clinical outcome the reported sex-dependent differences might also be related to clinical outcome, age, or original clinical syndrome. (67), This needs to be considered in our feasibility study as well. Although, both male and female patients had a comparable risk for in-of hospital mortality as assessed by RACHS-1 and operation time as well as time on CPB was similar (Table 2), length of PICU stay and mean VIS during the first 24 h after surgery was higher in male patients (Table 3).

Limitations

The present feasibility study was conducted as a single-center study enrolling a small number of consecutive heterogenous patients in regards to sex, age, cardiac anomalies, and subsequently complexity of cardiac surgeries. In all analyzed patients, surgery was conducted using CPB. The study protocol did not include a control group to evaluate the analyzed biomarkers in healthy children or children without cardiac surgery. Unfortunately, it would not have been justifiable from an ethics perspective, as we would need to draw blood from healthy infants and children, which can be a traumatic experience in pediatric patients. Since our cohort already has central venous access before the start of the operations, it was completely painless and easy to obtain blood samples at all time points from our pediatric patients. Furthermore, the concentration of analyzed biomarkers could be influenced by preoperative preparation of patients such as fasting or anesthesia induction as the baseline values were obtained after anesthesia induction directly before surgery. In summary, the results of this pilot study need to be confirmed by a clinical study analyzing a larger number of patients.

5 Conclusion

A valid measurement of the regulation of CIRBP in the clinical setting of cardiac surgery in children is possible. Measurements of potential biomarkers in a larger clinical trial in a pediatric patient cohort using small serum samples during cardiac surgery are essential to validate the promising preliminary results.

This feasibility study shows that multiple analytes can be quantified in a minimal serum volume (25 µl) using a customized multiplex magnetic bead panel. Moreover, a valid measurement of the release of CIRBP into the circulation in a clinical setting of cardiac surgery in children was possible. Measurements of potential biomarkers in a larger clinical trial in a pediatric patient cohort using small serum sample volumes collected during cardiac surgery are essential to validate these promising preliminary results.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by Ethics Committee of Charité—Universitätsmedizin Berlin, Germany (decision EA2/180/19). The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

JL, RS, and KS contributed to conception and design of the study. Sample acquisition was performed by JL, RS, AH and LB Analysis of biomarkers was performed by LB, GT and RF JL, RS, AH organized the database. RF and DH performed the statistical analysis. Chest x-ray analysis was performed by HM Research and clinical infrastructure were provided by JP and FB JL wrote the first draft of the manuscript. RS, RF, DH, GT, and KS wrote sections of the manuscript. All authors contributed to the article and approved the submitted version.

Funding

This study was financially supported by Stiftung KinderHerz Deutschland gGmbH, Essen, Germany (grant number 2511-3-19-020), Deutsche Stiftung für Herzforschung (grant number F/37/20), Frankfurt am Main, Germany and Robert-Enke-Stiftung, Barsinghausen, Germany. We acknowledge support from the German Research Foundation (DFG) and the Open Access Publication Fund of Charité—Universitätsmedizin Berlin. Jana Lücht is participant in the BIH-Charité Junior Clinician Scientist Program funded by the Charité—Universitätsmedizin Berlin and the Berlin Institute of Health at Charité—Universitätsmedizin Berlin.

Acknowledgments

We acknowledge the Berlin Institute of Health (BIH) @ Charité, BIH Metabolomics Platform for providing the MagPix® Instrument.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Durandy Y. Minimizing systemic inflammation during cardiopulmonary bypass in the pediatric population. *Artif Organs*. (2014) 38(1):11–8. doi: 10.1111/aor.12195

2. Warren OJ, Smith AJ, Alexiou C, Rogers PLB, Jawad N, Vincent C, et al. The inflammatory response to cardiopulmonary bypass: part 1-mechanisms of pathogenesis. *J Cardiothorac Vasc Anesth*. (2009) 23(2):223–31. doi: 10.1053/j.jvca.2008.08.007

3. Doguet F, Litzler P, Tamion F, Richard V, Hellot M, Thuillez C, et al. Changes in mesenteric vascular reactivity and. *Ann Thorac Surg*. (2004) 77(6):2130–7. doi: 10.1016/j.athoracsur.2003.10.034

4. Aydin NB, Gercekoglu H, Aksu B, Ozkul V, Sener T, Kiygil I, et al. Endotoxemia in coronary artery bypass surgery: a comparison of the off-pump technique and conventional cardiopulmonary bypass. *J Thorac Cardiovasc Surg*. (2003) 125 (4):843–8. doi: 10.1067/mtc.2003.323

5. Seghaye MC, Grabitz RG, Duchateau J, Busse S, Dabritz S, Koch D, et al. Inflammatory reaction and capillary leak syndrome related to cardiopulmonary bypass in neonates undergoing cardiac operations. *J Thorac Cardiovasc Surg*. (1996) 112:687–97. doi: 10.1016/S0022-5223(96)70053-3

6. Boehne M, Sasse M, Karch A, Dziuba F, Horke A, Kaussen T, et al. Systemic inflammatory response syndrome after pediatric congenital heart surgery: incidence, risk factors, and clinical outcome. *J Card Surg*. (2017) 32(2):116–25. doi: 10.1111/jocs.12879

7. Güvener M, Korun O, Demirtürk OS. Risk factors for systemic inflammatory response after congenital cardiac surgery. *J Card Surg*. (2015) 30(1):92–6. doi: 10.1111/jocs.12465

8. Hassinger AB, Wald EL, Goodman DM. Early postoperative fluid overload precedes acute kidney injury and is associated with higher morbidity in pediatric cardiac surgery patients. *Pediatr Crit Care Med*. (2014) 15(2):131–8. doi: 10.1097/PCC.0000000000000043

9. Kubicki R, Grohmann J, Siepe M, Benk C, Humburger F, Rensing-Ehl A, et al. Early prediction of capillary leak syndrome in infants after cardiopulmonary bypass†. *Eur J Cardio-Thoracic Surg*. (2013) 44(2):275–81. doi: 10.1093/ejcts/ezt028

10. Siehr SL, Shi S, Hao S, Hu Z, Jin B, Hanley F, et al. Exploring the role of polycythemia in patients with cyanosis after palliative congenital heart surgery. *Pediatr Crit Care Med*. (2016) 17(3):216–22. doi: 10.1097/PCC.0000000000000654

11. Rehm M, Zahler S, Lötsch M, Welsch U, Conzen P, Jacob M, et al. Endothelial glycocalyx as an additional barrier determining extravasation of 6% hydroxyethyl starch or 5% albumin solutions in the coronary vascular bed. *Anesthesiology*. (2004) 100(5):1211–23. doi: 10.1097/00000542-200405000-00025

12. Chappell D, Jacob M, Hofmann-Kiefer K, Bruegger D, Rehm M, Conzen P, et al. Hydrocortisone preserves the vascular barrier by protecting the endothelial glycocalyx. *Anesthesiology*. (2007) 107(5):776–84. doi: 10.1097/01.anes.0000286984.39328.96

13. Van den Berg BM, Vink H, Spaan JAE. The endothelial glycocalyx protects against myocardial edema. *Circ Res*. (2003) 92(6):592–4. doi: 10.1161/01.RES.0000065917.53950.75

14. Rehm M, Bruegger D, Christ F, Conzen P, Thiel M, Jacob M, et al. Shedding of the endothelial glycocalyx in patients undergoing major vascular surgery with global and regional ischemia. *Circulation*. (2007) 116(17):1896–906. doi: 10.1161/CIRCULATIONAHA.106.684852

15. Maruyama I, Bell CE, Majerus PW. Thrombomodulin is found on endothelium of arteries, veins, capillaries, and lymphatics, and on syncytiotrophoblast of human placenta. *J Cell Biol*. (1985) 101:363–71. doi: 10.1083/jcb.101.2.363

16. Boehme MWJ, Galle P, Stremmel W. Kinetics of thrombomodulin release and endothelial cell injury by neutrophil-derived proteases and oxygen radicals. *Immunology*. (2002) 107(3):340–9. doi: 10.1046/j.1365-2567.2002.01469.x

17. Steppan J, Hofer S, Funke B, Brenner T, Henrich M, Martin E, et al. Sepsis and major abdominal surgery lead to flaking of the endothelial glycocalix. *J Surg Res*. (2011) 165(1):136–41. doi: 10.1016/j.jss.2009.04.034

18. Lin SM, Wang YM, Lin HC, Lee KY, Huang CD, Liu CY, et al. Serum thrombomodulin level relates to the clinical course of disseminated intravascular coagulation, multiorgan dysfunction syndrome, and mortality in patients with sepsis. *Crit Care Med*. (2008) 36(3):683–9. doi: 10.1097/CCM.0B013E31816537D8

19. Johansen ME, Johansson PI, Ostrowski SR, Bestle MH, Hein L, Jensen ALG, et al. Profound endothelial damage predicts impending organ failure and death in sepsis. *Semin Thromb Hemost*. (2015) 41(1):19–25. doi: 10.1055/s-0034-1398377

20. Fiedler U, Scharpfenecker M, Koidl S, Hegen A, Grunow V, Schmidt JM, et al. The tie-2 ligand angiopoietin-2 is stored in and rapidly released upon stimulation from endothelial cell weibel-palade bodies. *Blood*. (2004) 103(11):4150–6. doi: 10.1182/blood-2003-10-3685

21. Scharpfenecker M, Fiedler U, Reiss Y, Augustin HG. The tie-2 ligand angiopoietin-2 destabilizes quiescent endothelium through an internal autocrine loop mechanism. *J Cell Sci*. (2005) 118(4):771–80. doi: 10.1242/jcs.01653

22. Lemieux C, Maliba R, Favier J, Théorêt JF, Merhi Y, Sirois MG. Angiopoietins can directly activate endothelial cells and neutrophils to promote proinflammatory responses. *Blood*. (2005) 105(4):1523–30. doi: 10.1182/blood-2004-09-3531

23. Parikh SM, Mammoto T, Schultz A, Yuan HT, Christiani D, Karumanchi SA, et al. Excess circulating angiopoietin-2 may contribute to pulmonary vascular leak in sepsis in humans. *PLoS Med*. (2006) 3(3):356–70. doi: 10.1371/journal.pmed.0030046

24. Hippenstiel S, Krüll M, Ikemann A, Risau W, Clauss M, Suttorp N. VEGF Induces hyperpermeability by a direct action on endothelial cells. *Am J Physiol—Lung Cell Mol Physiol*. (1998) 274(5):678–84. doi: 10.1152/ajplung.1998.274.5.L678

25. Namiki A, Brogi E, Kearney M, Kim EA, Wu T, Couffinhal T, et al. Hypoxia induces vascular endothelial growth factor in cultured human endothelial cells. *J Biol Chem*. (1995) 270(52):31189–95. doi: 10.1074/jbc.270.52.31189

26. Berse B, Brown LF, Van de Water L, Dvorak HF, Senger DR. Vascular permeability factor (vascular endothelial growth factor) gene is expressed differentially in normal tissues, macrophages, and tumors. *Mol Biol Cell*. (1992) 3(2):211–20. doi: 10.1091/mbc.3.2.211

27. Salgado R, Benoy I, Bogers J, Weytjens R, Vermeulen P, Dirix L, et al. Platelets and vascular endothelial growth factor (VEGF): a morphological and functional study. *Angiogenesis*. (2001) 4(1):37–43. doi: 10.1023/A:1016611230747

28. Mittermayer F, Pleiner J, Schaller G, Weltermann A, Kapiotis S, Jilma B, et al. Marked increase in vascular endothelial growth factor concentrations during Escherichia coli endotoxin-induced acute inflammation in humans. *Eur J Clin Invest*. (2003) 33(9):758–61. doi: 10.1046/j.1365-2362.2003.01192.x

29. Dulak J, Józkowicz A, Dembinska-Kiec A, Guevara I, Zdzienicka A, Zmudzinska-Grochot D, et al. Nitric oxide induces the synthesis of vascular endothelial growth factor by rat vascular smooth muscle cells. *Arterioscler Thromb Vasc Biol*. (2000) 20(3):659–66. doi: 10.1161/01.ATV.20.3.659

30. Weltermann A, Wolzt M, Petersmann K, Czerni C, Graselli U, Lechner K, et al. Large amounts of vascular endothelial growth factor at the site of hemostatic plug formation in vivo. *Arterioscler Thromb Vasc Biol*. (1999) 19(7):1757–60. doi: 10.1161/01.ATV.19.7.1757

31. Benest A V, Kruse K, Savant S, Thomas M, Laib AM, Loos EK, et al. Angiopoietin-2 is critical for cytokine-induced vascular leakage. *PLoS One*. (2013) 8(8):1–9. doi: 10.1371/journal.pone.0070459

32. Lobov IB, Brooks PC, Lang RA. Angiopoietin-2 displays VEGF-dependent modulation of capillary structure and endothelial cell survival in vivo. *Proc Natl Acad Sci USA*. (2002) 99(17):11205–10. doi: 10.1073/pnas.172161899

33. Siner JM, Bhandari V, Engle KM, Elias JA, Siegel MD. Elevated serum angiopoietin 2 levels are associated with increased mortality in sepsis. *Shock*. (2009) 31(4):348–53. doi: 10.1097/SHK.0b013e318188bd06

34. Pierce RW, Shabanova V, Canarie M, Pinto M, Da Silva YS, Bhandari V, et al. Angiopoietin level trajectories in toddlers with severe sepsis and septic shock and their effect on capillary endothelium. *Shock*. (2019) 51(3):298–305. doi: 10.1097/SHK.0000000000001172

35. Giuliano JS, Lahni PM, Bigham MT, Manning PB, Nelson DP, Wong HR, et al. Plasma angiopoietin-2 levels increase in children following cardiopulmonary bypass. *Intensive Care Med*. (2008) 34(10):1851–7. doi: 10.1007/s00134-008-1174-9

36. Abrahamov D, Erez E, Tamariz M, Dagan O, Pearl E, Abrahamov Y, et al. Plasma vascular endothelial growth factor level is a predictor of the severity of postoperative capillary leak syndrome in neonates undergoing cardiopulmonary bypass. *Pediatr Surg Int*. (2002) 18(1):54–9. doi: 10.1007/s003830200012

37. Sochet AA, Wilson EA, Das JR, Berger JT, Ray PE. Plasma and urinary FGF-2 and VEGF-A levels identify children at risk for severe bleeding after pediatric cardiopulmonary bypass: a pilot study. *Med Res Arch*. (2020) 8(6). doi: 10.18103/mra.v8i6.2134

38. de Melo Bezerra Cavalcante CT, Castelo Branco KM, Pinto Júnior VC, Meneses GC, de Oliveira Neves FM, de Souza NMG, et al. Syndecan-1 improves severe acute kidney injury prediction after pediatric cardiac surgery. *J Thorac Cardiovasc Surg*. (2016) 152(1):178–186.e2. doi: 10.1016/j.jtcvs.2016.03.079

39. Bruegger D, Brettner F, Rossberg I, Nussbaum C, Kowalski C, Januszewska K, et al. Acute degradation of the endothelial glycocalyx in infants undergoing cardiac surgical procedures. *Ann Thorac Surg*. (2015) 99(3):926–31. doi: 10.1016/j.athoracsur.2014.10.013

40. Nishiyama H, Itoh K, Kaneko Y, Kishishita M, Yoshida O, Fujita J. A glycine-rich RNA-binding protein mediating cold-inducible suppression of mammalian cell growth. *J Cell Biol*. (1997) 137(4):899–908. doi: 10.1083/jcb.137.4.899

41. Nishiyama H, Higashitsuji H, Yokoi H, Itoh K, Danno S, Matsuda T, et al. Cloning and characterization of human CIRP (cold-inducible RNA-binding protein) cDNA and chromosomal assignment of the gene. *Gene*. (1997) 204(1–2):115–20. doi: 10.1016/S0378-1119(97)00530-1

42. Wellmann S, Bührer C, Moderegger E, Zelmer A, Kirschner R, Koehne P, et al. Oxygen-regulated expression of the RNA-binding proteins RBM3 and CIRP by a HIF-1-independent mechanism. *J Cell Sci*. (2004) 117(9):1785–94. doi: 10.1242/jcs.01026

43. Haley B, Paunesku T, Protic M, Woloschak GE. Response of heterogeneous ribonuclear proteins (hnRNP) to ionising radiation and their involvement in DNA damage repair. *Int J Radiat Biol*. (2009) 85(8):643–55. doi: 10.1080/09553000903009548

44. Qiang X, Yang WL, Wu R, Zhou M, Jacob A, Dong W, et al. Cold-inducible RNA-binding protein (CIRP) triggers inflammatory responses in hemorrhagic shock and sepsis. *Nat Med*. (2013) 19(11):1489–95. doi: 10.1038/nm.3368

45. Ode Y, Aziz M, Wang P. CIRP Increases ICAM-1+phenotype of neutrophils exhibiting elevated iNOS and NETs in sepsis. *J Leukoc Biol*. (2018) 103(4):693–707. doi: 10.1002/JLB.3A0817-327RR

46. Zhou Y, Dong H, Zhong Y, Huang J, Lv J, Li J. The cold-inducible RNA-binding protein (CIRP) level in peripheral blood predicts sepsis outcome. *PLoS One*. (2015) 10(9):e0137721. doi: 10.1371/journal.pone.0137721

47. Denning NL, Aziz M, Murao A, Gurien SD, Ochani M, Prince JM, et al. Extracellular CIRP as a novel endogenous TREM-1 ligand to fuel inflammation. *bioRxiv*. (2019) 5(5):478–85. doi: 10.1172/jci.insight.134172

48. Zhou M, Aziz M, Denning N-L, Yen H-T, Ma G, Wang P. Extracellular CIRP induces macrophage endotoxin tolerance through IL-6R–mediated STAT3 activation. *JCI Insight*. (2020) 5(5):e133715. doi: 10.1172/jci.insight.133715

49. Yang WL, Sharma A, Wang Z, Li Z, Fan J, Wang P. Cold-inducible RNA-binding protein causes endothelial dysfunction via activation of Nlrp3 inflammasome. *Sci Rep*. (2016) 6:26571. doi: 10.1038/srep26571

50. Gaies MG, Jeffries HE, Niebler RA, Pasquali SK, Donohue JE, Yu S, et al. Vasoactive-inotropic score is associated with outcome after infant cardiac surgery: an analysis from the pediatric cardiac critical care consortium and virtual PICU system registries. *Pediatr Crit Care Med*. (2014) 15(6):529–37. doi: 10.1097/PCC.0000000000000153

51. Khwaja A. KDIGO Clinical practice guidelines for acute kidney injury. *Nephron—Clin Pract*. (2012) 120(4):179–84. doi: 10.1159/000339789

52. Sonntag J, Grunert U, Stöver B, Obladen M. The clinical relevance of subcutaneous-thoracic ratio in preterm newborns as a possibility for quantification

of capillary leak syndrome TT—die klinische bedeutung der weichteildicke in röntgen-thoraxaufnahmen bei frühgeborenen mit einem geburtsgewicht. *Z Geburtshilfe Neonatol*. (2003) 207(6):208–12. doi: 10.1055/s-2003-45171

53. Goldstein SL, Currier H, Graf JM, Cosio CC, Brewer ED, Sachdeva R. Outcome in children receiving continuous venovenous hemofiltration. *Pediatrics*. (2001) 107 (6):1309–12. doi: 10.1542/peds.107.6.1309

54. Jenkins KJ, Gauvreau K, Newburger JW, Spray TL, Moller JH, Iezzoni LI. Consensus-based method for risk adjustment for surgery for congenital heart disease. *J Thorac Cardiovasc Surg*. (2002) 123(1):110–8. doi: 10.1067/mtc.2002.119064

55. Marcelletti C, Corno A, Giannico S, Marino B. Inferior vena cava-pulmonary artery extracardiac conduit. A new form of right heart bypass. *J Thorac Cardiovasc Surg*. (1990) 100(2):228–32. doi: 10.1016/S0022-5223(19)35562-X

56. de Leval MR, Kilner P, Gewillig M, Bull C. Total cavopulmonary connection: a logical alternative to atriopulmonary connection for complex fontan operations. Experimental studies and early clinical experience. *J Thorac Cardiovasc Surg*. (1988) 96(5):682–95. doi: 10.1016/S0022-5223(19)35174-8

57. Ali FN, Hassinger A, Price H, Langman CB. Preoperative plasma FGF23 levels predict acute kidney injury in children: results of a pilot study. *Pediatr Nephrol*. (2013) 28(6):959–62. doi: 10.1007/s00467-012-2395-2

58. Hanudel MR, Wesseling-Perry K, Gales B, Ramos G, Campbell V, Ethridge K, et al. Effects of acute kidney injury and chronic hypoxemia on fibroblast growth factor 23 levels in pediatric cardiac surgery patients. *Pediatr Nephrol*. (2016) 31 (4):661–9. doi: 10.1007/s00467-015-3257-5

59. Volovelsky O, Gist KM, Terrell TC, Bennett MR, Cooper DS, Alten JA, et al. Early postoperative measurement of fibroblast growth factor 23 predicts severe acute kidney injury in infants after cardiac surgery. *Clin Nephrol*. (2018) 90 (3):165–71. doi: 10.5414/CN109359

60. Volovelsky O, Terrell TC, Swain H, Bennett MR, Cooper DS, Goldstein SL. Pre-operative level of FGF23 predicts severe acute kidney injury after heart surgery in children. *Pediatr Nephrol*. (2018) 33(12):2363–70. doi: 10.1007/s00467-018-4024-1

61. Allan CK, Newburger JW, McGrath E, Elder J, Psoinos C, Laussen PC, et al. The relationship between inflammatory activation and clinical outcome after infant cardiopulmonary bypass. *Anesth Analg*. (2010) 111(5):1244–51. doi: 10.1213/ANE.0b013e3181f333aa

62. Rosenthal LM, Tong G, Wowro S, Walker C, Pfitzer C, Böttcher W, et al. A prospective clinical trial measuring the effects of cardiopulmonary bypass under mild hypothermia on the inflammatory response and regulation of cold-shock protein RNA-binding motif 3. *Ther Hypothermia Temp Manag*. (2020) 10(1):60–70. doi: 10.1089/ther.2018.0038

63. Gu CH, Cui Q, Wang YY, Wang J, Dou YW, Zhao R, et al. Effects of insulin therapy on inflammatory mediators in infants undergoing cardiac surgery with cardiopulmonary bypass. *Cytokine*. (2008) 44(1):96–100. doi: 10.1016/j.cyto.2008.06.014

64. Hövels-Gürich HH, Schumacher K, Vazquez-Jimenez JF, Qing M, Hüffmeier U, Buding B, et al. Cytokine balance in infants undergoing cardiac operation. *Ann Thorac Surg*. (2002) 73(2):601–8. doi: 10.1016/S0003-4975(01)03391-4

65. Gessler P, Pretre R, Bürki C, Rousson V, Frey B, Nadal D. Monocyte function-associated antigen expression during and after pediatric cardiac surgery. *J Thorac Cardiovasc Surg*. (2005) 130(1):54–60. doi: 10.1016/j.jtcvs.2005.01.008

66. Madhok AB, Ojamaa K, Haridas V, Parnell VA, Pahwa S, Chowdhury D. Cytokine response in children undergoing surgery for congenital heart disease. *Pediatr Cardiol*. (2006) 27(4):408–13. doi: 10.1007/s00246-006-0934-y

67. Trotter A, Mück K, Grill HJ, Schirmer U, Hannekum A, Lang D. Gender-related plasma levels of progesterone, interleukin-8 and interleukin-10 during and after cardiopulmonary bypass in infants and children. *Crit Care*. (2001) 5(6):343–8. doi: 10.1186/cc1067

68. Chappell D, Jacob M, Hofmann-Kiefer K, Rehm M, Welsch U, Conzen P, et al. Antithrombin reduces shedding of the endothelial glycocalyx following ischaemia/reperfusion. *Cardiovasc Res*. (2009) 83(2):388–96. doi: 10.1093/cvr/cvp097

69. Svennevig K, Hoel TN, Thiara AS, Kolset SO, Castelheim A, Mollnes TE, et al. Syndecan-1 plasma levels during coronary artery bypass surgery with and without cardiopulmonary bypass. *Perfusion*. (2008) 23(3):165–71. doi: 10.1177/0267659108098215

70. Öhlin AK, Larsson K, Hansson M. Soluble thrombomodulin activity and soluble thrombomodulin antigen in plasma. *J Thromb Haemost*. (2005) 3(5):976–82. doi: 10.1111/j.1538-7836.2005.01267.x

71. Bajzar L, Nesheim M, Morser J, Tracy PB. Both cellular and soluble forms of thrombomodulin inhibit fibrinolysis by potentiating the activation of thrombin-activable fibrinolysis inhibitor. *J Biol Chem*. (1998) 273(5):2792–8. doi: 10.1074/jbc.273.5.2792

72. Boehme MWJ, Deng Y, Raeth U, Bierhaus A, Ziegler R, Stremmel W, et al. Release of thrombomodulin from endothelial cells by concerted action of TNF-α and neutrophils: in vivo and in vitro studies. *Immunology*. (1996) 87(1):134–13440.

73. Wöhrle S, Bonny O, Beluch N, Gaulis S, Stamm C, Scheibler M, et al. FGF Receptors control vitamin D and phosphate homeostasis by mediating renal FGF-23 signaling and regulating FGF-23 expression in bone. *J Bone Miner Res*. (2011) 26(10):2486–97. doi: 10.1002/jbmr.478

74. Larsson T, Nisbeth U, Ljunggren Ö, Jüppner H, Jonsson KB. Circulating concentration of FGF-23 increases as renal function declines in patients with chronic kidney disease, but does not change in response to variation in phosphate intake in healthy volunteers. *Kidney Int*. (2003) 64(6):2272–9. doi: 10.1046/j.1523-1755.2003.00328.x

75. Christov M, Waikar SS, Pereira RC, Havasi A, Leaf DE, Goltzman D, et al. Plasma FGF23 levels increase rapidly after acute kidney injury. *Kidney Int*. (2013) 84(4):776–85. doi: 10.1038/ki.2013.150

76. Leaf DE, Rajapurkar M, Lele SS, Mukhopadhyay B, Rawn JD, Frendl G, et al. Increased plasma catalytic iron in patients may mediate acute kidney injury and death following cardiac surgery. *Kidney Int*. (2015) 87(5):776–85. doi: 10.1038/ki.2014.374

77. Singh S, Grabner A, Yanucil C, Schramm K, Czaya B, Krick S, et al. Fibroblast growth factor 23 directly targets hepatocytes to promote inflammation in chronic kidney disease. *Kidney Int*. (2016) 90(5):985–96. doi: 10.1016/j.kint.2016.05.019

78. Chen X, Jiang J, Wu X, Li J, Li S. Plasma cold-inducible RNA-binding protein predicts lung dysfunction after cardiovascular surgery following cardiopulmonary bypass: a prospective observational study. *Med Sci Monit*. (2019) 25:3288–97. doi: 10.12659/MSM.914318

79. Rosenthal LM, Leithner C, Tong G, Streitberger KJ, Krech J, Storm C, et al. RBM3 and CIRP expressions in targeted temperature management treated cardiac arrest patients—a prospective single center study. *PLoS One*. (2019) 14(12):1–15. doi: org/10.1371/journal.pone.0226005

80. Miller-Hance WC, Tacy TA. Gender differences in pediatric cardiac surgery: the cardiologist's perspective. *J Thorac Cardiovasc Surg*. (2004) 128(1):7–10. doi: 10.1016/j.jtcvs.2004.04.008

81. Kochilas LK, Vinocur JM, Menk JS. Age-dependent sex effects on outcomes after pediatric cardiac surgery. *J Am Heart Assoc*. (2014) 3(1):1–11. doi: 10.1161/JAHA.113.000608

82. Marelli A, Gauvreau K, Landzberg M, Jenkins K. Sex differences in mortality in children undergoing congenital heart disease surgery: a United States population-based study. *Circulation*. (2010) 122(11 SUPPL. 1):234–40. doi: 10.1161/CIRCULATIONAHA.109.928325

83. Dibardino DJ, Pasquali SK, Hirsch JC, Benjamin DK, Kleeman KC, Salazar JD, et al. Effect of sex and race on outcome in patients undergoing congenital heart surgery: an analysis of the society of thoracic surgeons congenital heart surgery database. *Ann Thorac Surg*. (2012) 94(6):2054–60. doi: 10.1016/j.athoracsur.2012.05.124

frontiers | Frontiers in Pediatrics

TYPE Original Research
PUBLISHED 05 February 2024
DOI 10.3389/fped.2024.1276215

OPEN ACCESS

EDITED BY
Zhen-Yu Zhang,
KU Leuven, Belgium

REVIEWED BY
Vivian De Waard,
Academic Medical Center, Netherlands
Hiroki Yagi,
The University of Tokyo Hospital, Japan

*CORRESPONDENCE
Veronika C. Stark
✉ ve.stark@uke.de

RECEIVED 11 August 2023
ACCEPTED 17 January 2024
PUBLISHED 05 February 2024

CITATION
Stark VC, Olfe J, Diaz-Gil D, von Kodolitsch Y, Kozlik-Feldmann R, Reincke J, Stark M, Wiegand P, Zeller T and Mir TS (2024) TGFβ level in healthy and children with Marfan syndrome—effective reduction under sartan therapy.
Front. Pediatr. 12:1276215.
doi: 10.3389/fped.2024.1276215

TGFβ level in healthy and children with Marfan syndrome—effective reduction under sartan therapy

Veronika C. Stark[1]*, Jakob Olfe[1], Daniel Diaz-Gil[1,2], Yskert von Kodolitsch[3], Rainer Kozlik-Feldmann[1], Johannes Reincke[1], Maria Stark[4], Peter Wiegand[1], Tanja Zeller[5,6] and Thomas S. Mir[1]

[1]Clinic for Pediatric Heart Medicine and Adults with Congenital Heart Disease, University Heart and Vascular Center, University Medical Center Hamburg-Eppendorf, Hamburg, Germany, [2]Department of Cardiac Surgery & Department of Pediatric, Boston Children's Hospital/ Harvard Medical School, Boston, MA, United States, [3]Department of Cardiology, University Heart and Vascular Center, University Medical Center Hamburg-Eppendorf, Hamburg, Germany, [4]Institute of Medical Biometry and Epidemiology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany, [5]Department of General and Interventional Cardiology, University Center of Cardiovascular Science, University Heart and Vascular Center, University Medical Center Hamburg-Eppendorf, Hamburg, Germany, [6]Deutsches Zentrum für Herzkreislaufforschung, Hamburg, Germany

Introduction: Transforming growth factor β (TGFβ) metabolism plays an important role in the pathogenesis of Marfan syndrome (MFS). Accordingly, drug therapy uses TGFβ receptor blockade to slow down the cardiovascular manifestations, above all aortic root dilatation. Angiotensin II type 1 receptor blockers (ARBs) have been shown to reduce TGFβ levels in adults. Data on childhood are lacking and are now being investigated in the TiGer For Kids study presented here.
Methods: We examined 125 children without chronic disease and 31 pediatric Marfan patients with a proven *FBN1* variant with regard to TGFβ levels. In addition, we measured TGFβ levels during the initiation of ARB therapy in pediatric Marfan patients.
Results: In children without chronic disease, TGFβ levels were found to decrease from childhood to adolescence ($p < 0.0125$). We could not measure a relevantly increased TGFβ level in pediatric Marfan patients. However, we showed a significant suppression of the TGFβ level after treatment with ARBs ($p < 0.0125$) and a renewed increase shortly before the next dose.
Discussion: The TGFβ level in childhood changes in an age-dependent manner and decreases with age. The TGFβ level drops significantly after taking ARBs. Based on our experience and data, a TGFβ receptor blockade in childhood seems reasonable. So far, TGFβ level cannot be used as an MFS screening biomarker.

KEYWORDS
Marfan, TGFβ, sartan, connective tissue disorder, genetic aortic disease, aortic dilatation

Introduction

Marfan syndrome (MFS) is classically caused by a pathogenic fibrillin-1 (*FBN1*) variant (1, 2). The dysfunction of fibrillin-1 itself as an extracellular matrix protein associated with microfibrils was, for a long time, known to be the only cause for this structural weakness of connective tissue in MFS. However, in 2003, Neptune et al. showed a function of fibrillin-1 for the regulation of transforming growth factor β (TGFβ). A pathogenic variant in fibrillin-1 results in an enhancement of TGFβ, whereas

TGFβ activation then prohibits regeneration of vascular smooth muscle cells in, for example, the aortic wall (3). Accordingly, both the altered fibrillin structure itself and the dysregulation of TGFβ cause dilatation of the aortic root, and other cardiovascular, skeletal, skin, and ocular manifestations appear.

Due to this exceeding activation of TGFβ in MFS, medical therapy with angiotensin II type 1 receptor blockers (ARBs), also known as sartans, was expected to be highly effective and started in patients with MFS (4). Blockade of angiotensin II type 1 receptor causes the downregulation of TGFβ and stimulates the regeneration of vascular smooth muscle cells with protection of connective tissue, especially in the aortic wall. Aortic root dilatation could thus be prevented (5). ARBs are therefore, apart from β-adrenergic receptor antagonists (β-blockers), which have been the only cardiovascular medical treatment for MFS patients for a long time, a new option (6). The positive correlation of TGFβ dysregulation with the appearance of cardiovascular pathologies in MFS and other genetic aortic syndromes was already shown in adult patients (7, 8). The decrease of TGFβ concentrations after initiation of therapy could also be shown (9). Moreover, Franken et al. showed that therapy with sartans (losartan) leads to a significant decrease in aortic diameters in adult patients with haploinsufficient *FBN1* variants. This was not demonstrated in the group with dominant-negative gene variants (10). Corresponding data concerning sartan treatment in childhood are still lacking. Especially, measurements of TGFβ levels in MFS children with ARB therapy are missing but essential to evaluate the effectiveness of this therapy. It may be reasonable to initiate therapy in early childhood before the appearance of, especially, cardiovascular pathologies to prevent symptoms of MFS (11).

The aim of this prospective study is to evaluate the serum TGFβ level in children without chronic disease and in comparison to children with connective tissue disorder MFS with and without medical therapy. We investigate four primary research hypotheses: (1) TGFβ serum levels are higher in MFS patients than in healthy children. (2) TGFβ levels are higher in patients with MFS patients with aortic root dilatation than in healthy children. (3) TGFβ serum levels in patients with MFS reduce under medical treatment after 6 h. (4) Sinus valsalvae Z-scores in MFS patients reduce under medical treatment.

Materials and methods

Our TiGer For Kids study is a monocentric prospective cohort study with the overall aim of comparing serum TGFβ levels in children without chronic disease with those of children with MFS and evaluating potential uses of TGFβ as a biomarker.

Subjects

Between April 2017 and May 2020, we examined and obtained blood samples from children without chronic disease and pediatric Marfan patients with and without treatment. In the following, children without chronic disease are also referred to as healthy children.

We included healthy children whenever they presented to the emergency room or admitted to the pediatric ward with uncomplicated pediatric diseases (mild upper airway infection, gastroenteritis, commotio cerebri, motor and development disorders, and social and behavioral problems) without any cardiovascular disease or drugs, cancer, inflammatory or autoimmune disorder, diabetes, nor drugs that could affect the extracellular matrix. To exclude the influence of inflammation or renal impairment on the TGFβ level, we examine the difference of the TGFβ value between low and high c-reactive protein (CRP) and creatinine values of the patients with the TGFβ value.

We included children with MFS while visiting our specialized pediatric Marfan Clinic in the Pediatric Cardiology in the University Heart and Vascular Center Hamburg for first presentation or clinical follow-up. We diagnosed MFS according to the revised Ghent Criteria (12).

Protocol: clinical examination and questionnaire

Baseline study

At the presentation of healthy children and pediatric Marfan patients, they received a standardized questionnaire about health and a blood sample. The questionnaire was used to precisely document and evaluate the patients' previous medical history. The individual risk for a possible chronic, especially cardiovascular, disease was also recorded on the basis of family history. Blood sampling in non-chronically ill children was performed at the time when it was medically indicated. This can affect any time of the day or night. The TGFβ sample of Marfan patients was taken during Marfan consultation hours, mostly between 12 and 3 pm. Accordingly, there was no standardized time of measurement. In addition to the TGFβ level measurement, other laboratory parameters (CRP, creatinine) were analyzed to investigate their influence on the TGFβ level.

In addition, Marfan patients were examined according to the Ghent Criteria, and electrocardiogram (ECG) and echocardiography were performed. An experienced investigator performed echocardiography with the Philips diagnostic ultrasound system EPIQ7 (Amsterdam, Netherlands) with 12, 8, and 5 MHz probes.

Intervention study

As soon as medical therapy was indicated, we took a blood sample for measurements of TGFβ. Patients were admitted to the ward for 24 h. The first TGFβ measurement took place between 8 and 9 a.m. After we applied the ARBs, we repeated TGFβ measurement after 1, 2, 6, and 12 h. In our Marfan Clinic, we usually administer Valsartan two times a day. We start with a dose of approximately 1.5 mg/kg body weight daily and increase the therapy in the course of time. If therapy with losartan has already been started outside the clinic or patients favor losartan, we leave it at that. Thus, during the follow-up visit (6 and 12

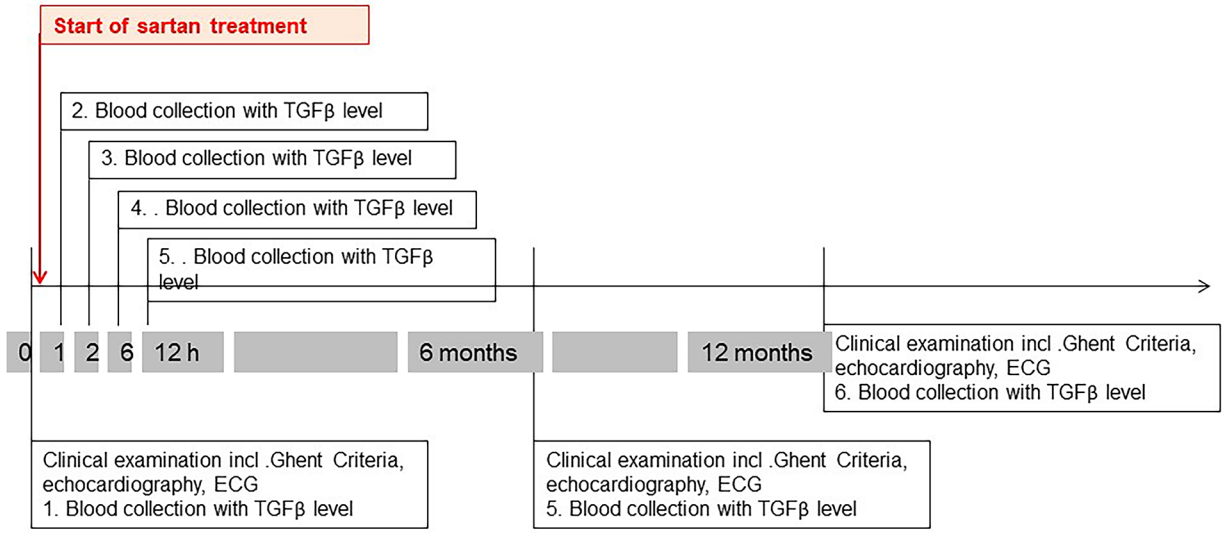


FIGURE 1
Timeline of care for Marfan patients with medical therapy.

months), we repeated the examinations from the baseline visit. The follow-up blood collection was also not standardized in terms of the time of day or in relation to the sartan intake. It was based on the time of presentation at the clinic. A timeline for the care of the MFS patients with medical treatment is shown in Figure 1.

TGFβ measurements

Serum monovettes were centrifuged for 10 min at 3,000 g and 18°C. After filling and sealing of the tubes, the rack was stored directly in the working freezer at −80°C. Finally, TGFβ was determined in the laboratory by means of enzyme-linked immunosorbent assay (ELISA). For TGFβ measurement, we used the Quantikine human TGF 1 immunoassay (R&D Systems Inc. Minneapolis; catalogue number DB100B) according to the manufacturer's instructions. In order to avoid interfering variables, the TGFβ measurements were carried out simultaneously for all serum samples so that the experimental conditions in the laboratory were identical for all samples. The samples were measured in duplicate at points to ensure the accuracy of the values.

Data analysis

In accordance with applicable data protection, the patients were pseudonymized, and a laboratory code and a study code were assigned to each child. The data were collected and archived in a database using Filemaker software V.10 Pro Advanced (Santa Clara, CA) and Microsoft Excel 2007 (Microsoft, Redmond, WA). We performed statistical analysis with SPSS 26 (SPSS, Chicago, IL).

We categorized patients into four age groups: infants (1 day- 24 months), children (25 months-11 years), adolescents (12–14 years), and adults (15–18 years).

In the descriptive statistics, we reported absolute numbers with relative frequencies for categorical data and mean values (M) ± standard deviation (SD) and quantiles for continuous data. All TGFβ values are given in pg/ml.

For analysis, TGFβ levels, CRP values, and creatinine values were approximated to a normal distribution using logarithmic transformation. The first and second primary hypothesis, as well as secondary comparisons in healthy children considering TGFβ levels between sex, low or high CRP, and low or high creatinine, were evaluated using unpaired *t*-tests. Furthermore, TGFβ levels were compared between age groups in healthy children using analysis of variance. The third and fourth primary hypotheses were analyzed using paired *t*-tests.

We adjusted the analysis results of the primary hypotheses using Bonferroni correction, which led to an adjusted significance level of 0.0125. All *p* values of the primary analysis, which were lower than the adjusted significance level, were considered to be statistically significant. We reported 95% confidence intervals and any results of secondary hypotheses in a descriptive way.

Ethical standard

Informed and written consent was always obtained prior to blood sampling and testing by the doctors involved in the study. From the age of 6 years, in accordance with the recommendation of the Federal Court of Justice, the written consent of the child was obtained in addition to the verbal consent of the legal guardians. The study was approved by our Institutional Review Board [Ethics Committee Hamburg (PV 5457)].

Results

We measured TGFβ levels in 125 children without chronic disease (9.4 ± 5.7 y; male 57.6%) and 31 pediatric Marfan patients (6.1 ± 5.6 y, male 51.6%) with a proven *FBN1* variant.

We present the age distribution of the healthy children and pediatric Marfan patients in Table 1. We demonstrate the clinical characteristics of the healthy and Marfan children in Table 1 and those of the Marfan patients with medical treatment in Table 2.

TGFβ level in children without chronic disease

In children without chronic disease, median TGFβ level declines the older the children get (Figure 2). At the beginning of puberty and adolescence, TGFβ is lower than in younger children ($p = 0.001$). Concerning sex we did not identify any differences of TGFβ level at any age in children without connective tissue disorder ($p = 0.87$). Regarding the presence of inflammation ($p = 0.83$) or impaired kidney function (0.47), we could not show any influence on TGFβ levels in our studies.

TGFβ level in pediatric Marfan patients

Baseline TGFβ serum levels were 6,137 (95% CI: 5,360; 6,914) pg/ml in MFS patients without medication and 6,526 (95% CI: 6,027; 7,026) pg/ml in healthy children.. We could not show a significant difference between both groups ($p > 0.0125$). In Figures 3, 4, we illustrate the comparison of TGFβ serum levels between MFS patients and healthy children by means of boxplots.

We also compared TGFβ levels between children without chronic disease [6,517 (95%-CI: 6,014; 7,020) pg/ml] and pediatric Marfan patients with aortic root dilatation [6,986 (95%-CI: 5,633; 8,339) pg/ml]. Again, there was no significant difference ($p = 0.28$) (Figure 5).

In 11 patients (5.5 ± 3.8 y, male: 72.7%), medical treatment was indicated. After administration of Valsartan, the lowest TGFβ serum levels were reached after 6 h, with an average reduction of 1,288 pg/ml (95% CI: 85;2,491, $p < 0.0125$), followed by a return toward baseline at the 11.5-hour mark [delta from baseline −590 pg/ml (95% CI: −2,932;1,751, $p > 0.0125$), Figure 6]. Measuring TGFβ at random times 12 months later did not show a TGFβ level decrease in comparison to baseline. There was no significant change in the z-score of the sinus valsalvae of the Marfan patients during the short observation period of 1 year. In our patient collective, no relevant difference in TGFβ levels between haploinsufficient or dominant-negative gene variants could be detected at neither baseline nor after ARB treatment.

TABLE 1 Distribution of age and clinical characteristics of healthy children (control) and Marfan patients (MFS); ns, not significant.

Patient group	MFS ($n = 31$)	Control ($n = 125$)	
Age (years) at TGFβ measurement (mean ± SD)	6.1 ± 5.6	9.4 ± 5.7	
Age group (*n*, %)			
0–24 months	11 (35.5)	22 (17.6)	ns
2–11 years	14 (45.2)	43 (34.4)	ns
12–14 years	1 (3.2)	30 (24.0)	<0.05
15–18 years	5 (16.1)	30 (24.0)	ns
Sex (*n*, %)			ns
Female	15 (48.4)	53 (42.4)	
Male	16 (51.6)	72 (57.6)	
FBN1 positive (*n*, %)	31 (100.0)	0 (0.0)	
Ghent criteria positive (*n*, %)	20 (64.5)	0 (0.0)	

TABLE 2 Clinical characteristics of Marfan patients with medical treatment ($n = 11$).

Age (years) at first TGFβ measurement (mean ± SD)	5.5 ± 3.8
Age group (*n*, %)	
0–24 months	4 (36.4)
2–11 years	6 (54.5)
12–14 years	1 (9.1)
15–18 years	0 (0.0)
Sex (*n*, %)	
Female	3 (27.3)
Male	8 (72.7)
FBN1 positive (*n*, %)	11 (100.0)
Ghent criteria positive (*n*, %)	11 (100.0)

Discussion

Our TiGer For Kids study is, so far, the largest study to examine TGFβ levels in healthy children and in comparison with MFS children.

We firstly investigated serum TGFβ levels in children without chronic disease and children with MFS. Secondly, we analyzed the role of the biomarker TGFβ with regard to effectiveness and possible therapy monitoring in Marfan patients on the basis of TGFβ measurements.

TGFβ level in children without chronic disease

In our study, we examined the serum TGFβ level in healthy children. TGFβ plays an essential role in many processes of life and is a physiological cell parameter in the context of cell growth and differentiation, apoptosis, embryogenesis, and development, but it is also relevant in immune processes, wound healing, inflammation, and neoplasia (13). Most tissue types possess TGFβ receptors (14). Thus, TGFβ plays a role not only in the regulation of the cardiovascular system but also in the development of lung diseases, tumors, and inflammatory processes. Even the physical activity before the measurement influences the resulting value significantly (15). Only the combination of structurally altered microfibril ECM with dysregulation of TGFβ causes the symptoms of Marfan syndrome. Measuring TGFβ levels in healthy children to detect a possible connective tissue weakness as a screening tool is therefore not useful. Nevertheless, TGFβ normal values in a

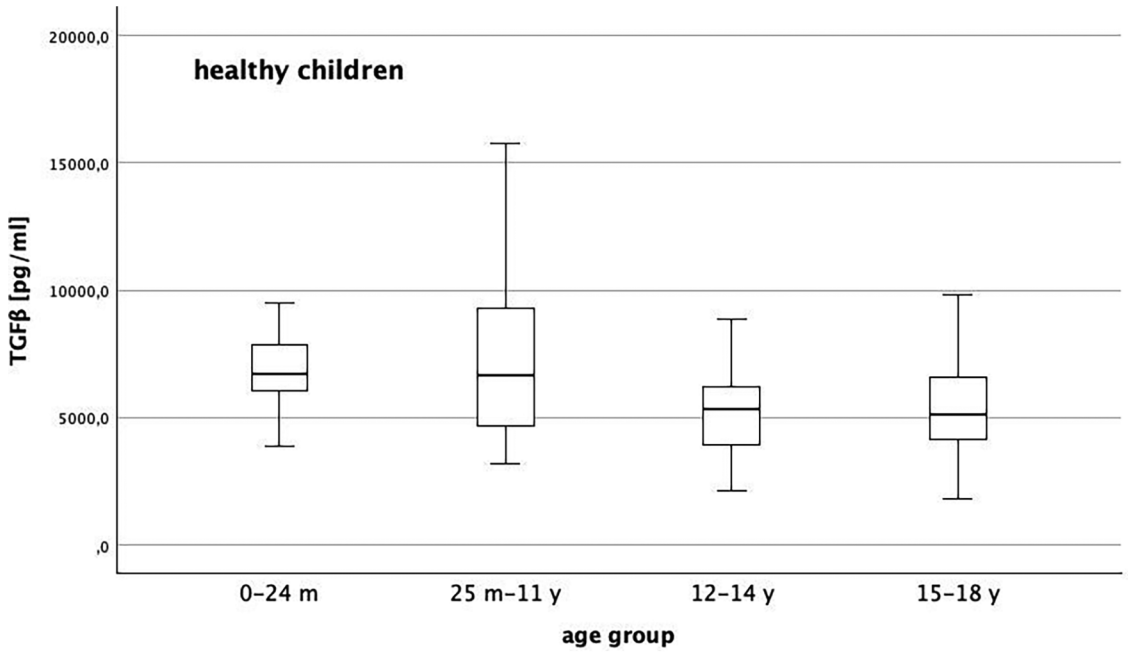


FIGURE 2
Distribution of TGFβ level in healthy children with a general decline of TGFβ the older the children get and lower levels with reach of puberty/adolescence ($p = 0.001$).

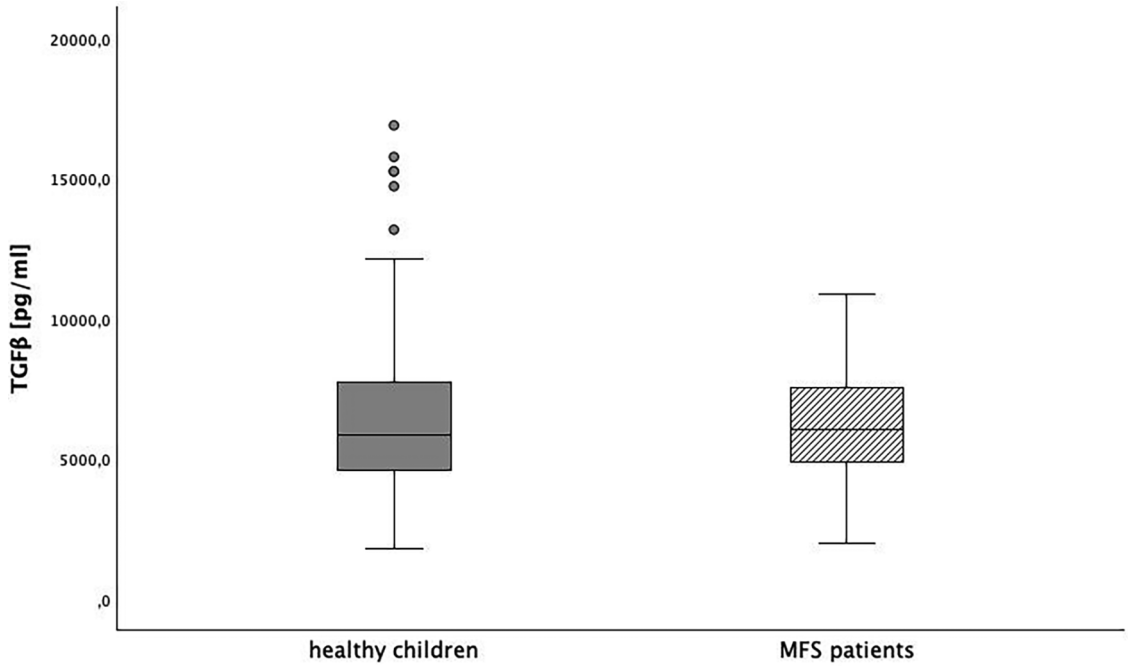


FIGURE 3
TGFβ level in healthy children and children with Marfan syndrome (MFS), $p > 0.0125$.

healthy collective would be helpful to classify the TGFβ level in diseased children. Our measurements showed a decreasing TGFβ level with age in healthy children, especially at the beginning of the second decade of life. Neither sex nor increased inflammatory or renal retention parameters had any influence on the TGFβ level. There are currently a few smaller studies looking

10.3389/fped.2024.1276215

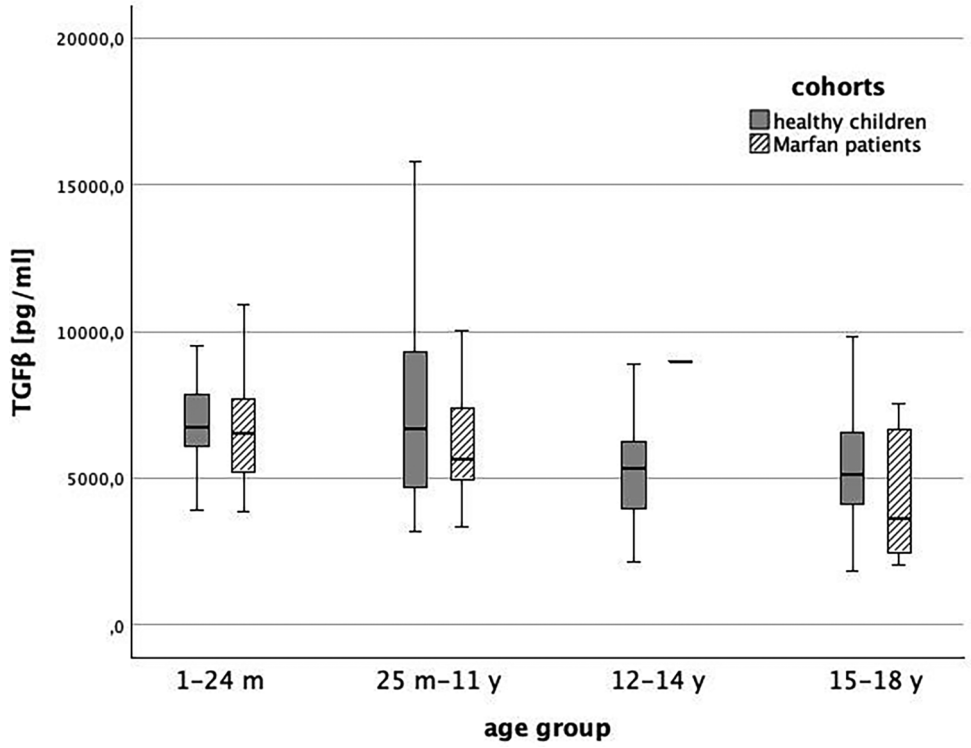


FIGURE 4
TGFβ level in healthy children (grey) and children with Marfan syndrome (striped) indifferent age groups (1 = 1-24 months, 2 = 25 months-11 years, 3 = 12-14 years, 4 = 15-18 years, $p > 0.0125$).

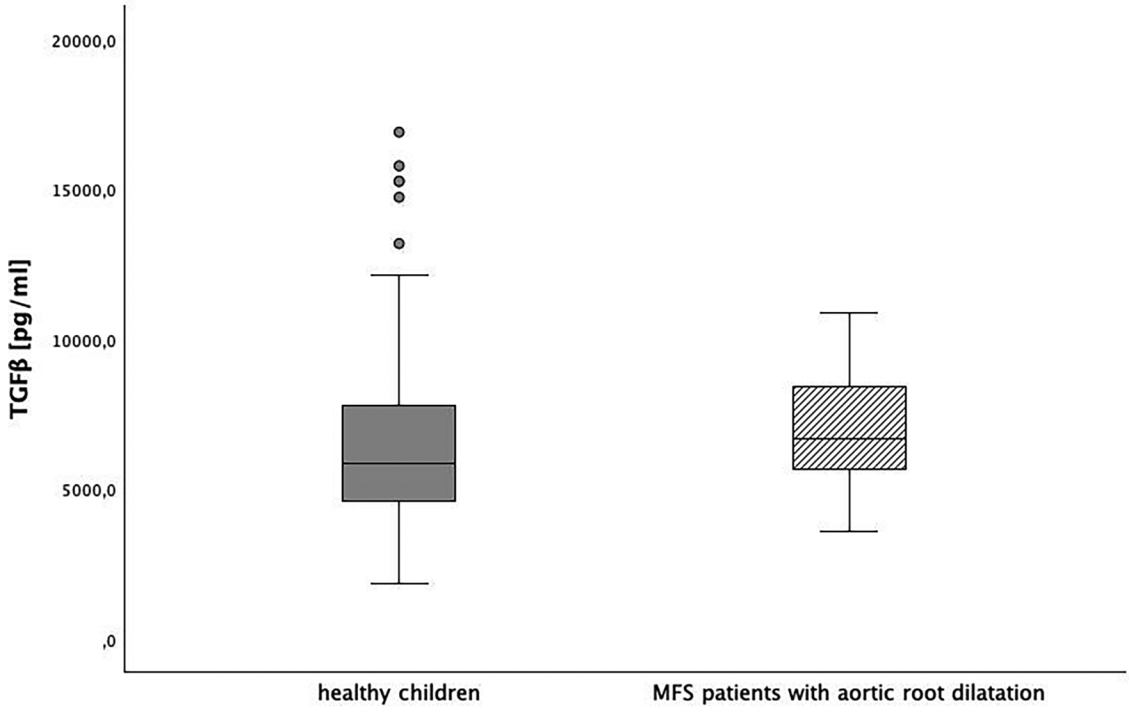


FIGURE 5
TGFβ level in healthy children and children with Marfan syndrome (MFS) with aortic root dilatation, $p = 0.028$.

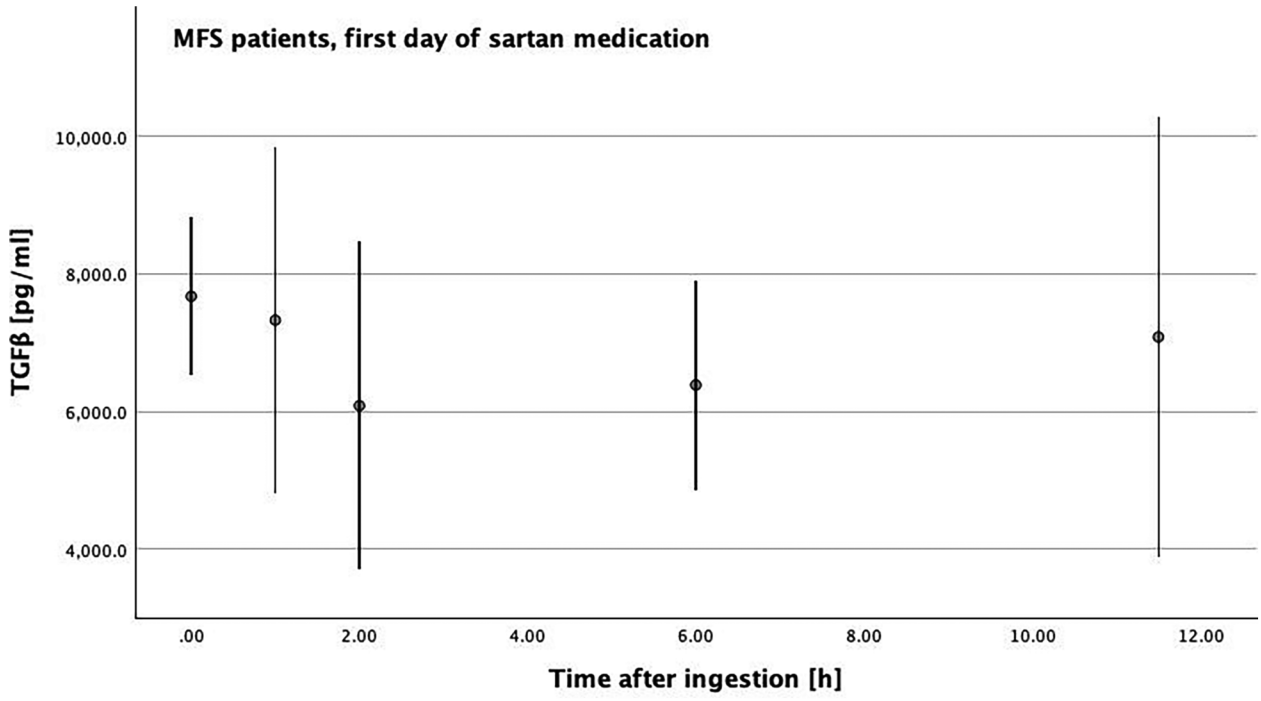


FIGURE 6
TGFβ level development 1, 2, 6, and 12 h after valsartan intake.

at TGFβ norm levels overall and those in childhood. Okamoto et al. compared the TGFβ levels of 55 healthy children with 44 healthy adults, showing significantly lower levels in adulthood, consistent with our findings (16). Rosensweig et al. published similar results of decreasing TGFβ levels from infancy through adolescence into adulthood (17). Our collective consisted of children who presented to the pediatric clinic without chronic and systemic diseases, especially without cardiovascular disease. However, we were unable to standardize the physiological processes that also influence TGFβ levels. This resulted in a relatively heterogeneous collective. We have discussed the study limits in this regard in the limitations section.

TGFβ level in pediatric Marfan patients

Apart from abnormal fibrillin 1, excessive TGFβ activation is essential for the pathogenesis of MFS (3, 18, 19). Thereby, elevated TGFβ levels have been proven in different compartments of the body. Elevated TGFβ levels in Marfan patients have been detected in aortic tissue samples and in the peripheral blood of adult Marfan patients at the same time (7). Thus, TGFβ as a biomarker for aortic dilatation in MFS patients could be suggested. In our pediatric collective, the levels of TGFβ in the serum of Marfan patients did not differ significantly from those children without chronic disease. The comparison of healthy children with Marfan patients with aortic root dilatation also showed no significant difference. This correlates with previous data where TGFβ was also not increased compared to healthy controls (20). In other studies, particularly involving adult patients with aortopathies and especially MFS, an increased TGFβ level could be measured compared to the healthy collective (8, 11, 21). The prerequisites for the inclusion of healthy comparison groups are not always defined in detail in the various publications on adult patients. As already mentioned, TGFβ level is a biomarker that is influenced in many ways and could also possibly be subject to significant diurnal fluctuations, especially during growth. Therefore, the selection of our healthy comparison cohort might have been too inconsistent. Again, so far, TGFβ is no sufficient parameter for screening for connective tissue disease.

TGFβ level in pediatric Marfan patients with ARB treatment

Beta-blockers have been the gold standard in the treatment of MFS for almost 50 years (19, 22). Accordingly, the experience gained by physicians and patients with the medication is great. In addition to the hemodynamic effect with the reduction of heart rate and lowering of blood pressure, they cause an increased distensibility of the aortic wall and a reduced pulse wave velocity. This effectively inhibits aortic root dilatation (23, 24). Beta-blockers are also effective in the pediatric population and are accordingly recommended and used at an early age (24–26).

Since an inhibition of the excessive activity of TGFβ in Marfan disease could be demonstrated by the use of ARBs (angiotensin II receptor type 1 blockers) in pregnant mice and is presumable in humans too, their use appears rational in young patients (5, 9,

25). For more than 15 years, studies investigating the perfect treatment have dominated the scientific world of MFS. A superior effect of ARBs in comparison to beta-blockers has not yet been proven (27). However, an equivalent effect has been demonstrated in numerous large patient groups (27–30). In addition, ARBs have been shown to have a low side-effect profile in childhood (31). Moreover, there are a number of studies that tend to recommend ARBs in Marfan patients, whereas studies exclusively recommending beta-blockers are lacking (31–33). Therapy with sartans has been shown to be effective in adulthood, particularly in patients with haploinsufficient gene variants (10, 21). Our measurements showed no relevant difference between the TGFβ levels of haploinsufficient and dominant-negative patients either without or with therapy. We measured pediatric TGFβ levels before and during therapy with ARBs to assess the potential of TGFβ levels for therapy monitoring. Patients with sartan treatment showed an effective TGFβ suppression during the day, with the lowest level of six hours after ingestion and a renewed rise right before the second dose. Concerning TGFβ suppression, our results suggest that therapy with sartans in childhood seems to be reasonable, even though the z-score of the aortic diameter did not change significantly during the short period of observation. The next step is to correlate the TGFβ level reduction after ARBs use with the reduction in aortic root diameter over a longer period of time. Starting ARB therapy before the development of an aortic aneurysm does not appear to be indicated yet. Cook et al. investigated and explained the contrary TGFβ effect in Marfan patients. The early use of TGFβ inhibition in mice without aortic aneurysm even increased the risk of developing aortic dilatation or dissection. Only after aortic dilatation occurs does TGFβ inhibition reduce the progression of the disease. Accordingly, therapy should be started as early as possible after the occurrence of the aortic aneurysm (34). In line with our results, it seems to be reasonable to apply sartans twice daily for a constant suppression. The assumption remains that ARBs could even establish themselves as a superior therapy due to their effect that goes far beyond the antihypertensive effect. Based on our data and data published since then, TGFβ is neither suitable as a screening parameter for MFS nor as a biomarker for the progression of aortic aneurysms. Other cytokines from the TGFβ pathway such as IL11 are being investigated in order to find laboratory chemical, measurable parameters to perhaps one day enable a prognostic assessment of the disease (35).

Study limitations

Overall,the TGFβ-levels are broadly distributed not only in the children without chronic disease but also in the MFS patients. Of course, a standardized examination and timing would have produced clearer results. However, in our clinical practice, this could not be realized in both patient groups. Especially, the inclusion of healthy children with blood sampling was difficult. According to the ethics vote, blood sampling was only allowed if it was already indicated for other clinical reasons or a peripheral indwelling cannula was inserted. Thus, the timing and physiological fluctuations and prerequisites of the patients were different. Furthermore, pediatric Marfan patients received a TGFβ level measurement in the context of a routine blood collection whenever and under which conditions the presentation in our consultation took place. We accepted this for obtaining the first TGFβ measurements from the children. A clear statement that the TGFβ level differs or not between non-diseased patients and patients with MFS can therefore not be conclusively assessed by our study.

In addition to the broad distribution of the TGFβ values, it is also noticeable that in individual patients, the valley level of TGFβ before the next drug administration exceeds the initial level (Figure 6). We also explain this by the pronounced susceptibility of the TGFβ level to disturbances, in particular by physiological factors (e.g., physical stress, food intake), which were not standardized in this study.

Furthermore, although our healthy population includes children without chronic and cardiac diseases, it is known that infections or trauma can also influence the TGFβ level. However, no correlation with increased TGFβ could be found with analysis of the CRP value.

We did not find a clear TGFβ reduction after a half year or a year of ARB treatment. The TGFβ measurement after 6 and 12 months again was carried out at the time of the presentation in our Marfan consultation and not in a clear temporal relation to the ARB intake. In addition, as explained previously, the TGFβ level is very susceptible to interference and fluctuates over the course of the day. Accordingly, the follow-up level cannot be classified under these non-standardized conditions and is not helpful for the assessment of an effective therapy. Possibly, valley level measurements during the course of therapy could provide further information and improve the usefulness of this biomarker in therapy monitoring. Our aim was to measure circulating TGFβ in order to establish an uncomplicated parameter for everyday clinical use. However, it is known that the activated TGFβ level is particularly relevant and that it is expressed in the affected tissue. We did not take and examine any tissue samples in our pediatric population.

In our study, we have measured the total TGFβ level in serum, as in previous studies of adult Marfan patients. However, it is now known that serum contains high concentrations of platelet-derived TGFβ1, which is released during blood clotting. However, the free, active TGFβ component appears to be particularly relevant to the disease (36). Future studies should possibly determine the total level and the free TGFβ in plasma.

Conclusion

This study is so far the largest examination of serum TGFβ levels in children. We conclude that, first, TGFβ decreases with age, especially at the reach of puberty. Second, TGFβ level does not differ significantly between children without chronic disease and those with MFS. The screening of TGFβ levels to recognize a connective tissue disease does not appear to make sense. Third, sartan intake suppresses TGFβ level relevantly during the day with a rise again right before the second dose.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Ethics Committee Hamburg (PV 5457). The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

VS: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Software, Supervision, Validation, Visualization, Writing – original draft. JO: Conceptualization, Investigation, Methodology, Writing – review & editing. DD-G: Data curation, Investigation, Writing – review & editing. YvK: Methodology, Writing – review & editing. RK-F: Project administration, Supervision, Writing – review & editing. JR: Conceptualization, Data curation, Formal Analysis, Investigation, Software, Writing – review & editing. MS: Data curation, Formal Analysis, Methodology, Software, Writing – review & editing. PW: Data curation, Formal Analysis, Investigation, Software, Visualization, Writing – review & editing. TZ: Investigation, Methodology, Project administration, Writing – review & editing. TM: Conceptualization, Data curation, Investigation, Project administration, Supervision, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Dietz HC, Cutting CR, Pyeritz RE, Maslen CL, Sakai LY, Corson GM, et al. Marfan syndrome caused by a recurrent de novo missense mutation in the fibrillin gene. *Nature*. (1991) 352(6333):337–9. doi: 10.1038/352337a0

2. Faivre L, Collod-Beroud G, Loeys BL, Child A, Binquet C, Gautier E, et al. Effect of mutation type and location on clinical outcome in 1,013 probands with marfan syndrome or related phenotypes and FBN1 mutations: an international study. *Am J Hum Genet*. (2007) 81(3):454–66. doi: 10.1086/520125

3. Neptune ER, Frischmeyer PA, Arking DE, Myers L, Bunton TE, Gayraud B, et al. Dysregulation of TGF-β activation contributes to pathogenesis in marfan syndrome. *Nat Genet*. (2003) 33(3):407–11. doi: 10.1038/ng1116

4. von Kodolitsch Y, Rybczynski M, Detter C, Robinson PN. Diagnosis and management of marfan syndrome. *Future Cardiol*. (2008) 4(1):85–96. doi: 10.2217/14796678.4.1.85

5. Habashi JP. Losartan, an AT1 antagonist, prevents aortic aneurysm in a mouse model of marfan syndrome. *Science*. (2006) 312(5770):117–21. doi: 10.1126/science.1124287

6. Singh MN, Lacro RV. Recent clinical drug trials evidence in marfan syndrome and clinical implications. *Can J Cardiol*. (2016) 32(1):66–77. doi: 10.1016/j.cjca.2015.11.003

7. Kim KL, Yang JH, Song SH, Kim JY, Jang SY, Kim JM, et al. Positive correlation between the dysregulation of transforming growth factor-β_1 and aneurysmal pathological changes in patients with marfan syndrome. *Circ J*. (2013) 77(4):952–8. doi: 10.1253/circj.CJ-12-0874

8. Hillebrand M, Millot N, Sheikhzadeh S, Rybczynski M, Gerth S, Kölbel T, et al. Total Serum transforming growth factor-β1 is elevated in the entire Spectrum of genetic aortic syndromes: tGF-β1 serum levels in GAS. *Clin Cardiol*. (2014) 37(11):672–9. doi: 10.1002/clc.22320

9. Matt P, Schoenhoff F, Habashi J, Holm T, Van Erp C, Loch D, et al. Circulating transforming growth factor-β in marfan syndrome. *Circulation*. (2009) 120(6):526–32. doi: 10.1161/CIRCULATIONAHA.108.841981

10. Franken R, den Hartog AW, Radonic T, Micha D, Maugeri A, van Dijk FS, et al. Beneficial outcome of losartan therapy Depends on type of *FBN1* mutation in marfan syndrome. *Circ Cardiovasc Genet*. (2015) 8(2):383–8. doi: 10.1161/CIRCGENETICS.114.000950

11. Franken R, den Hartog AW, de Waard V, Engele L, Radonic T, Lutter R, et al. Circulating transforming growth factor-β as a prognostic biomarker in marfan syndrome. *Int J Cardiol*. (2013) 168(3):2441–6. doi: 10.1016/j.ijcard.2013.03.033

12. Loeys BL, Dietz HC, Braverman AC, Callewaert BL, De Backer J, Devereux RB, et al. The revised Ghent nosology for the marfan syndrome. *J Med Genet*. (2010) 47(7):476–85. doi: 10.1136/jmg.2009.072785

13. Santibañez JF, Quintanilla M, Bernabeu C. TGF-β/TGF-β receptor system and its role in physiological and pathological conditions. *Clin Sci*. (2011) 121(6):233–51. doi: 10.1042/CS20110086

14. Blobe GC, Schiemann WP, Lodish HF. Role of transforming growth factor β in human disease. Epstein FH, editor. *N Engl J Med*. (2000) 342(18):1350–8. doi: 10.1056/NEJM200005043421807

15. Czarkowska-Paczek B, Bartlomiejczyk I, Przybylski J. The serum levels of growth factors: pDGF, TGF-beta and VEGF are increased after strenuous physical exercise. *J Physiol Pharmacol*. (2006) 57(2):189–97.

16. Okamoto Y, Gotoh Y, Uemura O, Tanaka S, Ando T, Nishida M. Age-dependent decrease in serum transforming growth factor (TGF)-beta 1 in healthy Japanese individuals; population study of serum TGF-beta 1 level in Japanese. *Dis Markers*. (2005) 21(2):71–4. doi: 10.1155/2005/381215

17. Rosensweig JN, Omori M, Page K, Potter CJ, Perlman EJ, Thorgeirsson SS, et al. Transforming growth factor-β1 in plasma and liver of children with liver disease. *Pediatr Res*. (1998) 44(3):402–9. doi: 10.1203/00006450-199809000-00023

18. Takeda N, Inuzuka R, Maemura S, Morita H, Nawata K, Fujita D, et al. Impact of pathogenic *FBN1* variant types on the progression of aortic disease in patients with marfan syndrome. *Circ: Genomic and Precision Medicine*. (2018) 11(6). doi: 10.1161/CIRCGEN.117.002058

19. Judge DP, Dietz HC. Marfan's syndrome. *Lancet*. (2005) 366(9501):1965–76. doi: 10.1016/S0140-6736(05)67789-6

20. Cui JZ, Harris KC, Raedschelders K, Hollander Z, Potts JE, De Souza A, et al. Aortic dimensions, biophysical properties, and plasma biomarkers in children and adults with marfan or loeys-dietz syndrome. *CJC Open*. (2021) 3(5):585–94. doi: 10.1016/j.cjco.2020.12.018

21. study group COMPARE, Franken R, Radonic T, den Hartog AW, Groenink M, Pals G, et al. The revised role of TGF-β in aortic aneurysms in marfan syndrome. *Neth Heart J*. (2015) 23(2):116–21. doi: 10.1007/s12471-014-0622-0

22. Shores J, Berger KR, Murphy EA, Pyeritz RE. Progression of aortic dilatation and the benefit of long-term β-adrenergic blockade in marfan's syndrome. *N Engl J Med*. (1994) 330(19):1335–41. doi: 10.1056/NEJM199405123301902

23. Groenink M, de Roos A, Mulder BJM, Spaan JAE, van der Wall EE. Changes in aortic distensibility and pulse wave velocity assessed with magnetic resonance imaging following beta-blocker therapy in the marfan syndrome. *Am J Cardiol*. (1998) 82 (2):203–8. doi: 10.1016/S0002-9149(98)00315-4

24. Rios AS, Silber EN, Bavishi N, Varga P, Burton BK, Clark WA, et al. Effect of long-term β-blockade on aortic root compliance in patients with marfan syndrome. *Am Heart J*. (1999) 137(6):1057–61. doi: 10.1016/S0002-8703(99)70362-5

25. Brooke BS, Patel N. Angiotensin II blockade and aortic-root dilation in marfan's syndrome. *N Engl J Med*. (2008) 358(26):2787–95. doi: 10.1056/NEJMoa0706585

26. Kang YN, Chi SC, Wu MH, Chiu HH. The effects of losartan versus beta-blockers on cardiovascular protection in marfan syndrome: a systematic review and meta-analysis. *J Formos Med Assoc*. (2020) 119(1):182–90. doi: 10.1016/j.jfma.2019.03.018

27. Mueller GC, Stierle L, Stark V, Steiner K, von Kodolitsch Y, Weil J, et al. Retrospective analysis of the effect of angiotensin II receptor blocker versus β-blocker on aortic root growth in paediatric patients with marfan syndrome. *Heart*. (2014) 100(3):214–8. doi: 10.1136/heartjnl-2013-304946

28. Milleron O, Arnoult F, Ropers J, Aegerter P, Detaint D, Delorme G, et al. Marfan sartan: a randomized, double-blind, placebo-controlled trial. *Eur Heart J*. (2015) 36 (32):2160–6. doi: 10.1093/eurheartj/ehv151

29. Lacro RV, Dietz HC, Sleeper LA, Yetman AT, Bradley TJ, Colan SD, et al. Atenolol versus losartan in children and young adults with marfan's syndrome. *N Engl J Med*. (2014) 371(22):2061–71. doi: 10.1056/NEJMoa1404731

30. Forteza A, Evangelista A, Sánchez V, Teixidó-Turà G, Sanz P, Gutiérrez L, et al. Efficacy of losartan vs. Atenolol for the prevention of aortic dilation in marfan syndrome: a randomized clinical trial. *Eur Heart J*. (2016) 37(12):978–85. doi: 10.1093/eurheartj/ehv575

31. Mullen M, Jin XY, Child A, Stuart AG, Dodd M, Aragon-Martin JA, et al. Irbesartan in marfan syndrome (AIMS): a double-blind, placebo-controlled randomised trial. *Lancet*. (2019) 394(10216):2263–70. doi: 10.1016/S0140-6736(19)32518-8

32. Groenink M, den Hartog AW, Franken R, Radonic T, de Waard V, Timmermans J, et al. Losartan reduces aortic dilatation rate in adults with marfan syndrome: a randomized controlled trial. *Eur Heart J*. (2013) 34(45):3491–500. doi: 10.1093/eurheartj/eht334

33. Chiu HH, Wu MH, Wang JK, Lu CW, Chiu SN, Chen CA, et al. Losartan added to β-blockade therapy for aortic root dilation in marfan syndrome: a randomized, open-label pilot study. *Mayo Clin Proc*. (2013) 88(3):271–6. doi: 10.1016/j.mayocp.2012.11.005

34. Cook JR, Clayton NP, Carta L, Galatioto J, Chiu E, Smaldone S, et al. Dimorphic effects of transforming growth factor-β signaling during aortic aneurysm progression in mice suggest a combinatorial therapy for marfan syndrome. *Arterioscler Thromb Vasc Biol*. (2015) 35(4):911–7. doi: 10.1161/ATVBAHA.114.305150

35. Lim WW, Dong J, Ng B, Widjaja AA, Xie C, Su L, et al. Inhibition of IL11 signaling reduces aortic pathology in murine marfan syndrome. *Circ Res*. (2022) 130(5):728–40. doi: 10.1161/CIRCRESAHA.121.320381

36. Han AJ, Alexander LC, Huebner JL, Reed AB, Kraus VB. Increase in free and total plasma TGF-β1 following physical activity. *CARTILAGE*. (2021) 13 (1_suppl):1741S–8S. doi: 10.1177/1947603520916523

frontiers | Frontiers in Pediatrics

TYPE Original Research
PUBLISHED 05 February 2024
DOI 10.3389/fped.2024.1285794

OPEN ACCESS

EDITED BY
Zhen-Yu Zhang,
KU Leuven, Belgium

REVIEWED BY
Alessandro Maloberti,
University of Milano Bicocca, Italy
Simona Cainap,
University of Medicine and Pharmacy Iuliu Hatieganu, Romania

*CORRESPONDENCE
Vicenç Hernández-González
✉ vicenc.hernandez@udl.cat

RECEIVED 26 September 2023
ACCEPTED 16 January 2024
PUBLISHED 05 February 2024

CITATION
Hernández-González V, Conesa-Milian E, Jové-Deltell C, Pano-Rodríguez Á, Legaz-Arrese A and Reverter-Masia J (2024) Global research trends on cardiac troponin and physical activity among pediatric populations: a bibliometric analysis and science mapping study.
Front. Pediatr. 12:1285794.
doi: 10.3389/fped.2024.1285794

Global research trends on cardiac troponin and physical activity among pediatric populations: a bibliometric analysis and science mapping study

Vicenç Hernández-González[1,2]*, Enric Conesa-Milian[1,2], Carme Jové-Deltell[1,2], Álvaro Pano-Rodríguez[1,2], Alejandro Legaz-Arrese[3] and Joaquin Reverter-Masia[1,2]

[1]Human Movement Research Group (RGHM), University of Lleida, Lleida, Spain, [2]Physical Education and Sport Section, University of Lleida, Lleida, Spain, [3]Section of Physical Education and Sports, Faculty of Health and Sport Sciences, University of Zaragoza, Zaragoza, Spain

Background: Cardiac troponin (cTn) is a reliable marker for evaluating myocardial damage. cTn is a very specific protein involved in myocardial injury, and it is a key factor in the diagnosis of coronary syndromes. Bibliometric analysis was applied in the present work, with the main goal of evaluating global research on the topic of cardiac troponin in pediatric populations.
Methods: Publications about cardiac troponin and physical activity in pediatric populations were retrieved from the Social Sciences Citation Index (SSCI) and the Science Citation Index Expanded (SCIE) of the Web of Science Core Collection, and they were then analyzed. The study was able to identify the key bibliometric indicators, such as publications, keywords, authors, countries, institutions, and journals. For the analysis, VOSviewer, R-based Bibliometrix (4.2.2), and MapChart were used.
Results: Initially, 98 documents were identified; however, once inclusion and exclusion criteria were applied, the number of documents decreased to 88. The search yielded 79 original research articles and 9 reviews, almost all of which were published in the past 2 decades. The total number of citations (Nc) of the retrieved publications was 1,468, and the average number of citations per article (Na) was 16.68. In general, 508 authors were found to have participated in research about troponin; they were associated with 256 institutions, and their work was published in 65 different journals from around the world. The authors hailed from 30 countries and/or regions. The year 2022 was the most productive year for the publication of the selected documents. The bibliometric analysis provided information regarding levels of cooperation among authors and institutions. In fact, China, the United States, and England were the most productive nations, and the journal with the greatest number of publications on the topic was Pediatric Cardiology.
Summary: The number of publications and the trend line show that research on this topic has not yet reached a stage of maturity. There are referent investigators, countries, and institutions that have laid the foundations for subsequent studies on the analyzed topic.

KEYWORDS

cardiac troponin, pediatric, bibliometrics, productivity, network analysis, Web of Science, sports science

1 Introduction

We have known for some time that continuous exercise produces changes and benefits in the heart (1) and that increasing cardiac capacity is positive. However, it has also been proven that, after engaging in exercise, athletes (2), including soccer players (3), rowers (4), swimmers (5), triathletes (6), and basketball players (7), experience higher levels of troponin, a protein that signals cardiac damage.

Troponin (Tn) is a regulatory protein responsible for the contraction of striated cardiac and skeletal muscles (8). This protein can be found in thin filaments, and it is made up of three subunits: C, T, and I. Troponin C (TnC) is responsible for binding to Ca2+, troponin T (TnT) attaches to tropomyosin, and troponin I (TnI) decreases the affinity of TnC to Ca2+, thereby inhibiting the contraction of myofilaments (9). Cardiac troponin (cTn) is a specific biomarker for heart damage and is the leading criterion for diagnosing myocardial injury (10, 11). The cTn isoforms of cardiac troponins T and I (cTnT and cTnI) are highly specific to myocardial cell damage and are key factors in the diagnosis of acute coronary syndromes and necrosis (12). In recent years, highly sensitive assays have been developed to determine the blood concentrations of cTnI and cTnT (hs-cTnI and hs-cTnT).

More advanced and sensitive tests have replaced the standard ones. These new tests, referred to as "high-sensitivity", can detect extremely low levels of cTn in 99% of the population, with a small amount of variation, >10% (13–15). They can also identify cTn levels in at least 50% of healthy individuals when they are at rest. However, this higher sensitivity can sometimes lead to false-positive results, meaning that the tests may indicate a problem, such as an acute myocardial infarction (AMI), when the elevated level was caused by something else, such as physical exercise (16–18). The fourth definition, or clinical criterion, for myocardial infarction (MI) "denotes the presence of acute myocardial injury detected by abnormal cardiac biomarkers in the setting of evidence of acute myocardial ischaemia" (19). Nevertheless, to diagnose myocardial injury, doctors look for elevated cTn levels above the upper reference limit, which represents the 99th percentile (URL), a value that is used as a reference range; this situation is considered acute if there is an increase and/or decrease in cTn values (19).

Numerous investigations have shown that, in healthy individuals, the blood concentration of cTn increases after prolonged exercise, (e.g., running a marathon) (20, 21) and after shorter exercise sessions (30–60 min) (2, 4). In addition to the duration of the exercise, it should be noted that the intensity of the exercise sessions is also very important in assessing the increase in troponin. In fact, in the study by Peretti et al. (22) it has been observed that short, high-intensity exercise caused an elevation in cardiac biomarkers in 62% of the population. It has also been observed that the degree of training can influence troponin release. The percentage of subjects with postexercise cTn levels above the URL ranged from 0% (23) to 100% (24) in individual studies. Controlled studies that use high-sensitivity assays and perform multiple blood draws after exercise report that a release of cTn is evidenced in practically all subjects. They also observed high individual variability in peak values during recovery (25, 2). The clinical relevance of the postexercise cTn increase in healthy subjects is not entirely clear. In this topic, it is important to highlight that the magnitude and kinetics of cTn after exercise are different from thoseobserved in acute myocardial infarction (19, 26). Thus, the data from different studies reflects consistent kinetics in all subjects with a rapid increase in cTn during the first hours after exercise, with most subjects reaching the maximum value after 3–6 h and with values returning close to baseline levels at 24 h postexercise (25, 2, 4, 6). Furthermore, in these studies, the increase in cTn occurred in the absence of clinical signs and symptoms. It is also important to note that the release of cTn is evidenced after short- and long-duration efforts, which are known to induce beneficial effects (27).

Cardiac troponin appears to be elevated in children and adolescents after they have engaged in aerobic exercise, which is a finding that is consistent across most studies (28, 29). In this context, it is relevant to review all the information about any investigation in which the main goal was the study of cardiac biomarker liberation (29).

To review an extensive source of information on any research topic, numerous studies have indicated bibliometric studies as effective for this type of analysis (30). Bibliometrics are used in the field of library and information science. As a method of statistical analysis, they play an important role in impact and tendency analyses (30). Additionally, they allow for the analysis of a significant amount of scientific literature within a given research area (31). Moreover, using bibliometrics can be a complementary orientation strategy for research, and it can play a significant function in decision making in the development of the research (32).

Furthermore, bibliometrics involve the analysis of the cooperation, citations, journals, and institutions that make research visible (33). These types of indicators allow for the identification and definition of the characteristics of the most productive authors and the existing collaborations between them; the centers that generate the research; the intrainstitutional and interinstitutional collaborations; the primary sources in which the works are published; their productivity, concentration, or dispersion; their national and international diffusion; and the repercussions and impact they have on subsequent work (34, 35).

Understanding the current status, areas of focus, productivity growth, and scientific collaboration on heart damage and physical exercise will allow established researchers to expand their circles of contacts, and encourage broader participation in discussions and forums for the exchange of ideas and the expansion of work groups and networks, or the integration of new members into them (36–38).

In recent years, bibliometric mapping has been widely analysed within the field of public health (39–43). Furthermore, there is a recently published, retrospective study on heart failure biomarkers (44) that presents a bibliometric analysis that aims to assess the state of research on biomarkers and heart failure.

However, to our knowledge, no bibliometric studies have been carried out on cardiac troponin as specifically linked to the field of sports science in pediatric populations. Understanding the current status, areas of focus, and future perspectives on cardiac troponin will help us to explore the intrinsic relationship between the discipline's knowledge structure and its development mechanisms in the field of health, providing deeper insight into the role that cardiac troponin plays. Doing so will also assist in the discovery of innovative strategies for clinical heart disease prevention and treatment problems.

The main objective of the present study was to analyse systematically the scientific findings on cardiac troponin in pediatric populations, providing a bibliometric view of research in the field of cardiac troponins. This bibliometric analysis will help identify relevant and potentially useful publications of cardiac biomarker measurements for cardiovascular risk assessment in the pediatric population. The bibliometric study will recognize the most influential authors, journals, institutes, articles and countries in the development of research on cardiac biomarkers. At the end of the document, relevant aspects of the research are discussed, as well as findings that guide future research.

2 Materials and methods

2.1 Search strategy and eligible criteria

Our raw data were retrieved and downloaded from the Web of Science Core Collection (WoSCC) Science Citation Index Expanded (SCIE) and Social Sciences Citation Index (SSCI) developed by Thomson Scientific. The Web of Science consists of many high-quality, high-impact scientific studies, making it the most comprehensive and inclusive collection of information available worldwide (33, 45). Due to differences in the citation data in each database, no database used for bibliometric studies is considered to be better (45, 46). The search strategy was performed using MeSH terms, which were employed in the following manner: TS = (Troponin OR Troponin Complex OR TnT OR hs-cTn OR cTn) AND TS = (Children OR Adolescence* OR Teen* OR Youth* OR Female Adolescent OR Male Adolescent) AND TS = (Exercise OR Physical Activity OR Physical Exercise OR Acute Exercise OR Isometric Exercise OR Aerobic Exercise OR Exercise Training OR Sport). In this manner, we retrieved all of the articles and reviews on troponin in children and adolescents as related to physical exercise that were published online between 1900 and 2023 from the WoSCC SCIE and SSCI.

To reduce the risk of bias, two independent authors obtained the information from all the documents on the same day (24th of February 2023).

Using Web of Science, the documents that met the inclusion and exclusion criteria were selected and exported. The search strategy process and study selection are detailed in Figure 1. For the analysis, only articles or reviews were taken into consideration, which led to the exclusion of one document based on the document type; we also excluded proceeding papers and editorial material, which led to the exclusion of seven documents. Those documents that, after review by the two authors, did not comply with the MeSH terms used in the search strategy were also excluded. Finally, 88 original articles and reviews were included in the analysis and further analyzed and visualized. Later, they were exported to an Excel document where the following information was recorded: the number of citations; name of the journal; year of publication; first and last names of the author and co-authors; total number of authors; geographical location, origin, and associated institute of the authors; title of the article; type of document (article or review); abstract; and the corresponding author. For the analysis of the authors, all individuals who participated in the study were counted. In the bibliometric analysis by country, the country of each author who participated in the study was taken into account, and the citations received were counted. Citations received by a country more than once were not counted if several authors from different institutions (but from the same country) had participated in the same study. The number of articles per country was counted as long as there was an author from the country in the study.

2.2 Bibliometric analysis

In this study, objective and evaluative bibliometrics were used to visualize and analyze findings on cardiac troponin research. Objective bibliometrics measure the quantity of literature and the number of citations, and they also involve citation analyses (47). The productivity, impact, and quality of a publication are expressed as the number of publications (Np), the number of citations (Nc), and the mean number of citations (Na). Evaluative bibliometrics provide quantitative evaluations of countries', authors', journals', and institutions' field contributions, and their measurable index is known as their h-index (48). This type of analysis can identify the articles that influence the history of a field, and it can uncover current research hotspots and future trends (49).

2.3 Statical analysis

We used SPSS 27.0 software (IBM, USA) to perform the correlation analysis. Microsoft Office Excel was used to conduct a linear regression analysis to evaluate the publication trend over time. A polynomial model was applied to predict the increase in publications. We used a popular bibliometric analysis tool, VOSviewer 1.6.18 (CWTS, The Netherlands) (50) for cooperative network identification and keyword co-occurrence analysis. We also used the Bibliometrix tool in R (4.2.2). The R package is intended to be used in quantitative scientometrics and informetrics (51). The tool offers various means for importing bibliographic data from Clarivate's Web of Science. Furthermore, the bibliometric packages permit the classification and analysis of vast quantities of historical research data from a defined period so as to acquire metadata from the database.

The analysis identified information based on the concurrent relation and map distance. The interpretation of the maps was

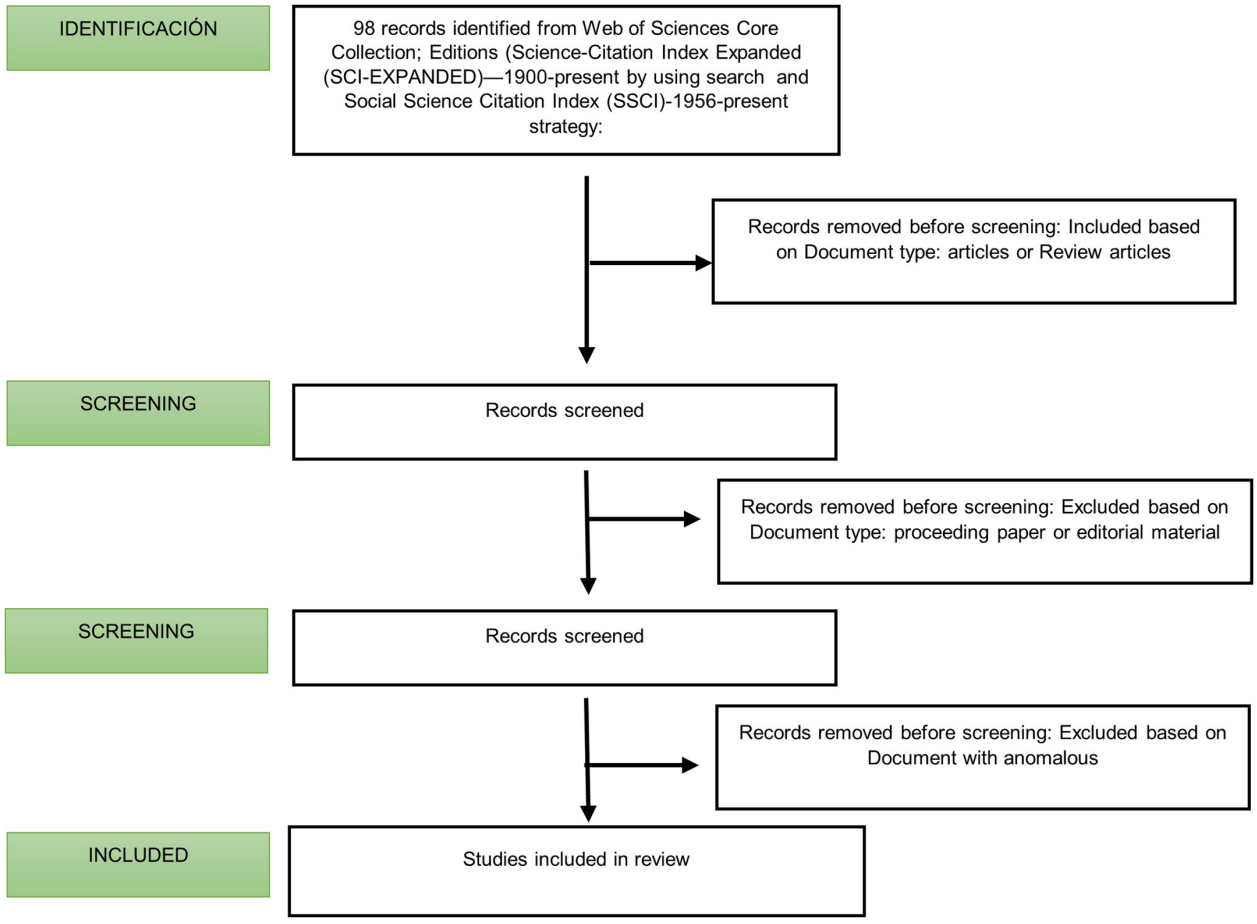


FIGURE 1
Flowchart of the present study.

simple due to the colors, sizes, and distance classifications (clusters) of the evaluated terms. In addition, the software can generate visual maps of knowledge. We also used the MapChart program to generate a personalized map of different regions of the world, accompanied by colors and descriptions.

3 Results

The study flowchart, shown in Figure 1, includes studies that were published between 1900 and 2023, records that were identified from the Web of Science Core Collection, and specifically from within the Social Sciences Citation Index (SSCI) and the Science Citation Index Expanded (SCIE) by using the search strategy. After applying the strategy, the search topic produced 98 documents.

3.1 The global publishing landscape

We analyzed a total number of 88 documents, divided in 79 articles and 9 reviews. Virtually all of the works were published within the last two decades. The total number of citations (Nc) of all of the retrieved publications was 1,468, and the average number of citations per article (Na) was 16.68. A total of 508 authors from 30 countries had published one or more papers on troponin. The 88 papers were published in 65 journals.

The works were published between 1997 and 2022, of which 85% were published after 2010. We performed an analysis of publication trends using 5-year intervals based on a ranking of the publication dates. Between 2018 and 2022, 43 documents were published, almost 50% of the total number of publications. The years 2021 ($n = 11$) and 2022 ($n = 14$) were the years of greatest production. There can be seen a visible improvement in the quantity of the data, and exponential growth can be observed in recent years. According to our linear regression analysis, there exists a positive correlation between the number of publications per year and the year of publication ($R^2 = 0.724$, $p < 0.001$) (Figure 2).

The analysis of publication terms can provide an idea about the principal research topics and trends. This was developed using VOSviewer software, taking into account the title, keywords, and abstract. Terms that appeared in at least five publications were considered, and 40 terms were selected for inclusion in the net. The results from this analysis are presented in Figure 3, and

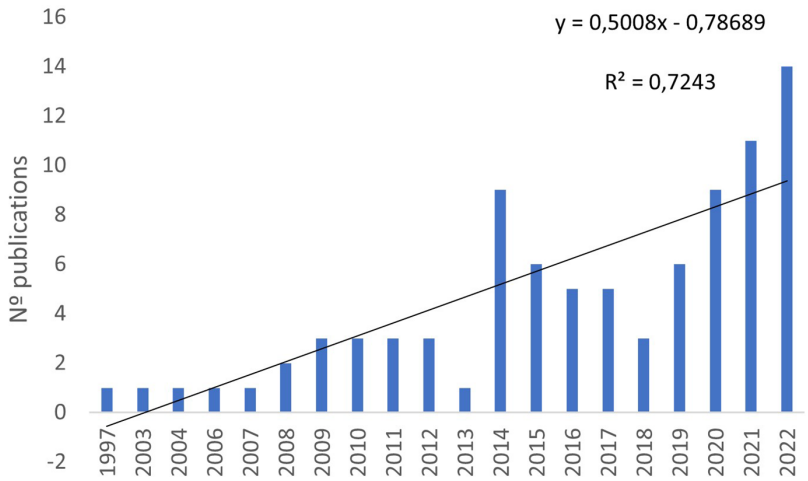


FIGURE 2
Distribution pattern of the articles (number of articles per year).

there are three distinct clusters. The red group, or first node, is related to terms such as "exercise", "children", "cardiac troponin", and "cardiac biomarkers", among others, with "exercise" being the most related term. The green group, a part of the second node, is related to terms such as "brain natriuretic peptide", "endurance exercise", "NT-proBNP", and "runners". In this second node, the term "brain natriuretic peptide" was the one that presented a stronger relationship. The third node, shown in blue, represents all of the terms related to "adolescent", "biomarkers", "troponin-t release" and "intensity", with the term

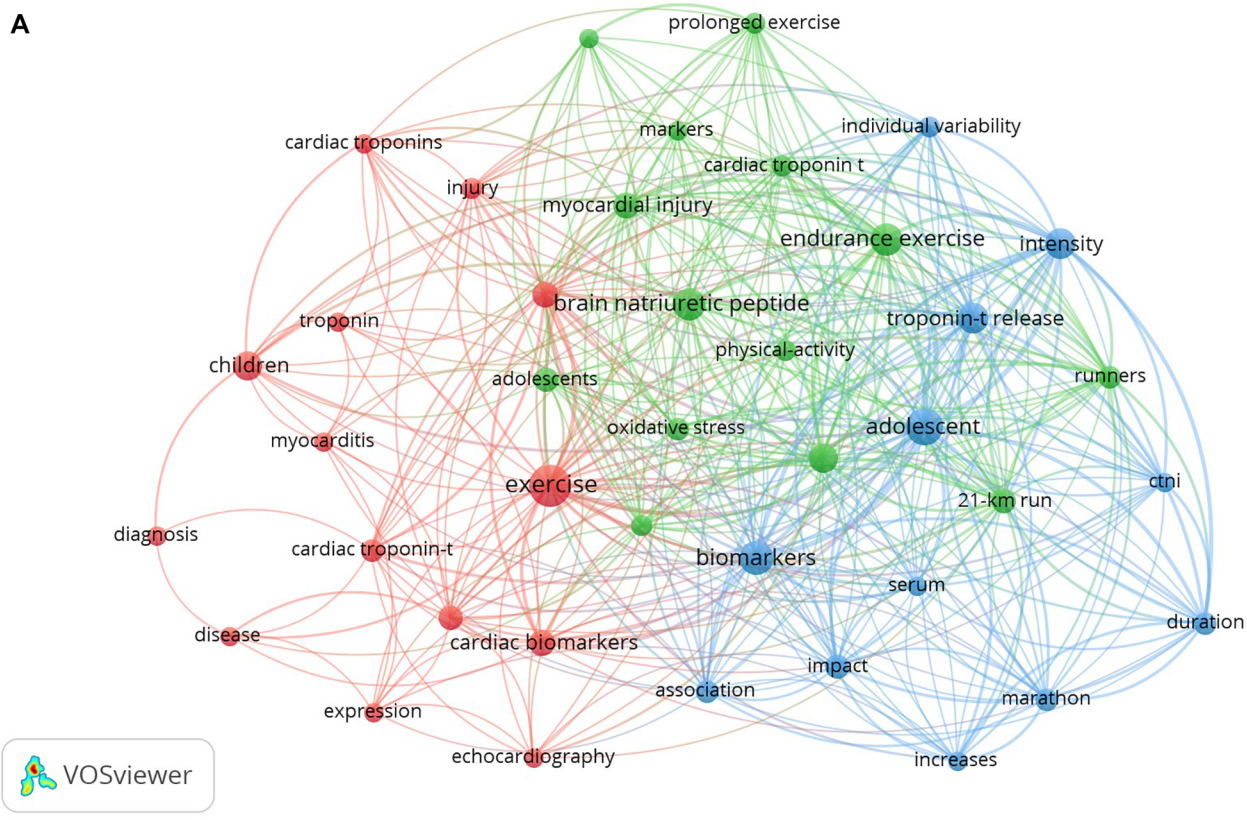


FIGURE 3
(Continued)

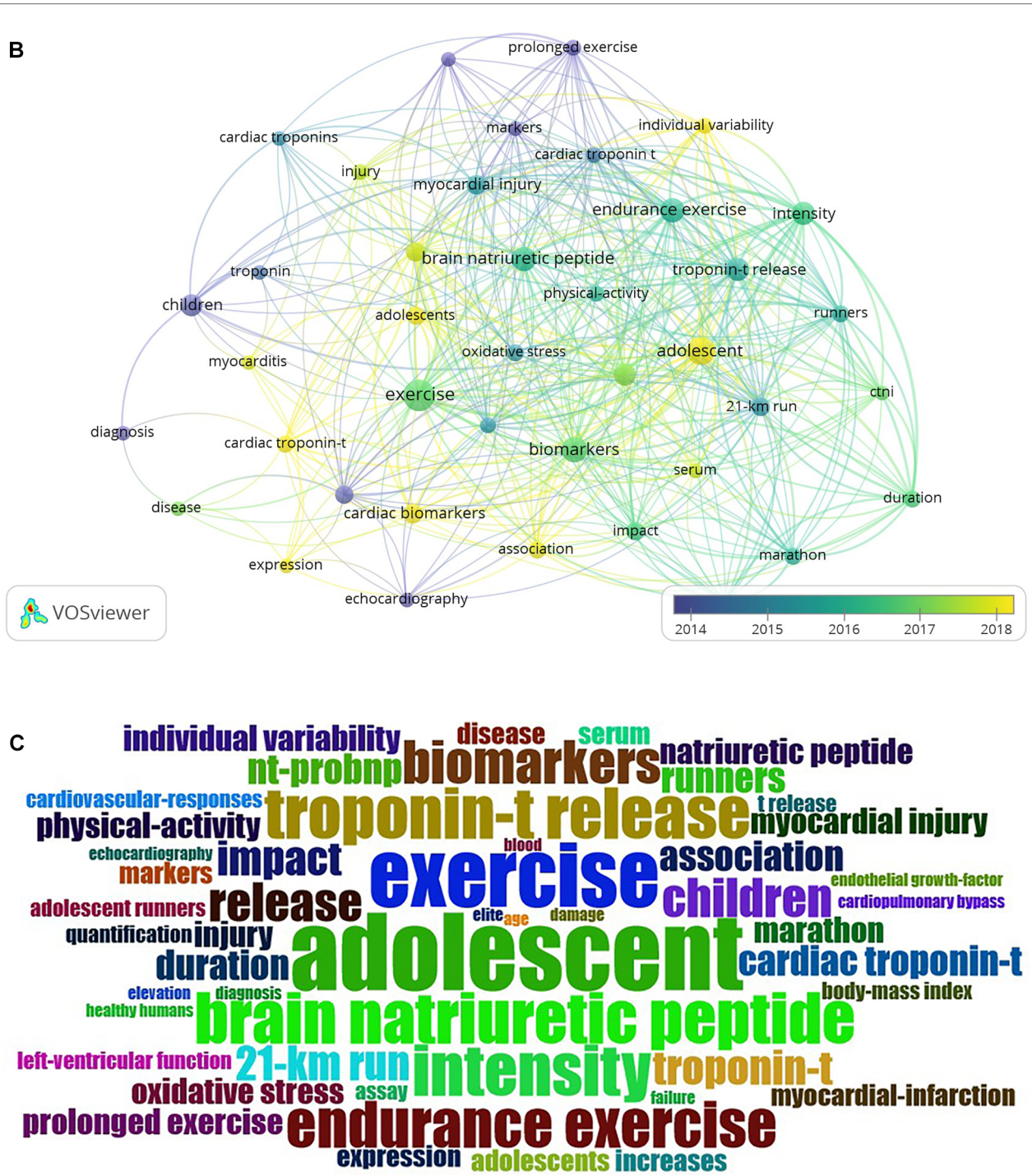


FIGURE 3
(A) The co-occurrence network of keywords. The size of the nodes indicates the frequency of occurrence. The curves between the nodes represent their co-occurrence in the same publication. The smaller the distance between two nodes, the higher the number of co-occurrences of the two keywords; (B) the relationship between the terms in time is illustrated. The color of the terms indicates their average publication period. This value is calculated by taking the average of the years of publication of all publications; (C) word Cloud for Cardiac Troponin topic.

"adolescent" being the most related. The most frequent words were "exercise", "adolescent", "biomarkers", "brain natriuretic peptide", and "endurance exercise" (see Figure 3A).

The most used terms were identified in the range from 2014 to 2018. The oldest terms are presented in blue, while the most current terms are presented in yellow. Based on the range of colors and the size of the circle, the most frequently recurring terms appeared between 2016 and 2017. The clusters with current terms were those related to "adolescent", "cardiac troponin-t", and "cardiac biomarkers". The cluster related to the

terms "children", "troponin", "diagnosis", and "cardiac troponin" refers to older terms. Some terms, such as "troponin" and "cardiac troponin" have evolved into terms that are more specific; such as "cardiac troponin-t", "cardiac biomarkers", and "NT-proBNP". In the same way, it seems that the most recent research has focused on the study of maturational stages, such as adolescence, as compared to younger ages, as was the case in 2014 or 2015 (Figure 3B).

Figure 3C shows a word cloud of the analyzed subject. As expected, the cloud illustrates the strong interaction between the words "adolescent", "exercise", "troponin-t release", and "brain natriuretic peptide".

3.2 Authors and bibliometric analysis of the co-authorship

A total of 508 authors contributed articles on the troponin's topic. The number of authors on each article ranged from 1 to 22 (mean = 7.43). Our analysis of the 10 most productive authors, based on their number of articles, but regardless of their authorship positions, showed that J.L. Nie, K. George, and J. Reverter-Masia were the authors with the greatest number of articles on the topic.

J.L. Nie, from the People's Republic of China, had 442 citations —the maximum number—with 18 articles listed, and an h-index of 10 in relation to the topic of troponin. The average number of citations per article was 23. However, K. George, from England, published 17 papers, with a total of 342 citations, resulting in an average of 20 citations per article and an h-index of 11. The third most prolific researcher was J. Reverter-Masia. Hailing from Spain, this researcher published 10 documents with more than 110 total citations, resulting in an h-index of 6 (see Table 1). We found that the total number of citations was related negative to the number of authors ($rs = -0.051$, $p < 0.001$).

The graphical representation of the authors' level of production on the cardiac troponin's topic over time is displayed in Figure 4. The sizes of the circles in the figure represent the numbers of published articles, and the colors represent the numbers of citations.

TABLE 1 The top 10 authors with the most documents on the topic of troponin.

Author	Np	h-index	First author	Last author	Co-author	Nc
Nie, J.L.	18	10	5	1	12	422
George, K.	17	11	0	5	12	342
Reverter-Masia, J.	10	6	0	7	3	110
Legaz-Arrese, A.	9	6	3	1	5	108
Tong, T.K.	9	8	1	1	7	288
Shi, Q.D.	9	7	0	5	4	225
Lopez-Laval, I.	7	5	1	0	6	84
Zhang, H.F.	7	4	1	0	6	44
Cirer-Sastre, R.	6	4	6	0	0	28
Tian, Y.	6	5	2	1	3	177
Fu, F.	6	5	2	1	3	165

Np, number of publications; Nc, number of citations.

The pattern of cooperation of each author's publishing was examined using VOSviewer (see Figure 5). There was a high level of collaboration between most of the main authors, creating three cooperative research networks. Authors with a minimum of two papers were considered for analysis. Of the 508 authors, 28 reached the threshold (Figure 4). K. George formed a collaborative network with 21 other researchers. Another cooperative research network was formed by J.L. Nie with 19 researchers. The third cooperative research network was formed around H.F. Zhang with 12 other researchers.

3.3 Countries, institutions, and bibliometric analysis of the collaboration

Researchers from a total of 30 countries published 88 articles on the topic analyzed. Table 2 shows the 10 most productive countries, with the People's Republic of China contributing the most, with 24 documents, followed by the USAand England, with 20 articles. These same three countries were also accorded the greatest number of citations. Regarding the average number of citations per article, the Canada was notable among the countries, with an average of 33, 50 citations per article, followed by England, with an average of 20, 80 citations per article.

The publications focusing on cardiac troponin were created in 30 different countries, with 19 of those being located in Europe, 4 in Asia, 4 in the Americas, 1 in Africa, and 2 in Oceania. Figure 6 illustrates the global distribution of these countries and regions. The top four countries alone (13.3%) produced almost 60% of the publications. Half of the countries produced only one document. It is important to note that a publication may be related to different countries or institutions due to multiple affiliations or authors as all author affiliations, with respect to both country and institution, were considered. The People's Republic of China produced the greatest quantity of publications, followed by the England and then USA.

Figure 7A presents our analysis of the collaboration between countries. The analysis was performed using VOSviewer software. Countries with two or more collaborative publications appear in the network. Four collaborative nodes were established. The first node, shown in red, involves five countries, and the USA had the most active associations within this network, with 20 collaborative documents produced. The main research collaborators of the USA included Austria, Germany, Belgium, and Italy. A second, smaller node, shown in green, focuses on Australia, which collaborated on seven papers. Its main research collaborators included Canada, France, and the Netherlands. A third node (shown in blue) centers on England, which produced 20 collaborative documents, with its main connection—to Spain —yielding 15 documents. Finally, a fourth node (shown in yellow) centers around the People's Republic of China with 24 documents; its main research collaborator was Scotland.

The analysis was developed using Bibliometrix software, and it shows the strong level of cooperation between England, Spain, Mexico, and China (see Figure 7B).

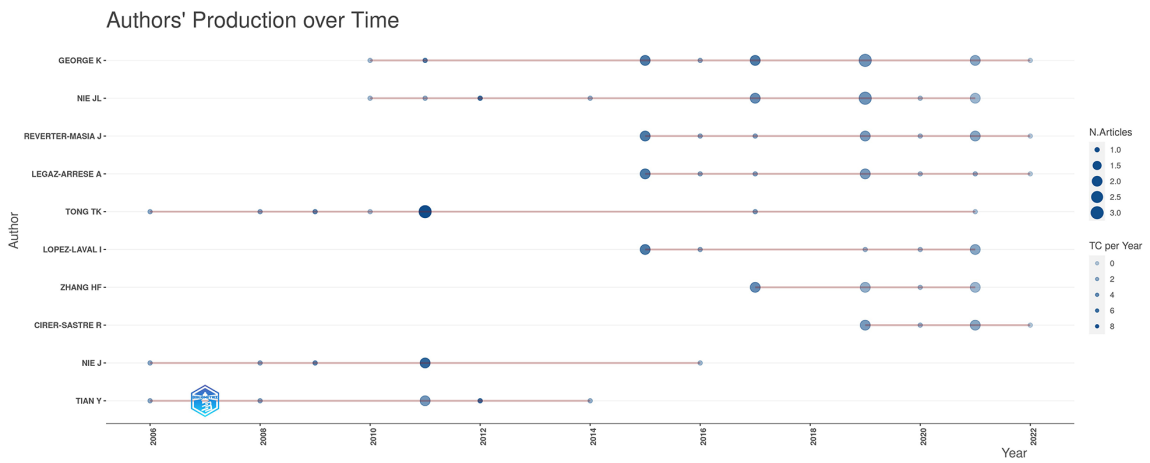


FIGURE 4
Authors' level of production over time on the subject of cardiac troponin. The circle sizes in the figure signify the numbers of documents, and the shades of the colors signify the numbers of citations.

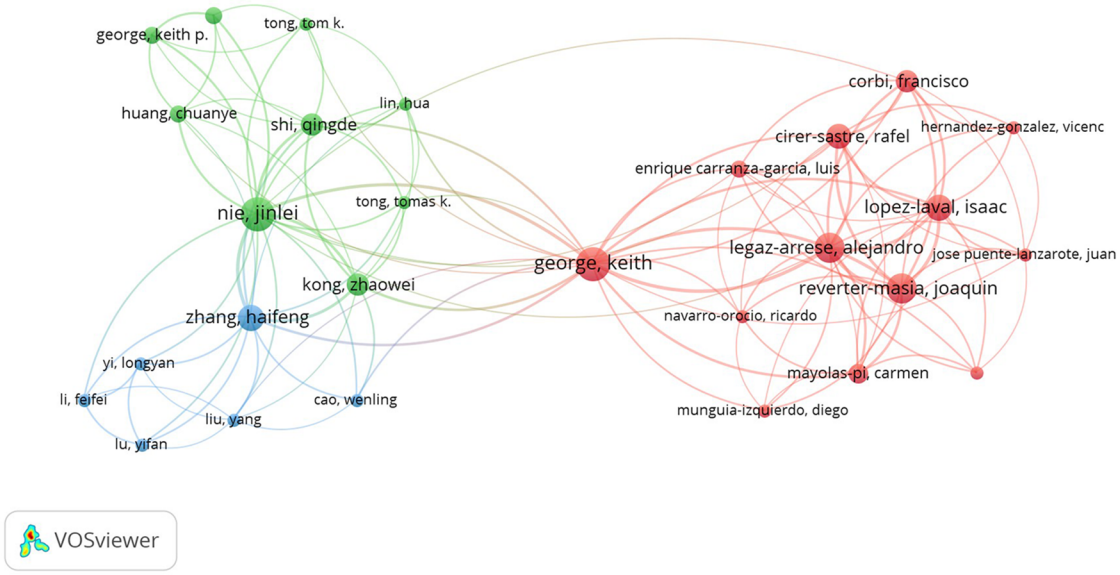


FIGURE 5
The authors' collaborative networks. The collaboration map of the authors reflects the scientific research cooperation between them. The circles/nodes signify the authors; the sizes of the circles/nodes signify the numbers of articles. The lines denote the strength of the authors' collaboration, and each color signifies a cluster.

In total, 256 institutions participated in the creation of 88 publications according to the available affiliation data. (A publication can be written by several authors, or an author can be affiliated with more than one institution.) The number of institutions per article ranged between 1 and 19. The average number of institutions involved in a collaboration was 3.9 institutions per article. Considering all of the institutions, 80.07% ($n = 205$) participated in only one publication; 14.5% ($n = 37$) participated in two publications; 3.6% ($n = 9$) participated in the creation of three to seven publications. Only five institutions (2%) were involved in the development of 10 or more publications. Liverpool John Moores University and Macao Polytechnic Institute were the two most prolific institutions with 17 publications each. Seven of the ten most productive institutions are located in China, two in Spain, and one in England. The two universities with the highest number of documents listed as the first or last institutions were Lleida University (80% of the documents) and China Institute of Sport Science (66.6%). In addition, the China Institute of Sport Science, together with Liaoning Normal University, were the

TABLE 2 The top countries with the greatest number of citations per document on the topic of troponin.

Location	Nc	Np	Na	h-index
People's Republic of China	457	24	19,04	12
England	416	20	20,80	12
USA	406	20	20,30	8
Spain	245	15	16,33	7
Italy	107	8	13,38	5
Australia	58	7	8,29	4
Germany	86	7	12,29	5
France	70	5	14,00	4
Austria	47	4	11,75	3
Canada	134	4	33,50	3

Np, number of publications; Nc, number of citations; Na, average number of citations.

institutions with the greatest mean for citations by document (35.83 and 33.17 citations per documents, respectively). There was a positivecorrelation between the total number of citations and the number of participating institutions (rs = 0.112, $p = 0.228$).

Most of the institutions are universities, but there is also evidence of the presence of research centers and institutes, and even some private institutions appear to be involved (Table 3).

In the collaboration network analysis (see Figure 8), a minimum of three collaborations between institutions were established. A total of 13 institutions reached the threshold, and four cooperation network nodes were formed. In the first of them, the red node, Macao Polytechnic Institute cooperated with institutions including Beijing Sport University, China Institute of Sport Science, Hong Kong Baptist University, and Liaoning Normal University, resulting in collaboration on 17 documents. Liverpool John Moore University Shown in green) had a strong partnership and cooperation with the University of Zaragoza and Lleida University with 17 documents), and the third node (shown in blue), illustrates the strong cooperation between Hebei Normal University and the University of Macau and the Provincial Key Lab of Measurement and Evaluation in Human Movement, resulting in collaboration on seven documents. We observed that Macao Polytechnic Institute and Liverpool John Moores University concentrated their collaboration networks, resulting in a near majority of the scientific production on the subject analyzed.

3.4 Journals analysis

Table 4 shows the 10 journals that published the most articles. Pediatric Cardiology was the most productive journal ($n = 4$), followed by Biomarkers, Frontiers in Physiology, International Journal of Environmental Research and Occupational Health, International Journal of Sports Medicine, Pediatric Exercise Science, and Scandinavian Journal of Medicine & Science in Sports, with 3 documents each. A total of 56.8% of the journals published one single document, while the remainder of the journals ($n = 15$) published the remaining 43.2% of the publications.

Among the most productive journals, the one with the highest number of citations was International Journal of Sports Medicine ($n = 105$), and the one with the fewest citations was Frontiers in Physiology ($n = 10$).

Of the 65 journals included in the list, 23 of them were ranked in Q1 (35.4%), 23 were ranked in Q2 (35.4%), 10 of them were ranked in Q3 (15.4%), and the remaining 9 were ranked in Q4

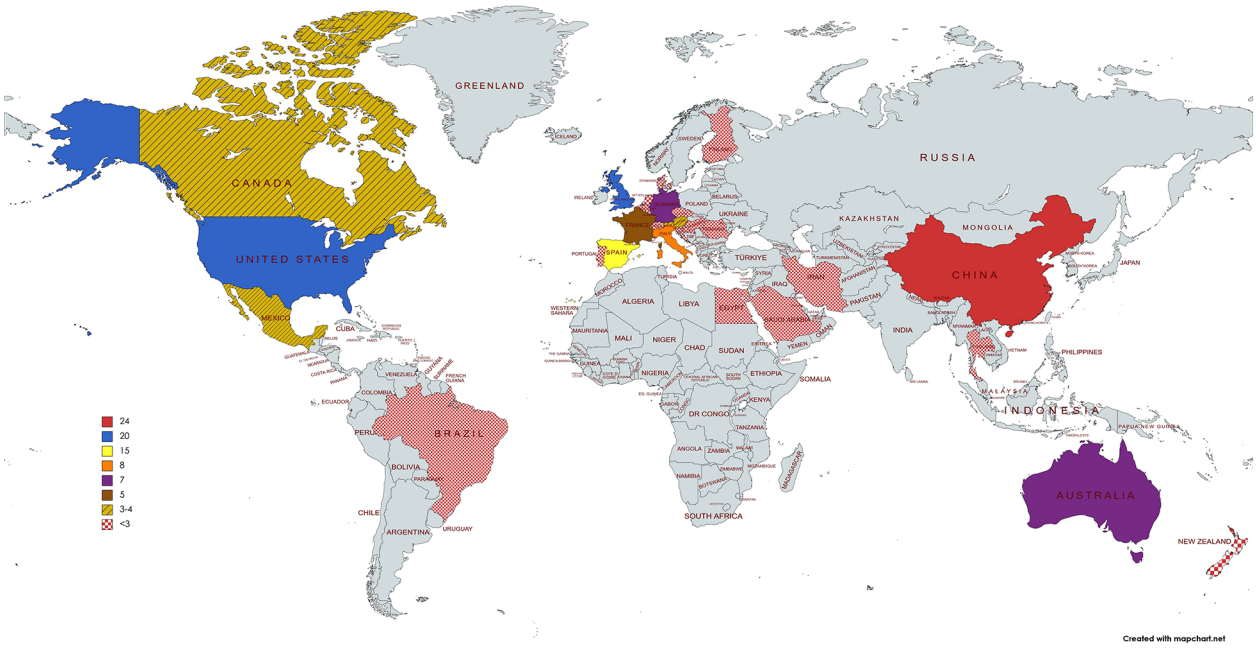


FIGURE 6
Distribution map showing the numbers of published articles per country (mapChart).

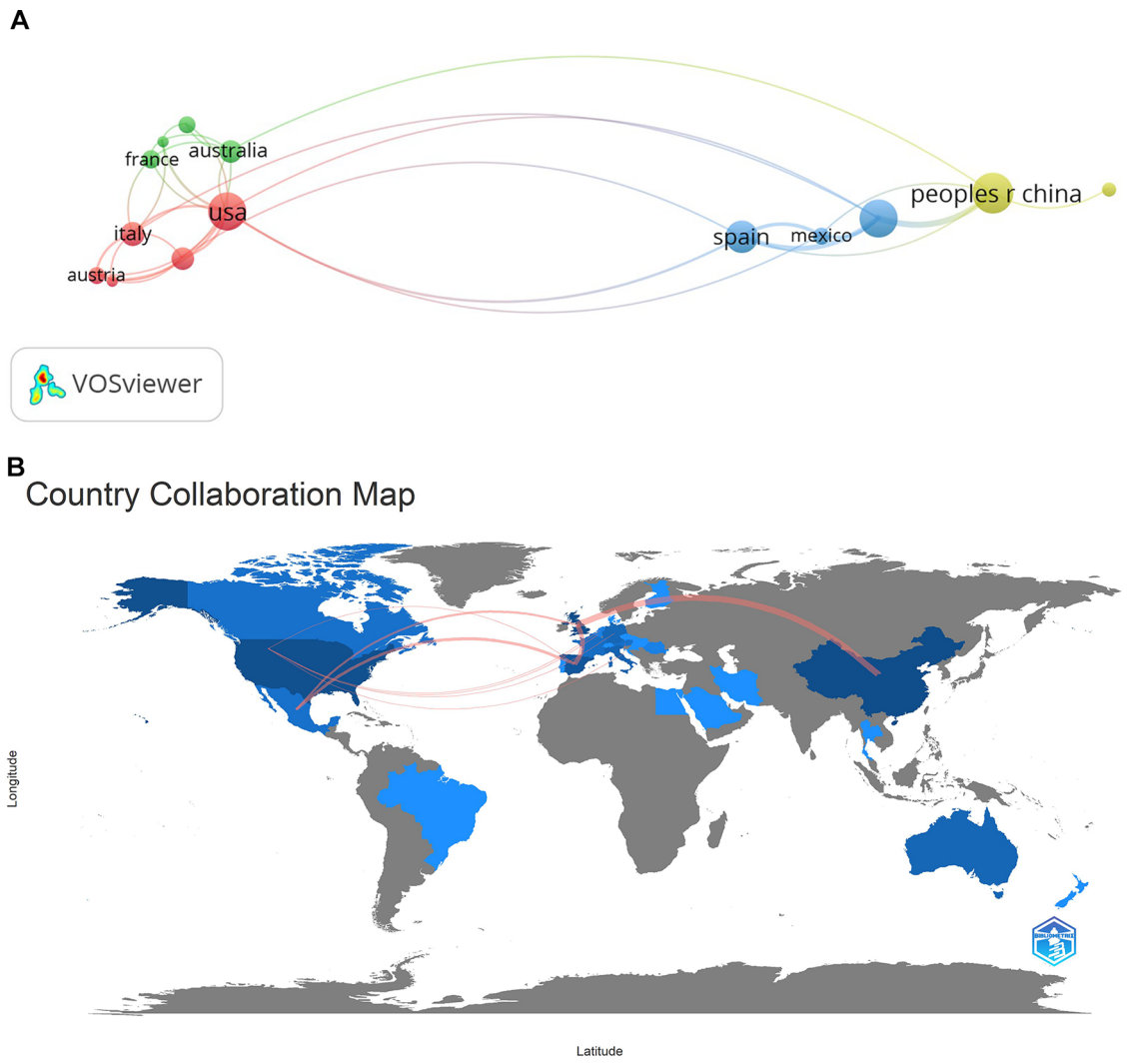


FIGURE 7
(A) Intercountry collaboration networks; (B) intercountry collaboration map.

(13.8%). Together, 70% of the studies were published in high-impact journals (Q1–Q2).

The IFs of the 65 journals ranged from 0.699 (Heart Surgery Forum) to 41,787 (Intensive Care Medicine).

We found 11 journals with an IF ranging between 0.699 and 1,929, 35 journals that had an IF ranging between 2,141 and 4,997, 12 journals whose impact factor ranged between 5,121 and 8,307, and 7 journals with an IF greater than 10,000.

TABLE 3 The top 10 institutions with the greatest numbers of citations per document.

Institution	Country	Np	No of documents as first or last institution	Nc	Na	h-index
Liverpool John Moores University	England	17	5	342	20.12	11
Macao Polytechnic Institute	China	17	8	384	22.59	9
Hong Kong Baptist University	China	12	4	310	25.83	9
University of Zaragoza	Spain	11	5	212	19.27	7
University of Lleida	Spain	10	8	110	11	6
Hebei Normal University	China	7	2	46	6.57	4
China Institute of Sport Science	China	6	4	215	35.83	6
Liaoning Normal University	China	6	0	199	33.17	6
Beijing Sport University	China	5	3	60	12	4
University of Macau	China	5	1	33	6.6	3

Np, number of publications; Nc, number of citations; Na, average number of citations per publication.

FIGURE 8
Institutional collaboration networks.

TABLE 4 The top 10 journals that published articles on the topic of troponin.

Journal title	Np	Nc	Na	Impact factor (2021)	Quartile
Pediatric Cardiology	4	20	5	1.838	Q3
Biomarkers	3	36	12	2.663	Q3
Frontiers in Physiology	3	10	3.33	4.755	Q1
International Journal of Environmental Research and Occupational Health	3	14	4.67	4.614	Q1
International Journal of Sports Medicine	3	105	35	2.997	Q2
Pediatric Exercise Science	3	22	7.33	2.395	Q3
Scandinavian Journal of Medicine and Science in Sports	3	79	26.33	4.645	Q1
Acta Paediatrica	2	20	10	4.056	Q1
Clinical Chemistry and Laboratory Medicine	2	24	12	8.49	Q1
European Journal of Applied Physiology	2	20	10	3.346	Q2

Np, number of publications; Nc, number of citations; Na, average number of citations.

The top 10 journals published 31.8% of the articles, and they account for more than 68% of the total citations. The journal with the highest number of citations was International Journal of Sports Medicine ($n = 105$), and the mean number of citations per article was 35 citations/article.

4 Discussion

In recent years, bibliometric studies have gained great momentum because they provide useful analytical indicators on the evolution of science, new lines of research, or new fields that are developing and are worth investigating. To our understanding, this is the first time that a bibliometric evaluation of the literature related to cardiac troponin in sports science has been carried out. We aimed to obtain a global overview, as well as to understand the foci, themes, and research frontiers in this field.

In this study, we collected data from 80 papers about cardiac troponin in pediatric populations published during the past 2 decades according to the SSCI and SCIE databases. We performed a series of bibliometric analyses and data visualizations using VOSviewer and the Bibliometrix (4.2.2) R package, revealing a growth trend in the number of publications produced in this field per year.

The publication analysis and trend curve on the topic showed that only one document was published prior to the 21st century. Since 2000, the number of documents has been progressively increasing, with 2022 being the year with the greatest level of production. Some research, such as that conducted by Aronson and Fermer (52), or more recently, one produced by Dong et al. (44), has pointed out the significant increase in interest in biomarker studies, showing a clear upwards trend since the end of the last decade. The growth trend in scientific production on cardiac troponin in young people shows that it has not yet reached a stage of maturity, and it could continue to grow in the coming years. In addition, numerous studies suggest that it is necessary to continue conducting research in this area, to establish standardized protocols and to perform more studies with larger populations (53–55).

The keyword co-occurrence analysis revealed that the words "exercise", "brain natriuretic peptide" and "adolescent" had the highest frequencies of co-occurrence in the research on the topic analysed, creating three clusters. This allows us to ascertain which topics attract more interest in the research community.

Word clouds are another visualization technique, but their goal is completely different, as they provide the user with an overview of the content of a collection of texts. The size of the word (as the source's size) indicates the frequency with which it appears in

the text (56). The goal of using a word cloud in an article is to enable searching for the most frequent terms, which indicates the subtopics that receive the most attention in those fields of study (57–59). Terms such as "adolescent", "exercise", and "troponin-t release" were the words that were viewed in the largest and most centralized cloud, which suggests a growing interest in these terms. Authors such as Bjornan et al. (56) suggest that the largest and most central words attract more users, which may lead to new work on that topic.

For the co-authorship analysis, metadata from all of the documents were used to reveal the most productive authors, as well as the most impactful sources. The analysis showed how a large number of authors (508) contributed to the documents; being 7.43 the average number of authors per article. As Mattson et al. (60) point out, this kind of analysis is not suited to determining individual contributions, and therefore, the role of each author is not very clear. Traditionally, in multiauthor articles, the first position is occupied by the senior contributor, while the final position is reserved for the supervisor (61). The authors with the greatest impact in the studied category generally held relevant positions, either as the main author or as the supervisor. This practice is becoming increasingly common due to the influence of experimental sciences, which accord equal importance to the first and last author based on the author/director relationship (43, 51). This interpretation is known as the FLAE approach, which stands for first–last–author–emphasis (62). In this sense, our work reflects how Nie and George are referents within the context of this topic, and they represent two key figures in the research on cardiac troponin in pediatric populations.

The h-index quantifies the research performance of individual scientists, incorporating both the number and visibility of their publications (43). In the present study, an even distribution of the h-index can be seen among the most productive authors, where the number of citations that a scientific subcommunity grants to a manuscript is undoubtedly and directly related to the number of researchers that make up said subcommunity (48).

As Jung et al. (63) show, in a context where there is great interest in intensifying international collaboration within scientific practice, our work aims to present a way to measure and visualize international collaborative work at an institutional level. The remarkable collaboration among the different authors, as observed in our study, is in line with findings from studies such as those by Zhu et al. (64) and Yu et al. (49). The joint analysis of collaboration indices to determine the relationships between the different authors of the documents allows us to better interpret the structure of international scientific collaboration networks in the study category (65). The analysis has enabled us to map and identify existing collaborations within the field of cardiac troponin in pediatric populations.

Studying the publication of documents in different countries can elucidate the importance and impact of each country in an area of study. Our work shows that all of the G7 members, with the exception of Japan, are among the most productive countries in this research area. The dominance pattern of the G7 has been seen in most scientific fields, reflecting the high economic activity and academic level of these countries (66–69, 31). Most of the articles are originated in three advanced economies: China, North America, and Western Europe. Undoubtedly, these territories, with strongly developed economies and access to the most innovative and advanced research, can support research in the field of medicine and health (70, 71). In 2022, the World Health Organization (WHO) presented in its Annual Report the finding that high-income countries spent a higher percentage of their GDPs on the health sector (72). As Zheng et al. suggest (73), this pattern is similar to that of other fields of scientific research, where collaborating countries tend to be geographically correlated and revolve around the most productive countries in terms of publication output.

Regarding our citation analysis, the most productive institutions in our study are located in China, the United States, and Europe. One reason may be that larger universities provide greater opportunities for scientists to collaborate and work on similar topics, and co-authorship can lead to higher citation rates (43).

The cooperative network of research institutions reveals the distribution of research strengths in the field of cardiac troponin. The United States, England, and China have the most extensive cooperative relationships. A wide range of research has produced results similar to ours in the field of medicine and health (31, 43, 74–76, 33). In the realm of science, collaborative work and institutional and disciplinary structures face the challenge of a global context. This new research paradigm has led to initiatives such as e-Science in countries like the United Kingdom. This is a program of global collaboration in key areas of science, and focused on the development of the country's next-generation infrastructure. According to Jirotka et al. (77), initiatives such as e-Science are necessary and essential for global collaboration, enabling the broad handling of scientific data in a multidisciplinary manner.

As some authors, including Forero-Peña et al. (78) and Rojas-Montesino et al. (74), suggest, there is a strong contrast between Latin America (excluding Mexico) and Africa vs. the US, Europe, and China, since it has been found that scientific contributions from geographic areas such as Africa and Latin America represent a low percentage in the global production of research on cardiac troponins due, as these same authors suggest, to low economic investment, limited institutional development, a limited number of researchers, and the high costs of reagents and equipment—even though this percentage has increased in the last decade.

Regarding the analysis of production and institutional collaboration, as seen in the co-occurrence network, Liverpool John Moores University and Macao Polytechnic Institute take central positions with the thickest line between them, which represents a very collaborative, narrow relationship. In addition, the connecting lines between countries are intertwined, indicating that academics and institutions from each country contribute their respective strengths to eliminate academic barriers and promote academic cooperation and exchange.

Previous studies have suggested that international research collaboration is motivated by the beneficial exchange of resources, skills, and expertise, as well as by sharing the high cost of research (79). In this topic, it is worth highlighting the work published by Adams in 2013 in the journal Nature, where he claimed that "the fourth era of research" would be dominated by

research driven by international collaboration. In his work, the author recommended incentivizing institutions to participate in international research to avoid the risk of marginalization and the loss of talented researchers (80).

Regarding the journals with the highest numbers of publications (Nps) on cardiac troponin in pediatric populations, we were able to observe how specific journals on pediatrics (Pediatric Cardiology, Pediatric Exercise Science, and Acta Pediatrica) were of great interest in regard to the publication of specific works on the theme of our analysis. In addition, it was possible to observe that the results obtained show that a significant number of studies were concentrated in a very specific and small core of journals. Our results are in line with other works where Bradford's Law was fulfilled (44, 43, 76, 81). One may recall that Bradford's Law is a model that estimates the exponential decrease in performance of expanding the search for references in scientific journals (82). Authors such as Highhouse et al. (83) point out that, very often, authors tend to send their papers to journals they consider to be the most important.

If we pay attention to the quartiles of the analysed publications, the vast majority were published in journals in the first and second quartiles. Publishing papers in high-impact journals (Q1 and Q2) has numerous advantages, starting with the fact that researchers who publish in high-impact journals can advance in their scientific careers and be recognized as experts in the subject or area of study (84). In addition, as indicated by Derntl (85) and Cáceres Castellano (86), publishing in high-impact journals helps researchers develop their criteria, increases self-esteem, strengthens researchers' confidence in what they do, generates ambition to continue researching and publishing more papers, and ensures the quality of new research through peer review.

The document with the greatest number of citation, is an article published in the Journal of Applied Physiology in 2012 (87). In a study carried out by Stephan van der Zwaard et al. (88), it was concluded that the Journal of Applied Physiology had published high-impact research, being a reference within the field of exercise physiology, obtaining impact values high. It is no coincidence, then, that it has always occupied the first positions among the most relevant journals, in the two categories in which it is classified within Web of Science, which are "Physiology" and "Sports Sciences".

Regarding future lines of research, it is proposed that researchers analyze proceedings and observe whether their inclusion produces changes in the rankings and/or in the indicators obtained in this work. It would also be interesting to analyze the performance of cardiac troponin research grants and how these translates into publications. Finally, it would be fascinating to follow the temporal evolution of the research groups already identified, as well as to detect the births of groups, the creation of new institutional collaborations, and the evolution of the impact of research in this field and its transfer to society.

4.1 Limitations

Even though bibliographic records have been obtained from the most relevant sources at the national and international levels, it is possible that papers have been overlooked due to failures in our search strategy. Articles and reviews were examinated, and there may be some proceedings derived from some participation or presentation at conferences that have not been included.

Second, although the choice of papers was reviewed by two investigators, biases that could stem from opinions or background knowledge were uncontrollable.

Finally, the rankings of institutions, authors, countries, and journals were based on data extracted and provided by WoSCC. It has been discussed in numerous works that there are cases in which the name of the author or the institution may be spelled differently, may be abbreviated, or the author may have affiliations with several institutions. This could lead to inaccurate productivity reports from these agencies or authors.

5 Conclusions

To the best of our knowledge, this is the first bibliometric analysis on the investigation of cardiac troponin and physical activity in pediatric populations. Terms such as "troponin" or "cardiac troponin" have given way to more specific terms such as "cardiac troponin-t", "cardiac biomarkers", and "NT-proBNP". The number of articles has progressively increased, especially in the last decade. The vast majority of the papers were published in a specific number of journals and mainly in a certain subject area (Pediatrics). A very specific index of referring authors was observed; only three authors had 10 or more articles. The number of works carried out in collaboration with foreign institutions was high, with an important presence of institutions such as Liverpool John Moores University and Macao Polytechnic Institute. Four large groups of researchers were identified, geographically located in the USA, England, Spain, and China. A total of 508 authors, hailing from 30 countries, participated. They were affiliated with 256 institutions, and the works were published in 65 different journals from around the world.

This study contributes to a better understanding of productivity and collaboration, and it identifies the main scientific institutions, sources chosen for scientific dissemination, and the main scientists.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Author contributions

VH-G: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Supervision, Writing – original draft, Writing – review & editing. EC-M: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Visualization, Writing –

review & editing. CJ-D: Conceptualization, Funding acquisition, Investigation, Writing – review & editing. ÁP-R: Funding acquisition, Investigation, Visualization, Writing – review & editing. AL-A: Conceptualization, Supervision, Writing – original draft. JR-M: Project administration, Supervision, Writing – original draft, Writing – review & editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article.

This research was funded by the State Program for Research, Development and InnovationOriented to the Challenges of Society, within the framework of the State Plan for R+D+I 2020–2024. The title of the project is: "Evaluación de diversos parámetros de salud y niveles de actividad física enla escuela primaria y secundaria", grant number PID2020-117932RB-I00. The consolidated research group is the Human Movement Generalitat de Catalunya, 021 SGR 01619.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Cordero A, Masiá MD, Galve E. Ejercicio físico y salud. *Rev esp Cardiol.* (2014) 67 (9):748–53. doi: 10.1016/j.recesp.2014.04.007

2. Legaz-Arrese A, López-Laval I, George K, Puente-Lanzarote JJ, Mayolas-Pi C, Serrano-Ostáriz E, et al. Impact of an endurance training program on exercise-induced cardiac biomarker release. *Am J Physio-Heart Circul Physiol.* (2015) 308 (8):913–20. doi: 10.1152/ajpheart.00914.2014

3. Cirer-Sastre R, Legaz-Arrese A, Corbi F, López-Laval I, Puente-Lanzarote J, Hernández-González V, et al. Effect of training load on post-exercise cardiac troponin T elevations in young soccer players. *Int J Environ Res Public Health.* (2019) 16(23):4853. doi: 10.3390/ijerph16234853

4. Legaz-Arrese A, López-Laval I, George K, Puente-Lanzarote JJ, Moliner-Urdiales D, Ayala-Tajuelo VJ, et al. Individual variability in cardiac biomarker release after 30min of high-intensity rowing in elite and amateur athletes. *Appl Physiol Nutr Metab.* (2015) 40(9):951–8. doi: 10.1139/apnm-2015-0055

5. Cirer-Sastre R, Legaz-Arrese A, Corbi F, López-Laval I, George K, Reverter-Masia J. Influence of maturational status in the exercise-induced release of cardiac troponin T in healthy young swimmers. *J Sci Med Sport.* (2021) 24(2):116–21. doi: 10.1016/j.jsams.2020.06.019

6. Legaz-Arrese A, López-Laval I, George K, Puente-Lanzarote J, Castellar-Otín C, Reverter-Masià J, et al. Individual variability of high-sensitivity cardiac troponin levels after aerobic exercise is not mediated by exercise mode. *Biomarkers.* (2015) 20(4):219–24. doi: 10.3109/1354750X.2015.1068851

7. López-Laval I, Legaz-Arrese A, George K, Serveto-Galindo O, González-Rave JM, Reverter-Masia J, et al. Cardiac troponin I release after a basketball match in elite, amateur and junior players. *Clin Chem Lab Med.* (2016) 54(2):333–8. doi: 10.1515/cclm-2015-0304

8. Sribhen K, Piyophirapong S, Wannasilp N. Cardiac troponin T concentrations in healthy adolescents. *Clin Chim Acta.* (2010) 411(19-20):1542–3. doi: 10.1016/j.cca.2010.05.042

9. Bohn MK, Higgins V, Kavsak P, Hoffman B, Adeli K. High-sensitivity generation 5 cardiac troponin T sex- and age-specific 99th percentiles in the CALIPER cohort of healthy children and adolescents. *Clin Chem.* (2019) 65(4):589–91. doi: 10.1373/clinchem.2018.299156

10. Sigurdardottir FD, Lyngbakken MN, Holmen OL, Dalen H, Hveem K, Røsjø H, et al. Relative prognostic value of cardiac troponin I and C-reactive protein in the general population (from the nord-trøndelag health [HUNT] study). *Am J Cardiol.* (2018) 121(8):949–55. doi: 10.1016/j.amjcard.2018.01.004

11. Thorsteinsdottir I, Aspelund T, Gudmundsson E, Eiriksdottir G, Harris TB, Launer LJ, et al. High-sensitivity cardiac troponin i is a strong predictor of cardiovascular events and mortality in the ages-Reykjavik community-based cohort of older individuals. *Clin Chem.* (2016) 62(4):623–30. doi: 10.1373/clinchem.2015.250811

12. Collinson P, Boa FG, Gaze DC. Measurement of cardiac troponins. *Review Article Ann Clin Biochem.* (2001) 38:423–49. doi: 10.1177/000456320103800501

13. Sandoval Y, Smith SW, Apple FS. Present and future of cardiac troponin in clinical practice: a paradigm shift to high-sensitivity assays. *Am J Med.* (2016) 129:354–65. doi: 10.1016/j.amjmed.2015.12.005

14. Clerico A, Zaninotto M, Padoan A, Masotti S, Musetti V, Prontera C, et al. Chapter five—evaluation of analytical performance of immunoassay methods for cTnI and cTnT: from theory to practice. *Adv Clin Chem.* (2019) 93:239–62. doi: 10.1016/bs.acc.2019.07.005

15. Whu HBA, Christenson RH, Greene D, Jaffe AS, Kavsak PA, Ordóñez-Llanos J, et al. Clinical laboratory practice recommendations for the use of cardiac troponin in acute coronary syndrome: expert opinion from the academy of the American association for clinical chemistry and the task force on clinical applications of cardiac bio-markers of the international federation of clinical chemistry and laboratory medicine. *Clin Chem.* (2018) 64(4):645–55. doi: 10.1373/clinchem.2017.277186

16. Alquézar Arbé A, Santaló Bel M, Sionis A. Interpretación clínica de la determinación de troponina T de elevada sensibilidad. *Med Clin.* (2015) 145:258–63. doi: 10.1016/j.medcli.2014.11.004

17. Haider DG, Klemenz T, Fiedler GM, Nakas CT, Exadaktylos AK, Leichtle AB. High sensitive cardiac troponin T: testing the test. *Int J Cardiol.* (2017) 228:779–83. doi: 10.1016/j.ijcard.2016.10.043

18. Meigher S, Thode HC, Peacock WF, Bock JL, Gruberg L, Singer AJ. Causes of elevated cardiac troponins in the emergency department and their associated mortality. *Acad Emerg Med.* (2016) 23(11):1267–73. doi: 10.1111/acem.13033

19. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, et al. Fourth universal definition of myocardial infarction (2018). *J Am Coll Cardiol.* (2018) 72 (18):2231–64. doi: 10.1016/j.jacc.2018.08.1038

20. Gresslien T, Agewall S. Troponin and exercise. *Int J Cardiol.* (2016) 221:609–21. doi: 10.1016/j.ijcard.2016.06.243

21. Legaz-Arrese A, George K, Carranza-Garcia LE, Munguía-Izquierdo D, Moros-García T, Serrano-Ostáriz E. The impact of exercise intensity on the release of cardiac biomarkers in marathon runners. *Eur J Appl Physiol.* (2011) 111:2961–7. doi: 10.1007/s00421-011-1922-3

22. Peretti A, Mauri L, Masarin A, Annoni G, Corato A, Maloberti A, et al. Cardiac biomarkers release in preadolescent athletes after an high intensity exercise. *High Blood Press Cardiovasc Prev.* (2018) 25(1):89–96. doi: 10.1007/s40292-017-0243-y

23. Roth HJ, Leithäuser RM, Doppelmayr H, Doppelmayr M, Finkernagel H, Von Duvillard SP, et al. Cardiospecificity of the 3rd generation cardiac troponin T assay during and after a 216km ultra-endurance marathon run in death valley. *Clin Res Cardiol.* (2007) 96(6):359–64. doi: 10.1007/s00392-007-0509-9

24. Middleton N, George K, Whyte G, Gaze D, Collinson P, Shave R. Cardiac troponin T release is stimulated by endurance exercise in healthy humans. *J Am Coll Cardiol.* (2008) 52(22):1813–4. doi: 10.1016/j.jacc.2008.03.069

25. Legaz-Arrese A, Carranza-García LE, Navarro Orocio R, Valadez-Lira A, Mayolas-Pi C, Munguia-Izquierdo D, et al. Cardiac biomarker release after endurance exercise in male and female adults and adolescents. *J Pediatr.* (2017) 191:96–102. doi: 10.1016/j.jpeds.2017.08.061

26. Thomas MR, Lip GYH. Novel risck markers and risk assessments for cardiovascular disease. *Crc Res.* (2017) 120(1):133–49. doi: 10.1161/CIRCRESAHA.116.309955

27. Ruiz JR, Castro-Piñero J, España-Romero V, Artero EG, Ortega FB, Cuenca MM, et al. Field-based ditness assessment in young people: the ALPHA health-related fitness test battery for children and adolescents. *Br J Sports Med*. (2011) 45 (6):518–24. doi: 10.1136/bjsm.2010.075341

28. Cirer-Sastre R, Legaz-Arrese A, Corbi F, George K, Nie J, Carranza-García LE, et al. Cardiac biomarker release after exercise in healthy children and adolescents: a systematic review and meta-analysis. *Pediatr Exerc Sci*. (2019) 31(1):28–36. doi: 10.1123/pes.2018-0058

29. Papamichail A, Androulakis E, Xanthopoulos A, Briasoulis A. Effect of training load on post-exercise cardiac biomarkers in healthy children and adolescents: a systematic review of the existing literature. *J Clin Med*. (2023) 12(6):2419. doi: 10.3390/jcm12062419

30. Ospina-Mateus H, Quintana Jiménez LA, Lopez-Valdez FJ, Salas Navarro K. Bibliometric análisis in motorcycle accident research: a global overview. *Scientometrics*. (2019) 121:793–815. doi: 10.1007/s11192-019-03234-5

31. Khan MS, Ullah W, Bin Riaz I, Bhulani N, Manning WJ, Tridandapani S, et al. Top 100 cited articles in cardiovascular magnetic resonance: a bibliometric analysis. *J Cardiovasc Magn Reason*. (2016) 18:87. doi: 10.1186/s12968-016-0303-9

32. Hernández-Gonzalez V, Carné-Torrent JM, Pano-Rodríguez A, Reverter-Masia J. The impact of Ph.D., funding, and continued publications by sports sciences PhDs, 1-year post PhD-defence. *Transinf*. (2022) 34:1–14. doi: 10.1590/2318-0889202234e210051

33. Hu S, Zhou W, Wang S, Xiao Z, Li Q, Zhou H, et al. Global research trends and hotspots on mitochondria in acute lung injury from 2012 to 2021: a bibliometric analysis. *Int J Environ Res Public Health*. (2023) 20:585. doi: 10.3390/ ijerph20010585

34. Aleixandre Benavent R, Porcel Torrens A. El factor de impacto y los cómputos de citasen la evaluación de la actividad científica y las revistas médicas. *Trastor Adict*. (2000) 2(4):264–71.

35. López Piñero JM, Terrada ML. Los indicadores bibliométricos y la evaluación de la actividad médico-científica (III) los indicadores de producción, circulación y dispersión, consumo de la información y repercusión. *Med Clín*. (1992) 98:142–8.

36. Van Raan AFJ. Evaluación de la excelencia científica de programas de investigación: un punto primordial en la toma de decisiones. *IPTS Report*. (1999) 40:40.

37. Barabásis AL, Jeong H, Néda Z, Ravasz E, Dchubert A, Vicsek T. Evolution of the social network of scientific collaborations. *Phys A Stat Mech App*. (2002) 311(3-4):590–614. doi: 10.1016/S0378-4371(02)00736-7

38. Aleixandre-Benavent R, Alonso-Arroyo A, González de Dios J, Sempere ÁP, Castelló-Cogollos L, Bolaños-Pizarro M, et al. Coautoría y redes de colaboración en la investigación española sobre esclerosis múltiple (1996-2010). *Rev Neurol*. (2013) 57(4):157–66. doi: 10.33588/rn.5704.2013125

39. Carvajal Tapia AE, Gutiérrez Tapia EA. Public health, environmental and occupational health: a bibliometric study of the scientific participation of South America. *Rev Med Chile*. (2019) 147:530–6. doi: 10.4067/S0034-98872019000400531

40. Sweileh WM, Zyoud SH, Al-Javi SW, Sawalha AF. Public, environmental, and occupational health research activity in Arab countries: bibliometric, citation, and collaboration analysis. *Archiv Public Health*. (2015) 73:1. doi: 10.1186/2049-3258-73-1

41. Gagné T, Lapalme J, McQueen DV. Multidisciplinarity in health promotion a bibliometric analysis of current research. *Health Promot Int*. (2018) 33(4):610–21. doi: 10.1093/heapro/dax002

42. Tricco AC, Runnels V, Sampson M, Bouchard L. Shifts in the use of population health, health promotion, and public health. *Can J Public Health*. (2008) 99(6):466–71. doi: 10.1007/BF03403777

43. Hernández-González V, Carné-Torrent JM, Jové-Deltell C, Pano-Rodríguez Á, Reverter-Masia J. The top 100 most cited scientific papers in the public, environmental & occupational health category of web of science: a bibliometric and visualized analysis. *Int J Environ Res Public Health*. (2022) 19:9645. doi: 10.3390/ijerph19159645

44. Dong X, Xie Y, Xu J, Qin Y, Zheng Q, Hu R, et al. Global historical retrospect and future prospects on biomarkers of heart failure: a bibliometric analysis and science mapping. *Heliyon*. (2023) 9:1–15. doi: 10.1016/j.heliyon.2023.e13509

45. Hernández-González V, Pano-Rodriguez A, Reverter-Masia J. Spanish doctoral theses in physical activity and sports sciences and authors' scientific publications (LUSTRUM 2013–2017). *Scientometrics*. (2020) 122:661–79. doi: 10.1007/s11192-019-03295-6

46. Ogunsakin RE, Ebenezer O, Ginindza TG. A bibliometric analysis of the literature on norovirus disease from 1991 to 2021. *Int J Environ Res Public Health*. (2022) 19:2508. doi: 10.3390/ijerph19052508

47. Wang S, Zhou H, Zheng L, Zhu W, Zhu L, Feng D, et al. Global trends in research of macrophages associated with acute lung injury over past 10 years: a bibliometric analysis. *Front Immunol*. (2021) 12:669539. doi: 10.3389/fimmu.2021.669539

48. Ortega-Rubio A, Murillo-Amador B, Troyo-Diéguez E, Valdez-Cepeda D. El índice h: sobrevaloración de su uso en la estimación del impacto del que hacer científico en méxico. *Terra Latinoamericana*. (2021) 39:39. doi: 10.28940/terra.v39i0.895

49. Yu Y, Li Y, Zhang Z, Gu Z, Zhong H, Zha Q, et al. A bibliometric analysis using VOSviewer of publications on COVID-19. *Ann Transl Med*. (2020) 8(13):816. doi: 10.21037/atm-20-4235

50. Van Eck NJ, Waltman L, Dekker R, Van den Berg J. A comparison of two techniques for bibliometric mapping: multidimensional scaling and VOS. *J Assoc Inf Sci Technol*. (2010) 61(12):2405–16. doi: 10.1002/asi.21421

51. Aria M, Cuccurullo C. Bibliometrix: una herramienta R para el análisis integral de mapas científicos. *J Informetr*. (2017) 11(4):959–75. doi: 10.1016/j.joi.2017.08.007

52. Aronson JL, Ferner RE. Biomarkers-a general review. *Curr Protoc Pharmacol*. (2017) 76:9. doi: 10.1002/cpph.19

53. Costache AD, Leon-Constantin MM, Roca M, Mas Taleru A, Anghel RC, Zota IM, et al. Cardiac biomarkers in sports cardiology. *J. Cardiovasc. Dev. Dis*. (2022) 9:453. doi: 10.3390/jcdd9120453

54. Kiess A, Green J, Willenberg A, Ceglarek U, Dähnert I, Jurkutat A, et al. Age-dependent reference values for hs-troponin T and NT-proBNP and determining factors in a cohort of healthy children (the LIFE child study). *Pediatr Cardiol*. (2022) 43:1071–83. doi: 10.1007/s00246-022-02827-x

55. Clerico A, Aimo A, Cantinotti A. High-sensitivity cardiac troponins in pediatric population. *Clin Chem Lab Med*. (2022) 60(1):18–32. doi: 10.1515/cclm-2021-0976

56. Bjørnar T, Bjørnestad S, Chen W, Nyre L. Word cloud visualisation of locative information. *J Location Based Services*. (2015) 9(4):254–72. doi: 10.1080/17489725.2015.1118566

57. Mulay P, Joshi R, Chaudhari A. Distributed incremental clustering algorithms: a bibliometric and word-cloud review analysis. *Sci Technol Libr*. (2020) 39:289–306. doi: 10.1080/0194262X.2020.1775163

58. Tugce Guler A, Waaijer CJF, Palmblad M. Scientific workflows for bibliometrics. *Scientometrics*. (2016) 107:385–98. doi: 10.1007/s11192-016-1885-6

59. Patil RR, Kumar S, Rani R, Agrawal P, Pippal SK. A bibliometric and word cloud analysis on the role of the internet of things in agricultural plant disease detection. *Appl. Syst. Innov*. (2023) 6:27. doi: 10.3390/asi6010027

60. Mattsson P, Sundberg CJ, Laget P. Is correspondence reflected in the author position? A bibliometric study of the relation between corresponding author and byline position. *Scientometrics*. (2011) 87:99–105. doi: 10.1007/s11192-010-0310-9

61. Bruni A, Giulia Serra F, Gallo V, Deregibus A, Castroflorio T. The 50 most-cited articles on clear aligner treatment: a bibliometric and visualized analysis. *Am J Orthod Dentofacial Orthop*. (2021) 159(4):343–62. doi: 10.1016/j.ajodo.2020.11.029

62. Tscharntke T, Hochberg ME, Rand TA, Resh VH, Krauss J. Author sequence and credit for contributions in multiauthored publications. *PLoS Biol*. (2007) 5 (1):13–4. doi: 10.1371/journal.pbio.0050018

63. Jung N, Ruiz-León AA. Lo local y lo global de la colaboración científica: ¿qué significa y cómo visualizarlo y medirlo? *Rev Esp Doc Cien*. (2018) 41(2):1–15. doi: 10.3989/redc.2018.2.1463

64. Zhu Y, Zhang C, Wang J, Xie Y, Wang L, Xu F. The top 100 highly cited articles on anterior cruciate ligaments form 2000 to 2019: a bibliometric and visualized analysis. *Orthop Traumatol Surg Res*. (2021) 107(8):1–8. doi: 10.1016/j.otsr.2021.102988

65. Russell JM, Madera Jaramillo MJ, Ainsworth S. El análisis de redes en el estudio de la colaboración científica. *Rev Hisp Anál. Redes Sociales*. (2009) 17(2):39–47.

66. Jia X, Dai T, Guo X. Comprehensive exploration of urban health by bibliometric analysis: 35 years and 11,299 articles. *Scientometrics*. (2014) 99(3):881–94. doi: 10.1007/s11192-013-1220-4

67. Yang L, Chen Z, Liu T, Gong Z, Yu Y, Wang J. Global trends of solid waste research from 1997 to 2011 by using bibliometric analysis. *Scientometrics*. (2013) 96 (1):133–46. doi: 10.1007/s11192-012-0911-6

68. Liu X, Zhan FB, Hong S, Niu B, Liu Y. A bibliometric study of earthquake research: 1900–2010. *Scientometrics*. (2012) 92(3):747–65. doi: 10.1007/s11192-011-0599-z

69. Mi J, Zhang L, Sun W, Wang Z, Yang P, Zhang J, et al. Research hotspots and new trends in the impact of resistance training on aging, bibliometric and visual analysis based on CiteSpace and VOSviewer. *Front Public Health*. (2023) 11:1133972. doi: 10.3389/fpubh.2023.1133972

70. Banerjee F, Khatri N, Kaur A, Elhence A. Bibliometric analysis of top 100 systematic reviews and meta-analyses in orthopaedic literature. *Indian J Orthop*. (2022) 56(5):762–70. doi: 10.1007/s43465-022-00604-9

71. Nguyen TT, Ha L, Nguyen LH, Vu LG, Do HT, Boyer L, et al. A global bibliometric analysis of intimate partner violence in the field of HIV/AIDS: implications for interventions and research development. *Front Public Health*. (2023) 11:1105018. doi: 10.3389/fpubh.2023.1105018

72. World Health Organization (WHO). *Annual Report. Access to Medicines and Health Products Programme*. Geneva, Switzerland: WHO (2020).

73. Zheng T, Wang J, Wang Q, Nie C, Shi Z, Wang X, et al. A bibliometric analysis of micro/nano-bubble related research: current trends, present application, and future prospects. *Scientometrics*. (2016) 109(1):53–71. doi: 10.1007/s11192-016-2004-4

74. Ogunsakin RE, Ebenezer O, Jordaan MA, Shapi M, Ginindza TG. Mapping scientific productivity trends and hotspots in remdesivir research publications: a bibliometric study from 2016 to 2021. *Int J Environ Res Public Health*. (2022) 19:8845. doi: 10.3390/ijerph19148845

75. Rojas-Montesino E, Méndez D, Espinosa-Parrilla Y, Fuentes E, Palomo I. Analysis of scientometric indicators in publications associated with healthy aging in

the world, period 2011–2020. *Int J Environ Res Public Health*. (2022) 19:8988. doi: 10.3390/ijerph19158988

76. Feng XW, Hadizadeh M, Cheong JPG. Global trends in physical-activity research of autism: bibliometric analysis based on the web of science database (1980–2021). *Int J Environ Res Public Health*. (2022) 19:7278. doi: 10.3390/ijerph19127278

77. Jirotka M, Lee CP, Olson GM. Supporting scientific collaboration: methods, tools and concepts. *Comput Supported Coop Work*. (2013) 22:667–715. doi: 10.1007/s10606-012-9184-0

78. Forero-Peña DA, Carrión-Nessi FS, Camejo-Ávila NA, Forero-Peña MJ. COVID-19 in Latin America: a systematic review and bibliometric analysis. *Rev. Salud Pública*. (2020) 22:246–52. doi: 10.15446/rsap.V22n2.86878

79. Chen K, Zhang Y, Fu X. International research collaboration: an emerging domain of innovation studies? *Res Policy*. (2019) 48(1):149–68. doi: 10.1016/j.respol.2018.08.005

80. Adams J. The fourth age of research. *Nature*. (2013) 497(7451):557–60. doi: 10.1038/497557a

81. Desai N, Veras L, Gosain A. Using bradford's law of scattering to identify the core journals of pediatric surgery. *J Surg Res*. (2018) 229:90–5. doi: 10.1016/j.jss.2018.03.062

82. Bradford SC. Sources of information on specific subjects. *Engineering*. (1934) 137:85–6.

83. Highhouse S, Zickar MJ, Melick SR. Prestige and relevance of the scholarly journals: impressions of SIOP members. *Ind Organ Psychol*. (2020) 13(3):273–90. doi: 10.1017/iop.2020.2

84. Torres-Salinas D, Cabezas-Clavijo A. Cómo Publicar en Revistas Científicas de Impacto: Consejos y Reglas Sobre Publicación Científica. EC·Working Paper. (2013):31. Available online at: https://digibug.ugr.es/bitstream/handle/10481/28137/C%F3mo%20Publicar%20en%20Revistas%20Cient%EDficas.pdf?sequence=1 (accessed Februray 01, 2021).

85. Derntl M. Basic of research paper writing and publishing. *Int J Technol Enhanc Learn*. (2014) 6:105–23. doi: 10.1504/IJTEL.2014.066856

86. Cáceres Castellanos G. La importancia de publicar los resultados de investigación. *Rev Fac Ing*. (2014) 23:7–8. doi: 10.19053/01211129.2795

87. Tian Y, Nie JL, Juang CY, George KP. The kinetics of highly sensitive cardiac troponin T release after prolonged treadmill exercise in adolescent and adult athletes. *J Appl Physio*. (2012) 113(3):418–25. doi: 10.1152/japplphysiol.00247.2012

88. Van der Zwaard S, Arie-Willem de Leeuw L, Meerhoff A, Bodine SC, Knobbe A. Article with impact: insights into 10 years of research with machine learning. *J Appl Physiology*. (2020) 129:967–79. doi: 10.1152/japplphysiol.00489.2020

frontiers | Frontiers in Pediatrics

TYPE Original Research
PUBLISHED 16 February 2024
DOI 10.3389/fped.2024.1345141

OPEN ACCESS

EDITED BY
Zhen-Yu Zhang,
KU Leuven, Belgium

REVIEWED BY
Lijian Xie,
Shanghai Children's Hospital, China
Ozgur Kasapcopur,
Istanbul University-Cerrahpasa, Türkiye

*CORRESPONDENCE
Ming-Guo Xu
✉ 18938690175@163.com

†These authors have contributed equally to this work

RECEIVED 27 November 2023
ACCEPTED 29 January 2024
PUBLISHED 16 February 2024

CITATION
Liao J-W, Guo X, Li X-X, Xian J-M, Chen C and Xu M-G (2024) Exploring the diagnostic value of CLR and CPR in differentiating Kawasaki disease from other infectious diseases based on clinical predictive modeling.
Front. Pediatr. 12:1345141.
doi: 10.3389/fped.2024.1345141

Exploring the diagnostic value of CLR and CPR in differentiating Kawasaki disease from other infectious diseases based on clinical predictive modeling

Jin-Wen Liao[1†], Xin Guo[2†], Xu-Xia Li[3], Jia-Ming Xian[2], Cheng Chen[2] and Ming-Guo Xu[3*]

[1]The Department of Pediatrics, Longgang District Maternity & Child Healthcare Hospital of Shenzhen City (Longgang Maternity and Child Institute of Shantou University Medical College), Shenzhen, Guangdong Province, China, [2]Neonatology, Longgang District Maternity & Child Healthcare Hospital of Shenzhen City (Longgang Maternity and Child Institute of Shantou University Medical College), Shenzhen, Guangdong Province, China, [3]The Department of Pediatrics, Third People's Hospital of Longgang District Shenzhen, Shenzhen, Guangdong Province, China

Background: Kawasaki disease (KD) is an important cause of acquired heart disease in children and adolescents worldwide. KD and infectious diseases can be easily confused when the clinical presentation is inadequate or atypical, leading to misdiagnosis or underdiagnosis of KD. In turn, misdiagnosis or underdiagnosis of KD can lead to delayed use of intravenous immunoglobulin (IVIG), increasing the risk of drug resistance and coronary artery lesions (CAL).
Objectives: The purpose of this study was to develop a predictive model for identifying KD and infectious diseases in children in the hope of helping pediatricians develop timely and accurate treatment plans.
Methods: The data Patients diagnosed with KD from January 2018 to July 2022 in Shenzhen Longgang District Maternity & Child Healthcare Hospital, and children diagnosed with infectious diseases in the same period will be included in this study as controls. We collected demographic information, clinical presentation, and laboratory data on KD before receiving IVIG treatment. All statistical analyses were performed using R-4.2.1 (https://www.rproject.org/). Logistic regression and Least Absolute Shrinkage with Selection Operator (LASSO) regression analyses were used to build predictive models. Calibration curves and C-index were used to validate the accuracy of the prediction models.
Results: A total of 1,377 children were enrolled in this study, 187 patients with KD were included in the KD group and 1,190 children with infectious diseases were included in the infected group. We identified 15 variables as independent risk factors for KD by LASSO analysis. Then by logistic regression we identified 7 variables for the construction of nomogram including white blood cell (WBC), Monocyte (MO), erythrocyte sedimentation rate (ESR), alanine transaminase (ALT), albumin (ALB), C-reactive protein to procalcitonin ratio (CPR) and C-reactive protein to lymphocyte ratio (CLR). The calibration curve and C-index of 0.969 (95% confidence interval: 0.960–0.978) validated the model accuracy.
Conclusion: Our predictive model can be used to discriminate KD from infectious diseases. Using this predictive model, it may be possible to provide an early determination of the use of IVIG and the application of antibiotics as soon as possible.

KEYWORDS

C-reactive protein to lymphocyte ratio, C-reactive protein to procalcitonin ratio, Kawasaki disease, infectious diseases, predictive model

1 Introduction

Kawasaki disease (KD) is a common vasculitis syndrome in childhood whose major complication is coronary artery lesions (CAL), which has a significant impact on the cardiovascular health of children and adolescents (1). KD is a major culprit in cardiovascular and cerebrovascular sequelae in children, adolescents and even in adulthood (2, 3). An epidemiologic survey in Shanghai from 2013 to 2017 showed KD incidence rates ranging from 68.8 to 107.3 per 100,000 children younger than 5 years of age (4). Japan has a relatively high prevalence, with surveys during 2018 showing a KD prevalence of 359 per 100,000 children aged 0–4 years (5). Europe has a relatively low incidence of KD, with an annual incidence of KD of approximately 10–15 per 100,000 children under 5 years of age (6). In Shanghai, China, 8.4% of KD patients receiving initial intravenous immunoglobulin (IVIG) develop drug resistance, and 9.1% of KD patients develop CAL (4). Also in Japan, 19.7% of KD patients who received initial IVIG therapy did not respond, 9.0% of KD patients were diagnosed with cardiac complications within 30 days of disease onset, and 2.6% of KD patients developed cardiac sequelae after the acute phase (5). The incidence of KD is increasing year by year, whereas the rate of CAL is decreasing, and these can be attributed to advances in the early diagnosis and initial treatment of KD.

However, KD is prevalent between the ages of 0 and 5 years, which is the same time when infectious diseases in children are prevalent. Early diagnosis of KD relies on specific clinical manifestations. However, when the clinical manifestations are inadequate or atypical, KD and infectious diseases can be easily confused with each other, leading to misdiagnosis or underdiagnosis of KD (7). Ultrasound findings of typical coronary artery abnormalities are also an important indicator for diagnosing KD, but CAL tends to be delayed, which makes diagnosing KD with ultrasound lagging behind, and the optimal window of time for initial IVIG therapy in KD is within 10 days of onset, with delayed treatment leading to increased risk of drug resistance and CALs (8, 9). A recent study in Turkey also showed that prolonged duration of IVIG treatment is the most important determinant of the occurrence of CAL (10). Therefore, in order to avoid underdiagnosis and misdiagnosis of KD, new diagnostic markers should be actively developed on the basis of clinical presentation and cardiac ultrasound. Although there is no single validated hematologic marker that can be used to differentiate KD from infectious diseases in children, a subset of studies have been devoted to exploring clinical models for the combined identification of KD from other diseases by laboratory markers and blood biomarkers, with results suggesting that these models have more robust diagnostic performance (7, 11). This reveals that clinical predictive models that combine multiple indicators may be an important way out to solve the dilemma of KD diagnosis.

In fact many factors have been identified as biomarkers of Kawasaki disease, such as inflammatory biomarkers such as white blood cells (WBC), C-reactive protein (CRP) and procalcitonin (PCT), immunomarkers, proteomic markers, and genomic markers, but the common problem with these markers is that they have low sensitivity or specificity, and are of limited value when used individually to discriminate between KD and infectious diseases in children (12). C-reactive protein to procalcitonin ratio (CPR) helps to differentiate bacterial inflammation from non-bacterial inflammation, and C-reactive protein to lymphocyte ratio (CLR) is strongly correlated with the degree of infectious or non-infectious inflammatory response (13–15). Whether CLR and CPR are risk factors for KD is not yet known, and CLR and CPR have not yet been included in clinical prediction models for KD diagnosis.

In order to better identify children with Kawasaki disease (KD) and infectious diseases, we aimed to develop a clinical prediction tool with good predictive performance and strong interpretability by collecting demographic information and laboratory data from children, using lasso regression for variable screening and logistic regression for modelling, with a view to enhancing the early identification of children with KD by paediatricians.The study protocol and presentation of results were informed by the TRIPOD report list (16).

2 Methods

2.1 Data collection and inclusion criteria

The data Patients diagnosed with KD from January 2018 to July 2022 in Shenzhen Longgang District Maternity & Child Healthcare Hospital, and children diagnosed with infectious diseases in the same period will be included in this study as controls. Clinical information and laboratory data were collected separately for comparison between the KD and infection groups, and laboratory data for all KD patients were collected during the acute phase of KD and prior to treatment with IVIG. All children with KD were diagnosed according to the diagnostic criteria of the 2017 American Heart Association (AHA) guidelines (9). According to the guideline diagnostic criteria, a diagnosis of classic KD is made if the following conditions are met: fever for at least 5 days and at least 4 of the 5 main clinical features: 1. Erythema and cracking of lips, strawberry tongue, and/or erythema of oral and pharyngeal mucosa; 2. Bilateral bulbar conjunctival injection without exudate; 3. Rash: maculopapular, diffuse erythroderma, or erythema multiforme-like; 4. Erythema and edema of the hands and feet in acute phase and/or periungual desquamation in subacute phase; 5. Cervical lymphadenopathy ($\geq$1.5 cm diameter), usually unilateral. Incomplete Kawasaki Disease is based on the flowchart mentioned in the guidelines for assessing suspected incomplete Kawasaki Disease. Infants were excluded from the study if they met any of the following criteria: autoimmune disease, inherited metabolic disease; unexplained fever; abandonment of hospitalization or incomplete information. Eventually 20 patients with KD and 4,132 infected children were excluded, and then 187 patients with KD and 1,190 patients with infectious diseases were included.

The study was conducted in accordance with the Declaration of Helsinki (revised 2013) and approved by the Ethics Committee of Shenzhen Longgang District Maternity & Child Healthcare Hospital (protocol code IRB No. LGFYYXLLL-2022-025 in 2022.09.29), which also approved the waiver of informed consent as this was a retrospective study and therefore did not require informed consent consent.

2.2 Power analysis

Our study focuses on two key variables, CLR and CPR. Therefore, we calculated the sample size based on these two variables using a specific formula. We set the parameters to have a type I error of $\alpha = 0.05$, a type II error of $\beta = 0.1$, a sample size ratio of K = 1:1, and a threshold of $\Delta = 0$. This ultimately led to a maximum sample size of 54. It is clear that the samples we collected greatly exceeded this maximum sample size.

2.3 Variable selection

Based on clinical experience and previous clinical studies (11, 17), two researchers from the team collected clinical information and laboratory data from children with KD and infected children. Variables collected included gender, age, weight, clinical presentation, white blood cell (WBC), hemoglobin (HGB), Hematocrit (HCT), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), Platelet (PLT), Mean platelet volume (MPV), Platelet distribution width (PDW), Monocyte (MO), erythrocyte sedimentation rate (ESR), alanine transaminase (ALT), albumin (ALB), aspartate transaminase (AST), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), CLR and CPR. The study was retrospective and masked information such as patient name and hospitalization number when obtaining subject information from the medical record system to minimize selection bias in the study. The data collectors were full-time pediatricians who were familiar with the inclusion and exclusion criteria of the study subjects. Laboratory data are measured by the examiner according to uniform standards, while the examiner does not know in advance that the subject will be included in the study, which reduces information bias.

2.4 Statistical analysis

All statistical analyses were performed using R-4.2.1 (https://www.rproject.org/). In order to demonstrate the characteristics of the distribution of the clinical and laboratory data in the two groups, we have performed descriptive statistics and one-way analyses of the parameters in the two groups. We tested whether the quantitative data of the two groups conformed to a normal distribution. Quantitative data that conformed to normal distribution were described statistically as mean ± standard deviation and analysed for differences using the independent samples *t*-test, while non-normally distributed measurements were described statistically as median (interquartile range) and analysed for differences using the Mann–Whitney U rank sum test. Count data were statistically described as frequencies and percentages and analysed for differences using the chi-square test. The "glmnet" package in the R software was used to perform least absolute shrinkage and selection operator (LASSO) regressions to screen for the best predictors of KD (18). The predictors selected for the LASSO regression were included in the multivariate logistic regression analysis using the "rms" package to build the predictive model. Differences of $P < 0.05$ were considered statistically significant.

2.5 Predictive model and nomogram construction

We used LASSO regression analysis to determine the best predictors of KD, and the minimum coefficient λ was determined by cross-validation. The factors screened by the LASSO regression were incorporated into the logistic regression analysis to construct the predictive model. Then we presented the prediction model as a nomogram. The C-index was used to assess the predictive performance of the model, and the closer the C-index was to 1, the better the predictive ability. In addition, we use calibration curves and receiver operating characteristic curves (ROC) to show the performance of the model in terms of calibration and discrimination.

3 Results

3.1 Baseline clinical characteristics

A total of 1,377 children were enrolled in this study, 844 (61%) boys and 533 (59%) girls with a median age of 1.00 (1.00–2.00) years.187 patients with KD were included in the KD group and 1,190 children with infectious diseases were included in the infected group. Based on univariate analysis, we observed no statistical difference in age, MCH, MPV, PBW, MO between the two groups.WBC, MCV, PLT, ESR, ALT, NLR, PLR, CLR, CPR were significantly higher in KD group than in the infected group ($p < 0.05$), whereas the levels of HGB, HCT, MCHC, ALB, AST were significantly lower in KD group than in the infected group ($p < 0.05$). The general profile of the included children is shown in Table 1.

3.2 Selection of predictors

The data were first downscaled using LASSO regression to screen for independent risk factors for KD (Figures 1A,B). When the coefficient λ is optimal, the coefficients λ of the excluded variables are compressed to zero, while the coefficients of the remaining variables in the model are not zero. The results of our analysis indicate that the optimal value of λ corresponds to 15 remaining variables (Figure 1B). Therefore, the results of LASSO analysis

TABLE 1 Characteristics of the distribution of demographic information and laboratory data on children with KD and children with infectious diseases.

	Overall, $N = 1,377$[a]	Infection disease $N = 1,190$[a]	KD, $N = 187$[a]	p-value[b]
AGE(years-old)	1.00 (1.00, 2.00)	1.00 (1.00, 2.00)	1.00 (1.00, 2.00)	0.003
GENDER (male)	844 (61%)	723 (61%)	121 (65%)	0.303
WBC ($\times10^9$/l)	9.5 (6.8, 13.6)	8.9 (6.6, 12.5)	15.0 (10.8, 18.2)	<0.001
HGB(g/l)	117 (110, 123)	118 (112, 125)	110 (103, 116)	<0.001
HCT	35.60 (33.70, 37.50)	35.80 (34.00, 37.80)	33.60 (31.70, 35.55)	<0.001
MCV	80 (78, 83)	80 (78, 83)	81 (78, 84)	0.035
MCH	27.00 (25.60, 27.60)	27.00 (25.22, 27.58)	27.00 (25.75, 27.65)	0.787
MCHC	328 (321, 336)	329 (321, 336)	327 (319, 334)	0.028
PLT($\times10^9$/l)	296 (228, 377)	281 (222, 363)	366 (306, 435)	<0.001
MPV	9.60 (9.10, 10.20)	9.60 (9.03, 10.10)	9.70 (9.20, 10.20)	0.205
PDW	9.90 (9.00, 11.00)	9.90 (9.00, 11.00)	9.90 (9.10, 11.10)	0.434
MO	0.66 (0.45, 0.94)	0.65 (0.45, 0.93)	0.69 (0.49, 0.98)	0.052
ESR(mm/h)	22 (12, 43)	20 (11, 33)	69 (48, 86)	<0.001
ALT(U/l)	17 (14, 24)	17 (13, 22)	34 (17, 86)	<0.001
ALB(g/l)	42.3 (39.3, 44.8)	42.8 (40.4, 45.3)	36.5 (33.0, 39.2)	<0.001
AST(U/l)	40 (32, 49)	41 (33, 49)	34 (26, 52)	<0.001
NLR	1.25 (0.67, 2.56)	1.12 (0.62, 2.18)	2.58 (1.53, 4.65)	<0.001
PLR	85 (60, 126)	82 (58, 122)	107 (79, 158)	<0.001
CLR	4 (1, 12)	3 (1, 9)	18 (10, 39)	<0.001
CPR	53 (12, 167)	45 (10, 153)	123 (42, 392)	<0.001

KD, Kawasaki disease; WBC, white blood cell count; HGB, hemoglobin; HCT, Hematocrit; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; PLT, platelet count; MPV, Mean platelet volume; PDW, Platelet distribution width; MO, Monocyte; ESR, erythrocyte sedimentation rate; ALT, alanine aminotransferase; ALB, albumin; AST, aspartate aminotransferase; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; CLR, C-reactive protein to lymphocyte ratio; CPR, C-reactive protein to procalcitonin ratio.
[a]Median (IQR) for quantitative data, *n* (%) for qualitative data.
[b]Mann–Whitney U rank sum test analysis of quantitative data; Pearson's Chi-squared test analysis of qualitative data.

suggested that the 20 predictors were reduced to 15 predictors. Through multivariate logistic regression, we further filtered out 7 potential predictors with P-values < 0.05 in the logistic regression results from the above 15 predictors as the final variables for constructing the model (Figure 2). The seven predictors that were finalized included WBC, MO, ESR, ALT, ALB, CLR, and CPR.

3.3 Quantitative analysis of the degree of impact of CPR, CLR

The effects of CPR and CLR on KD were analyzed by restricted cubic spline modeling after considering the effects exerted by other factors in the prediction model (19). The results suggested that when the value of CLR was greater than 4.1, the risk of KD gradually increased as the value of CLR gradually increased (Figure 3A). When the value of CPR was greater than 53.2, the risk of KD gradually increased as the value of CPR gradually increased (Figure 3B).

3.4 Development of nomogram

A risk prediction nomogram was constructed from the seven variables with P-values < 0.05 in the logistic regression results (Figure 4). The C-index of the nomogram was 0.969 (95% confidence interval: 0.960–0.978), indicating that the model has good discriminatory and predictive ability.

3.5 Validation of the accuracy of the prediction model

To validate the accuracy of the predictive model, the ROC of the nomogram indicates that the model has high accuracy (Figure 5). In addition, calibration is required to plot the curves to evaluate the predictive model, and it can be seen that the predicted probabilities of the model remain essentially the same as the actual probabilities (Figure 6).

4 Discussion

In this study, we developed a predictive model for early recognition of Kawasaki disease and childhood infectious diseases. We found that WBC, MO, ESR, ALT, ALB, CLR and CPR were independent risk factors for KD. A nomogram constructed from these variables can be very helpful for pediatricians to identify KD and infectious diseases in children, thus reducing misdiagnosis and underdiagnosis of KD, as well as the incidence of cardiovascular sequelae. From our prediction model, we can see that WBC, ESR, ALT, CLR and CPR are risk factors for KD, and conversely ALB and MO are protective factors for KD.

Among the factors that differentiate KD from infectious diseases, the level of MO before IVIG treatment has the most significant effect. Disturbed immune response is one of the important pathogenetic mechanisms of KD, in which monocytes and their molecular markers can be used as diagnostic indicators of KD (20). Eight immune cells, including monocytes, construct a diagnostic scoring system that can be used to differentiate KD from febrile infections (21). All of the above studies suggested that monocytes are a risk factor for KD, but our study shows the opposite result. This may be related to the different subtypes of circulating monocytes, with the predominant classical $CD14^{++}CD16^{-}$ monocytes having phagocytosis of debris and tissue repair, whereas intermediate $CD14^{++}CD16^{+}$ monocytes lead to pro-inflammatory responses and reactive oxygen species generation (22). However, the role of monocytes in the pathogenesis and diagnosis of KD remains unclear and further studies are needed.

ALB is a traditional protective factor for KD and is a biomarker for predicting KD (23). ALB levels ≤3 g/dl can assist in determining incomplete KD, and low ALB levels have also been identified as an independent risk factor for CAL progression in patients with KD (9, 24).

From our results it is clear that CPR alone has little effect on the diagnosis of KD and being included in the model improves

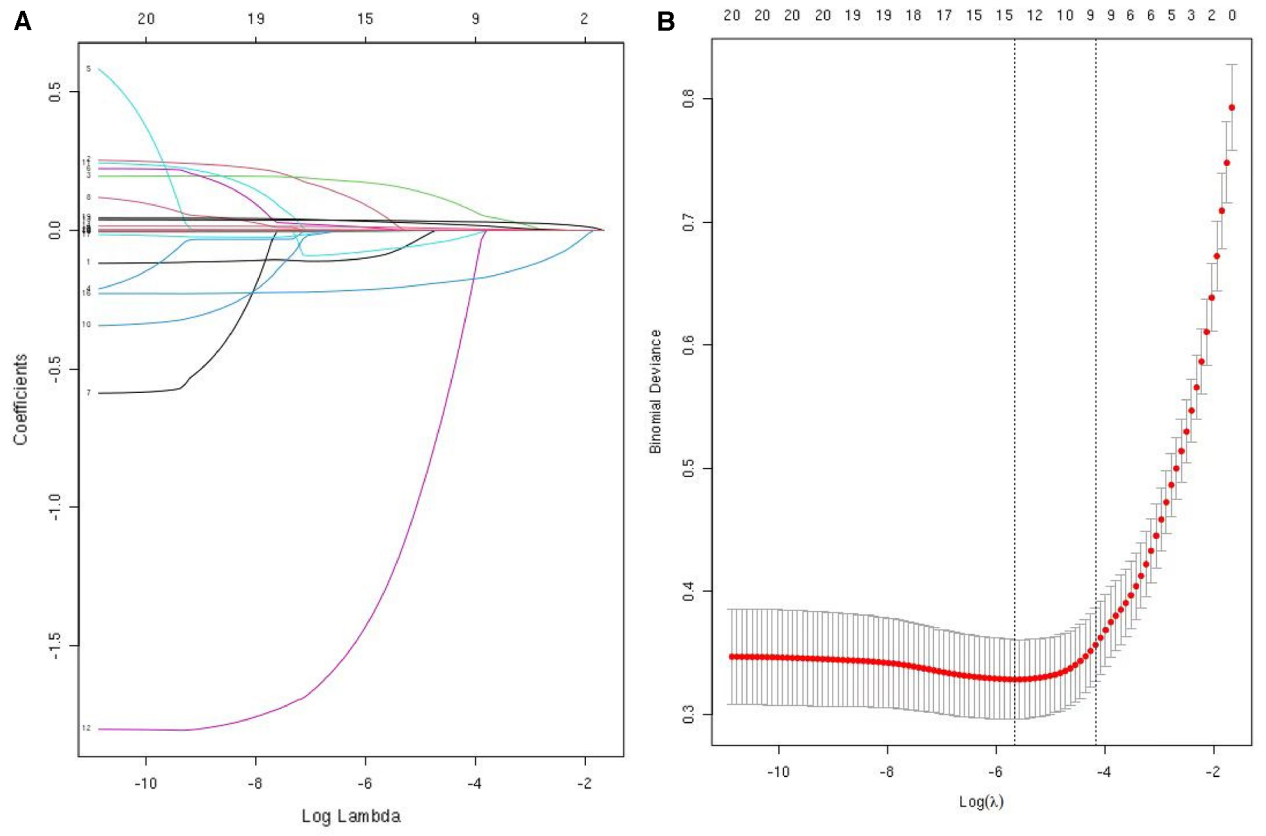


FIGURE 1
Use LASSO regression to select predictors. (A) LASSO regression was used to identify predictors. (B) Cross-validation and minimum criteria were used to adjust the penalty factor in the LASSO model. The vertical dashed line indicates the best lambda (the model that provides the best fit to the data).

its predictive role for KD. Up to now no study has examined the relationship between CPR and KD. However, CPR has been found to have high predictive value in predicting infections, solid tumors, and ischemic stroke, which may be related to the property that PCT is elevated in infectious diseases more often than CRP (13, 25–27). Thus this index integrates the distinction between infectious and non-infectious inflammation, making it a biomarker that may differentiate KD from infectious disease.

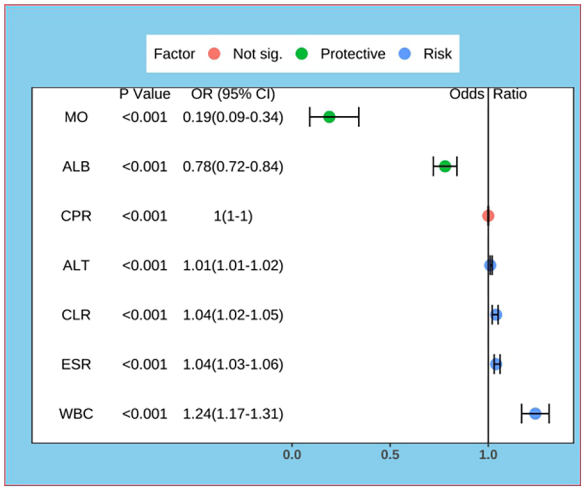


FIGURE 2
Forest plot for logistic regression of predictors. MO, Monocyte; ALB, albumin; CPR, C-reactive protein to procalcitonin ratio; ALT, alanine aminotransferase; CLR, C-reactive protein to lymphocyte ratio; ESR, erythrocyte sedimentation rate; WBC, white blood cell count.

Coincidentally, our study was the first to identify the role of CLR levels in the diagnosis of KD.CLR is a well-recognized indicator of inflammation with high predictive significance in both infectious and non-infectious inflammatory diseases (14, 15). CLR combines both inflammatory and immune factors in KD, and suggests that patients with KD have more intense inflammatory responses and immune disturbances compared to infected patients.

The ability of WBC, ESR and ALT alone to differentiate KD from infectious diseases is limited, so they need to be combined with other indicators for prediction (12). WBC and ALT can be used to differentiate KD from other febrile infections in children by constructing a nomogram in combination with other inflammatory indicators (23). ESR is highly expressed in KD and can be used as a diagnostic marker for KD (28).

Clinical predictive modeling, as a very effective tool, has a bright application prospect in KD diagnosis and prognosis. Liu et al. used eosinophil percentage, CRP, ALT, ALB, and WBC to construct a nomogram for predicting KD, and the AUC of the model was 0.873 (23). Huang et al. used total leukocyte count, prognostic

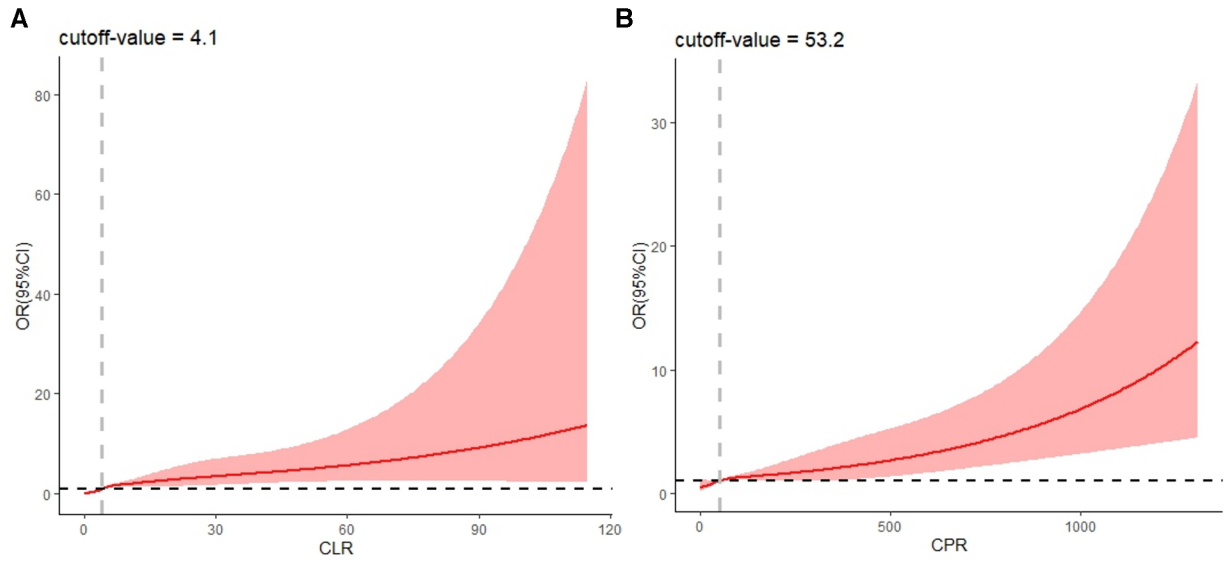


FIGURE 3
RCS plot of CLR and CPR (considering confounding effects of other predictors). CLR, C-reactive protein to lymphocyte ratio; CPR, C-reactive protein to procalcitonin ratio.

nutritional index (PNI), complement C3, and NLR to construct a nomogram for differentiating KD from other febrile children, with AUCs of 0.858 and 0.825 for the training and validation groups, respectively (17). Liu et al. used WBC, HGB, PCT, CRP, ALT, and ALB to construct a predictive model for KD, with an AUC of 0.873 (29). Weng et al. then found that protein S100-A8, protein S100-A9, protein S100-A12, neutrophil defensin 1, alpha-1-acid glycoprotein 1 combined with six commonly used laboratory markers CRP, ALT, WBC, platelet, segment and hemoglobin can be used to differentiate KD from other febrile patients with a prediction model consisting of an AUC value of 0.88 (95% confidence interval: 0.80–0.96) (30). Tsai et al. found that combining eight independent predictors of platelets, eosinophil, alanine aminotransferase, CRP, hemoglobin, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, and monocyte combined were used to distinguish KD from other febrile patients, and the sensitivity, specificity, and accuracy of the cohort were 0.824, 0.839, and 0.838, respectively (31). Our previous study incorporated WBC, hemoglobin, CRP, NLR, eosinophil-to-lymphocyte ratio, and PNI as indicators for constructing a KD prediction model with a C-index of 0.921 (11). In this study, we selected the indicators WBC, MO, ESR, ALT,

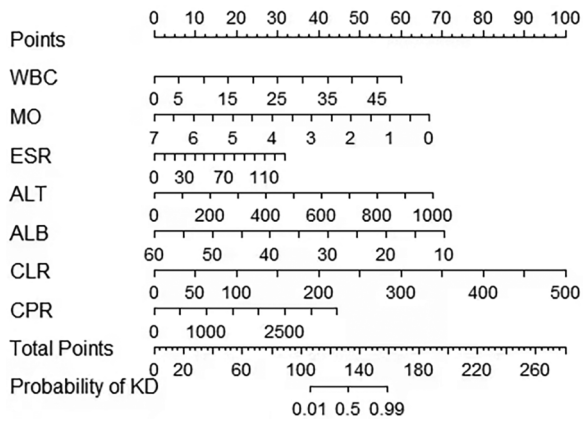


FIGURE 4
A nomogram to distinguish KD from infectious diseases in children. KD, Kawasaki disease; MO, Monocyte; ALB, albumin; CPR, C-reactive protein to procalcitonin ratio; ALT, alanine aminotransferase; CLR, C-reactive protein to lymphocyte ratio; ESR, erythrocyte sedimentation rate; WBC, white blood cell count.

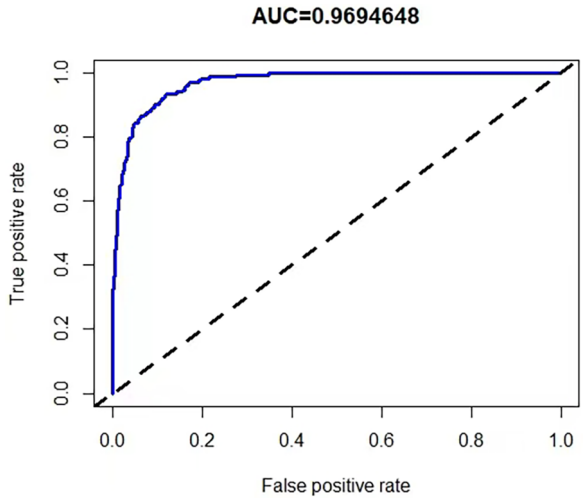


FIGURE 5
ROC curve for nomogram.

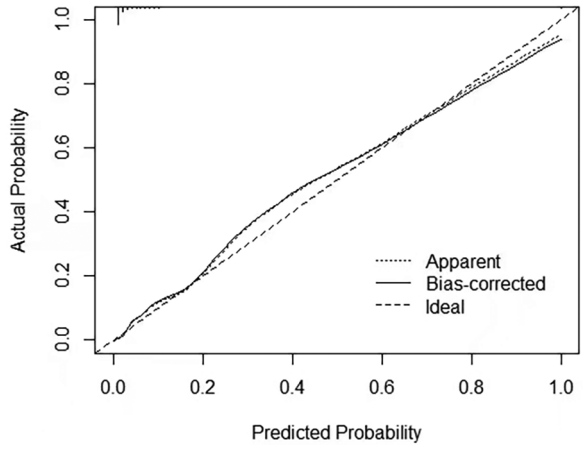


FIGURE 6
Calibration curve for nomogram.

ALB, CLR, and CPR to successfully construct a new KD prediction model with an AUC of 0.969, which achieved a new improvement in its predictive value over the previous models. In addition, compared with the above-mentioned studies, our study both used the 2017 AHA guidelines as the diagnostic criteria for KD. The current prediction models typically utilize a retrospective case-control study design, which provides some credibility to the conclusions drawn. However, when compared to prospective cohort study designs, retrospective case-control studies have limitations in controlling for bias and making causal inferences. Current prediction models commonly use children with infectious diseases as the control group, which is due to the clinical fact that KD is mainly distinguished from patients with infectious diseases.The current prediction models typically employ logistic regression for model construction.In terms of variable selection, Huang Y, GUO X, and Liu X utilize the traditional method of first considering individual variables and then aggregating them. This approach is feasible when dealing with fewer variables.When compared to their method of variable selection, the Lasso regression and support vector machines (SVM) utilized by ourselves and Weng K demonstrate superior adaptability to high-dimensional data, improved prediction performance, and greater interpretability.

Our established model still has some diagnostic limitations. Our study design is retrospective case-control, which has limitations in controlling for bias and making causal inferences. Therefore, the research conclusions should be validated in prospective cohort studies. Our model performs well in internal validation, but as we currently lack access to external data, external validation has not yet been conducted. Whether the model is overfitting still needs to be verified through multi-center cohort studies.Our model is primarily used to distinguish between children with Kawasaki disease and infectious diseases. It has not yet been applied to the differential diagnosis of Kawasaki disease and other diseases such as rheumatological autoimmune diseases. Therefore, there are certain limitations in the application scenarios of our model, and further improvements are needed.

5 Conclusion

Our study used common laboratory indicators WBC, MO, ESR, ALT, ALB, CPR, CLR to construct a prediction model of Kawasaki disease. By using the model, we can distinguish Kawasaki disease from other infectious diseases. Using this prediction model, it is helpful to the early diagnosis of Kawasaki disease and to start the use of IVIG as early as possible, thus reducing the incidence of CAL. It could also reduce the overuse of antibiotics.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The study was conducted in accordance with the Declaration of Helsinki (revised 2013) and approved by the Ethics Committee of Shenzhen Longgang District Maternity & Child Healthcare Hospital (protocol code IRB No. LGFYYXLLL-2022-025 in 2022.09.29). Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements due to the retrospective nature of the study.

Author contributions

J-WL: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Visualization, Writing – original draft, Writing – review & editing. XG: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Software, Writing – original draft, Writing – review & editing. X-XL: Data curation, Investigation, Visualization, Writing – original draft. J-MX: Conceptualization, Data curation, Investigation, Validation, Writing – original draft. CC: Data curation, Formal Analysis, Investigation, Supervision, Validation, Visualization, Writing – original draft. M-GX: Conceptualization, Funding acquisition, Project administration, Resources, Supervision, Validation, Visualization, Writing – review & editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article.

This study was supported by the Natural Science Foundation of Guangdong Province (2022A1515012468) and the Shenzhen Longgang District Science and Technology Development Special Fund [LGWJ2021-(61) and LGKCYLWS2021000020].

Acknowledgments

We would like to thank the Information Department of Longgang District Maternity & Child Healthcare Hospital of Shenzhen City (Longgang Maternity and Child Institute of Shantou University Medical College) for their help in data collection.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2024.1345141/full#supplementary-material

References

1. Gorelik M, Chung S, Ardalan K, Binstadt B, Friedman K, Hayward K, et al. 2021 American College of Rheumatology/Vasculitis Foundation Guideline for the management of kawasaki disease. *Arthritis & Rheumatology (Hoboken, NJ)*. (2022) 74(4):586–96. doi: 10.1002/art.42041

2. Fukazawa R, Kobayashi J, Ayusawa M, Hamada H, Miura M, Mitani Y, et al. JCS/JSCS 2020 guideline on diagnosis and management of cardiovascular sequelae in kawasaki disease. *Circ J*. 2020;84(8):1348–407. doi: 10.1253/circj.CJ-19-1094

3. Lin C, Lai J, Lee I, Chou I, Lin W, Lin M, et al. Kawasaki disease may increase the risk of subsequent cerebrovascular disease. *Stroke*. (2022) 53(4):1256–62. doi: 10.1161/STROKEAHA.120.032953

4. Xie L, Yan W, Huang M, Huang M, Chen S, Huang G, et al. Epidemiologic features of Kawasaki disease in Shanghai from 2013 through 2017. *Journal of Epidemiology*. (2020) 30(10):429–35. doi: 10.2188/jea.JE20190065

5. Ae R, Makino N, Kosami K, Kuwabara M, Matsubara Y, Nakamura Y. Epidemiology, treatments, and cardiac complications in patients with Kawasaki disease: the nationwide survey in Japan, 2017-2018. *J Pediatr*. (2020) 225:23–9.e2. doi: 10.1016/j.jpeds.2020.05.034

6. Piram M Epidemiology of Kawasaki disease in Europe. *Front Pediatr*. (2021) 9:673554. doi: 10.3389/fped.2021.673554

7. Jone PN, Korst A, Karimpour-Fard A, Thomas T, Dominguez SR, Heizer H, et al. Circulating microRNAs differentiate Kawasaki disease from infectious febrile illnesses in childhood. *J Mol Cell Cardiol*. (2020) 146:12–8. doi: 10.1016/j.yjmcc.2020.06.011

8. Qiu H, He Y, Rong X, Ren Y, Pan L, Chu M, et al. Delayed intravenous immunoglobulin treatment increased the risk of coronary artery lesions in children with Kawasaki disease at different status. *Postgrad Med*. (2018) 130(4):442–7. doi: 10.1080/00325481.2018.1468712

9. McCrindle B, Rowley A, Newburger J, Burns J, Bolger A, Gewitz M, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a scientific statement for health professionals from the American Heart Association. *Circulation*. (2017) 135(17):e927–e99. doi: 10.1161/CIR.0000000000000484

10. Varol F, Dedeoğlu R, Kiliç A, Bakar MT, Adrovic A, Şahin S, et al. Retrospective analysis of children diagnosed with Kawasaki disease. *Turk J Med Sci*. (2023) 53(4):979–89. doi: 10.55730/1300-0144.5662

11. Guo X, Liao J, Fan X, Xu M. Exploring the diagnostic value of eosinophil-to-lymphocyte ratio to differentiate Kawasaki disease from other febrile diseases based on clinical prediction model. *Sci Rep*. (2023) 13(1):3399. doi: 10.1038/s41598-023-30463-9

12. Chaudhary H, Nameirakpam J, Kumrah R, Pandiarajan V, Suri D, Rawat A, et al. Biomarkers for kawasaki disease: clinical utility and the challenges ahead. *Front Pediatr*. (2019) 7:242. doi: 10.3389/fped.2019.00242

13. Hahn W, Song J, Kim H, Park S. Is procalcitonin to C-reactive protein ratio useful for the detection of late onset neonatal sepsis? *J Matern Fetal Neonatal Med*. (2018) 31(6):822–6. doi: 10.1080/14767058.2017.1297410

14. Yang M, Chen X, Xu Y. A retrospective study of the C-reactive protein to lymphocyte ratio and disease severity in 108 patients with early COVID-19 pneumonia from January to March 2020 in Wuhan, China. *Med Sci Monit*. (2020) 26:e926393. doi: 10.12659/MSM.926393

15. Koyuncu S, Ismail O. The role of C-reactive protein to lymphocyte ratio in the differentiation of acute and perforated appendicitis. *Ulus Travma Acil Cerrahi Derg*. (2020) 26(5):760–4. doi: 10.14744/tjtes.2020.47973

16. Debray T, Collins G, Riley R, Snell K, Van Calster B, Reitsma J, et al. Transparent reporting of multivariable prediction models developed or validated using clustered data: tRIPOD-cluster checklist. *Br Med J*. (2023) 380:e071018. doi: 10.1136/bmj-2022-071018

17. Huang Y, Liu X, Xia H, Cui L, Lang X, Liu C, et al. Complement 3 and the prognostic nutritional index distinguish Kawasaki disease from other fever illness with a nomogram. *Children*. (2021) 8(9):825. doi: 10.3390/children8090825

18. Cheng X, Zhang Q, Fu Z, Shi Z, Xia P, Zhang Y, et al. Establishment of a predictive model for purulent meningitis in preterm infants. *Transl Pediatr*. (2022) 11(6):1018–27. doi: 10.21037/tp-22-236

19. Lusa L, Ahlin Č. Restricted cubic splines for modelling periodic data. *PLoS One*. (2020) 15(10):e0241364. doi: 10.1371/journal.pone.0241364

20. Ba H, Wang Y, Zhang L, Wang H, Huang Z, Qin Y. Prediction of immune infiltration diagnostic gene biomarkers in Kawasaki disease. *J Immunol Res*. (2022) 2022:8739498. doi: 10.1155/2022/8739498

21. Du S, Mansmann U, Geisler B, Li Y, Hornung R. A diagnostic model for Kawasaki disease based on immune cell characterization from blood samples. *Front Pediatr*. (2021) 9:769937. doi: 10.3389/fped.2021.769937

22. Han Z, Liu Q, Li H, Zhang M, You L, Lin Y, et al. The role of monocytes in thrombotic diseases: a review. *Front Cardiovasc Med*. (2023) 10:1113827. doi: 10.3389/fcvm.2023.1113827

23. Liu X, Huang Y, Xia H, Sun Y, Lang X, Li Q, et al. A nomogram model identifies eosinophilic frequencies to powerfully discriminate kawasaki disease from febrile infections. *Front Pediatr*. (2020) 8:559389. doi: 10.3389/fped.2020.559389

24. Xia Y, Qiu H, Wen Z, Shi H, Yu H, Li J, et al. Albumin level and progression of coronary artery lesions in kawasaki disease: a retrospective cohort study. *Front Pediatr*. (2022) 10:947059. doi: 10.3389/fped.2022.947059

25. Li F, Kong S, Xie K, Zhang Y, Yan P, Zhao W. High ratio of C-reactive protein/procalcitonin predicts Mycoplasma pneumoniae infection among adults hospitalized with community acquired pneumonia. *Scand J Clin Lab Invest*. (2021) 81(1):65–71. doi: 10.1080/00365513.2020.1858491

26. Vassallo M, Michelangeli C, Fabre R, Manni S, Genillier P, Weiss N, et al. Procalcitonin and C-reactive protein/procalcitonin ratio as markers of infection in patients with solid tumors. *Front Med (Lausanne)*. (2021) 8:627967. doi: 10.3389/fmed.2021.627967

27. Cho J, Jeong S, Lee J. Procalcitonin to C-reactive protein ratio is associated with short-term mortality in ischemic stroke patients: preliminary report. *Arch Med Sci*. (2022) 18(2):344–52. doi: 10.5114/aoms.2020.100207

28. Xiu-Yu S, Jia-Yu H, Qiang H, Shu-Hui D. Platelet count and erythrocyte sedimentation rate are good predictors of Kawasaki disease: rOC analysis. *J Clin Lab Anal*. (2010) 24(6):385–8. doi: 10.1002/jcla.20414

29. Liu X, Huang Y, Kuo H, Xia H, Yi-Sun, Huang W, et al. A novel nomogram model for differentiating Kawasaki disease from sepsis. *Sci Rep*. 2020;10(1):13745. doi: 10.1038/s41598-020-70717-4

30. Weng K, Li S, Chien K, Tsai K, Kuo H, Hsieh K, et al. Prediction model for diagnosis of Kawasaki disease using iTRAQ-based analysis. *Children*. (2021) 8(7):576. doi: 10.3390/children8070576

31. Tsai C, Chu C, Liu X, Weng K, Liu S, Huang Y, et al. A novel score system of blood tests for differentiating Kawasaki disease from febrile children. *PLoS One*. (2021) 16(1):e0244721. doi: 10.1371/journal.pone.0244721

frontiers | Frontiers in Pediatrics

TYPE Case Report
PUBLISHED 01 March 2024
DOI 10.3389/fped.2024.1302534

OPEN ACCESS

EDITED BY
Shikai Yu,
Tongji University, China

REVIEWED BY
Kai-Sheng Hsieh,
China Medical University, Taiwan
Manatomo Toyono,
Akita University, Japan

*CORRESPONDENCE
Han Ling
✉ hanl6610@sina.com
Long Deyong
✉ dragon2008@vip.sina.com

†These authors have contributed equally to this work

RECEIVED 26 September 2023
ACCEPTED 05 February 2024
PUBLISHED 01 March 2024

CITATION
Chencheng D, Min Z, Wanming S, Wen S, Baojing G, Yanyan X, Ling H and Deyong L (2024) Case Report: Ventricular preexcitation-induced dilated cardiomyopathy improved by the pharmacologic suppression of ventricular preexcitation in three infants, and literature review.
Front. Pediatr. 12:1302534.
doi: 10.3389/fped.2024.1302534

Case Report: Ventricular preexcitation-induced dilated cardiomyopathy improved by the pharmacologic suppression of ventricular preexcitation in three infants, and literature review

Dai Chencheng[1†], Zhong Min[2†], Shi Wanming[1], Shangguan Wen[1], Guo Baojing[1], Xiao Yanyan[1], Han Ling[1*] and Long Deyong[3*]

[1]Department of Pediatric Cardiology, Capital Medical University Affiliated Beijing Anzhen Hospital, Beijing, China, [2]Department of Ultrasound, Meizhou People's Hospital, Guangdong, China, [3]Department of Cardiology, Capital Medical University Affiliated Beijing Anzhen Hospital, Beijing, China

The therapy of ventricular preexcitation-induced dilated cardiomyopathy in very small infants or infants with a high risk of ablation is tough and related articles are rare. Effective pharmacotherapy to suppress ventricular preexcitation is valuable.

Aims: To evaluate the effectiveness and safety of pharmacotherapy for cardiac resynchronization in infants with ventricular preexcitation-induced dilated cardiomyopathy.

Methods and results: Three infants with ventricular preexcitation-induced dilated cardiomyopathy, due to the disappearance of ventricular preexcitation during the placement of catheter, intermittent WPW pattern, and right mid septal accessory pathway respectively, had received pharmacotherapy for cardiac resynchronization. The initial dosage of oral amiodarone was 5 mg/kg.d and it was followed by the maintenance dosage of 2–2.5 mg/kg.d 4 weeks later. Propafenone (15 mg/kg.d) served as a supplement since amiodarone was not adequate in case 3. The three infants achieved successful pharmacologic suppression of ventricular preexcitation 10, 6.5, and 4.5 weeks after the initiation of amiodarone respectively. They all got normalized contraction of interventricular septum and LVEF as well as reduced LVEDD gradually after the disappearance of ventricular preexcitation. No side effects associated with pharmacotherapy happened during the follow-up. Amiodarone had been withdrawn for 2 years and 5 months in Cases 1 and 2. They both remained free from ventricular preexcitation and retained normal LVEF and LVEDD.

Conclusions: Pharmacotherapy for cardiac resynchronization with oral amiodarone or in combination with propafenone for infants with ventricular preexcitation-induced dilated cardiomyopathy is effective and safe. Pharmacotherapy for cardiac resynchronization served as another therapeutic choice besides ablation.

KEYWORDS

ventricular preexcitation, dilated cardiomyopathy, left ventricular dyssynchrony, amiodarone, propafenone

Introduction

Type B ventricular preexcitation may cause abnormal interventricular septal motion and left ventricular (LV) dyssynchrony in patients with WPW pattern/syndrome, which can induce LV dysfunction and dilation. Some patients even develop ventricular preexcitation-induced dilated cardiomyopathy (DCM) (1–8). With more and more related cases being reported worldwide, ventricular preexcitation with ventricular dysfunction presumed due to dyssynchrony in larger patients (weight ≥ 15 kg) or when medical therapy is either not effective or associated with intolerable adverse effects in smaller patients had been listed as ablation indications (class IIa) (9, 10). However, for infants weighing less than 7 kg, ablations are hard to perform due to the small diameter of the femoral veins especially in the areas without special ablation catheters designed for pediatric patients. Medical treatments with anti-heart failure drugs do not respond well in most cases. The application of digoxin is limited due to ventricular preexcitation, which proposes another obstacle to the therapy.

Cardiac resynchronization aimed to suppress anterograde conduction of accessory pathways (APs) by effective pharmacotherapy is quite valuable in low-body-weight infants and infants with anteroseptal/mid septal APs which bring a high risk of Ⅲ°atrioventricular block secondary to ablation or patients who can not be ablated successfully. Related articles are quite limited. We have treated three cases of ventricular preexcitation-induced DCM with different situations successfully by the suppression of ventricular preexcitation through amiodarone or in combination with propafenone.

Methods

Patients

Three consecutive female infants with DCM and WPW pattern/syndrome, who underwent oral pharmacotherapy meditation to suppress ventricular preexcitation through amiodarone or combination with propafenone besides anti-heart failure drugs between July 2020 and May 2022, were included in this study. The vectors of the delta waves of the three cases suggested right anterolateral, posterolateral, and midseptal pathways (Figure 1). DCM was defined as a literature description (11). All the infants presented with the clinical signs and symptoms of chronic congestive heart failure, such as fatigue and exertional dyspnea, and they were at the low end of physical growth compared with infants in the same age group. Cases 1 and 2 never complained of tachycardia-related symptoms. Periodical Holters (ECG Holter's recordings) were performed on the two patients and showed no tachycardia episodes. Case 3 was admitted to the local hospital for paroxysmal supraventricular tachycardia (PSVT). After termination of it, continuous ECG monitoring for 1 month did not show the onset of PSVT. However, the left ventricular systolic function did not improve with the remission of PSVT. Incessant tachycardia as the cause of DCM was not considered. All patients underwent routine and comprehensive diagnostic screening for the common etiologies of DCM and the results were negative for all patients. They were treated with routine anti-heart failure chemotherapy. The dosage of drugs was not altered after the administration of amiodarone until the patients achieved recovery of their LV function. The Declaration of Helsinki was reflected in *a priori* approval by the institution's human research committee, and it was approved by the Ethics Committee of Capital Medical University affiliated with Beijing Anzhen Hospital.

Electrocardiography and echocardiography

Twelve-lead electrocardiography during sinus rhythm was conducted in all patients before and after the administration of pharmacotherapy. Transthoracic echocardiographies were performed with an iq echo system (GE Medical Systems). All patients underwent echocardiographic examinations before and 1, 3, 6, 12, 18, and 24 months after the pharmacotherapy. Their global LV function was assessed by measuring end-diastolic and end-systolic LV diameters from a parasternal long-axis M-mode echocardiogram. The left ventricular ejection fraction (LVEF) was calculated using the biplane Simpson's method. The basal interventricular septal thickness was measured from the apical 4-chamber view at the end-systole. Intraventricular dyssynchrony through M-mode echocardiography was quantified as the time delay between the peak septal systolic motion and the left posterior wall systolic motion (septal-to-posterior wall motion delay, SPWMD) (12). Speckle tracking echocardiography was applied for the evaluation of LV dyssynchrony. The two-dimensional LV longitudinal strain was analyzed through the apical 4-, 2- and 3- chamber long-axis views (13, 14). The standard deviation of the time to the peak systolic strain (Ts-SD) over 18 longitudinal segments was measured. Echocardiography was performed by the same physician and was analyzed online.

Pharmacotherapy for cardiac resynchronization

We planned to perform ablation for case 1 with propofol as the anesthetic. When placing the coronary sinus electrode, the delta wave disappeared abruptly. Ventricular pacing showed no retrograde conduction of the AP. Atrial pacing in several sites of the right atrium did not show antegrade conduction through it. The delta wave did not recover 1 h after the anesthetic was reduced and all the electrodes were removed. Two hours after returning back to the ward, persistent ventricular preexcitation appeared. Case 2 had intermittent ventricular preexcitation and the proportion of preexcitation was about 60%. Case 3 had a midseptal AP indicated by the EKG. The initial dosage of oral amiodarone was 5 mg/kg.d and the maintenance dosage of 2–2.5 mg/kg.d 4 weeks later. Case 2 encountered an episode of PSVT for about 1 h which was terminated by intravenous propafenone when she had been treated by amiodarone for

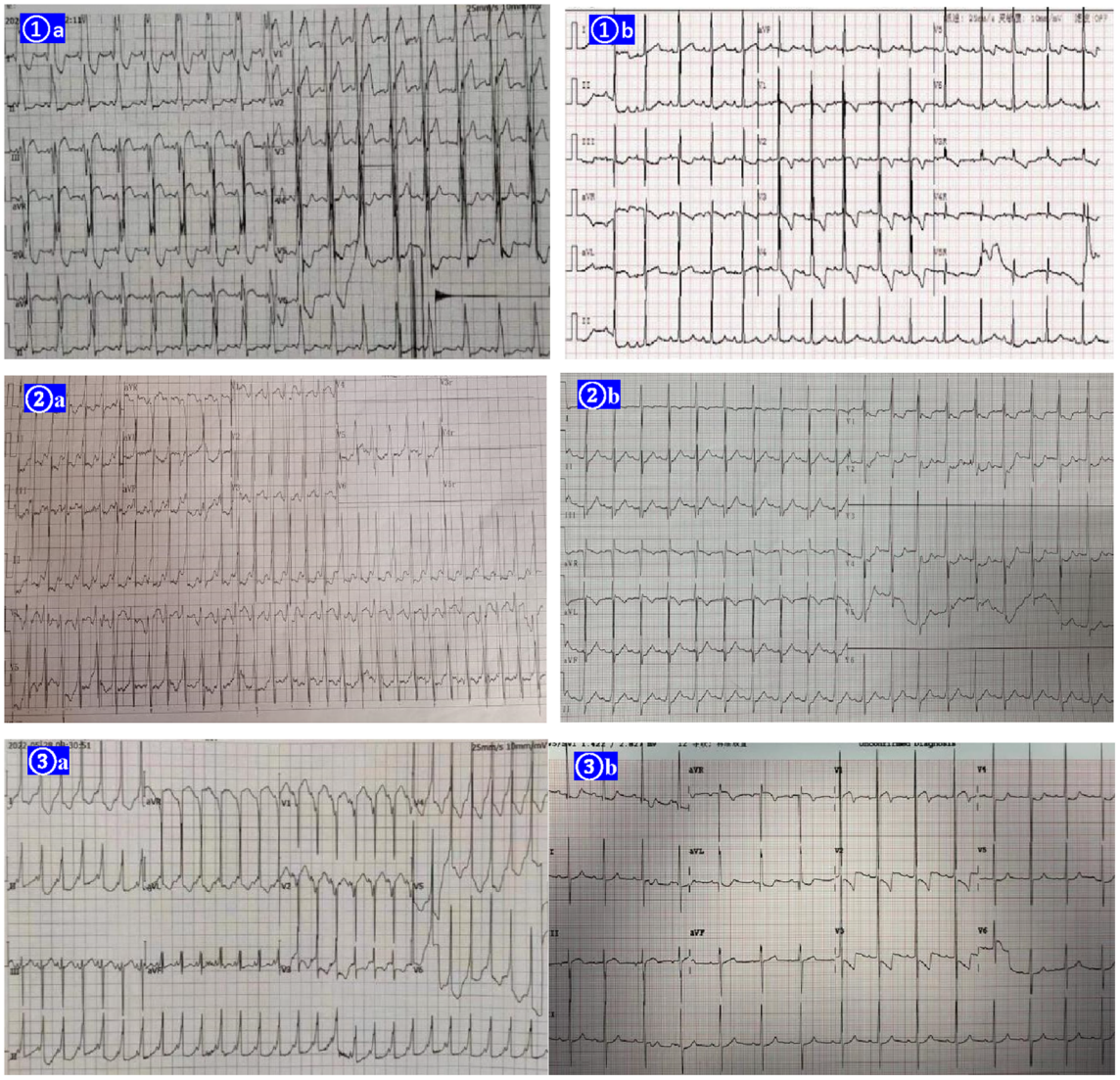


FIGURE 1
EKGs of the three cases before the therapy of amiodarone shown right postlateral, lateral, and midseptal manifest accessory pathways respectively (①A ②A ③A). Amiodarone alone (cases 1 and 2) or in combination with propafenone (case 3) suppressed the ventricular preexcitation successfully in the 3 cases (①B ②B ③B).

23 days. Her LV dysfunction did not deteriorate due to the second onset. After that, oral propafenone (15 mg/kg.d) was added. PSVT did not recur from then on.

Results

The clinical characteristics and echocardiographic investigations of the three infants are shown in Supplementary Table S1. The abnormal interventricular septal motion presented as obvious rightward systolic bulging (Figure 2A). The basal/middle segments of the interventricular septum moved similar to an aneurysm, with typical bulging during end-systole. The M-mode echocardiogram showed paradoxical motion between the interventricular septum and posterior wall of the LV (Figure 3A). The interventricular septal paradoxical motion of the basal segments was shown by the longitudinal strain analysis, with positive strains that were opposite to the other segments (Figure 4A).

The three infants achieved successful pharmacologic suppression of ventricular preexcitation using amiodarone or combination with propafenone 10, 6.5, and 4.5 weeks after the initiation of amiodarone respectively. Case 1 started to show intermittent ventricular preexcitation and the proportion of preexcitation was about 50% at the week 10, followed by her LVEF increasing gradually. Holter scans showed ventricular preexcitation disappeared completely at week 18. After 22 weeks of treatment, echocardiography showed that paradoxical motion of the IVS had disappeared. The LVEF and LVEDD completely returned to normal with cardiac resynchronization (Figure 2B, Supplementary Table S1). Cases 2 and 3 also experienced remarkable improvement in LVEF and reduced LVEDD following the disappearance of ventricular preexcitation

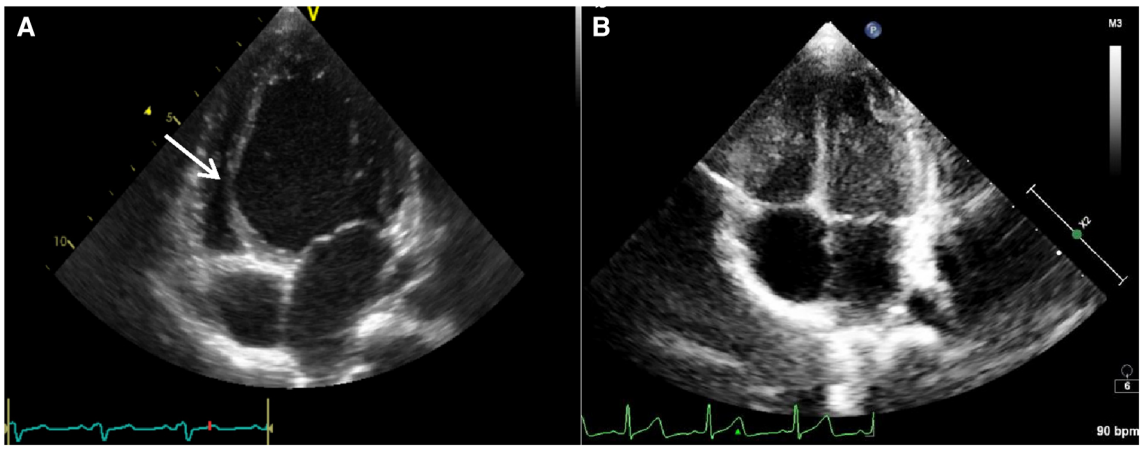


FIGURE 2
The parasternal long axis four-chamber view of case 1 showed the left ventricle was spherically dilated and the basal/middle segment of the interventricular septum (IVS) contracted paradoxically like an aneurysm (see the arrow) protruding into the compressed right ventricle before pharmacotherapy for cardiac resynchronization (**A**). The paradoxical motion of the interventricular septum disappeared and the diameter of LV returned to normal after successful pharmacotherapy for cardiac resynchronization (**B**).

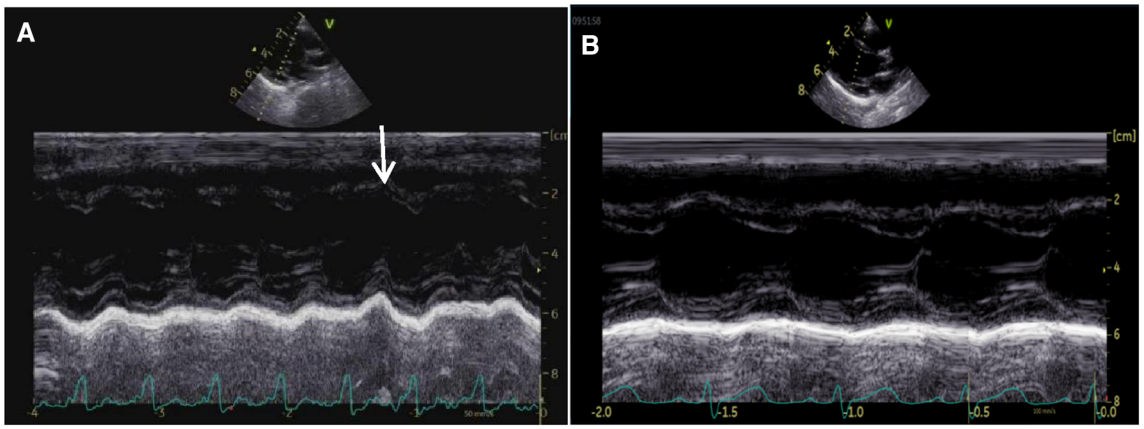


FIGURE 3
M-mode tracing from a parasternal long-axis view of case 2 before the therapy of amiodarone, showing interventricular septal paradoxical motion (**A**, arrow). The ventricular septum and LV post wall moved normally 6 months after the therapy of amiodarone (**B**).

(Supplementary Table S1). All three infants had normal thyroid function and no abnormalities were found in eyes and lungs during the follow-up. Amiodarone had been withdrawn for 2 years and 5 months in cases 1 and 2. Ventricular preexcitation did not recur in the 2 cases; they obtained normal growth and development and continued to retain normal LVEF and LVEDD.

Discussion

The development of ventricular preexcitation-induced dilated cardiomyopathy was heterogeneous. Some children still had better compensatory cardiac function in adolescence. However, infants tended to show obvious decompensated cardiac insufficiency. Previous studies have confirmed that ablation can reverse the disease (1–8, 11, 12). We reported ventricular preexcitation-induced dilated cardiomyopathy in China in 2013 firstly and have accumulated lots of experiences in ablation (1, 7, 8). However, ablation is not always preferable for every infant, especially those with low body weight, high risk, or difficulty in ablation. Pharmacotherapy for cardiac resynchronization may serve as a supplement for ablation in some instances.

Our first case had a proper indication for ablation since anti-heart failure drugs were ineffective. However, her ventricular preexcitation disappeared suddenly during the process. Ablation could not be performed since the AP had no retrograde conduction and antegrade conduction could not be provoked. So, pharmacologic suppression of ventricular preexcitation was tried. Her left ventricular function and diameter became completely normalized following the successful suppression of ventricular preexcitation. Even after the

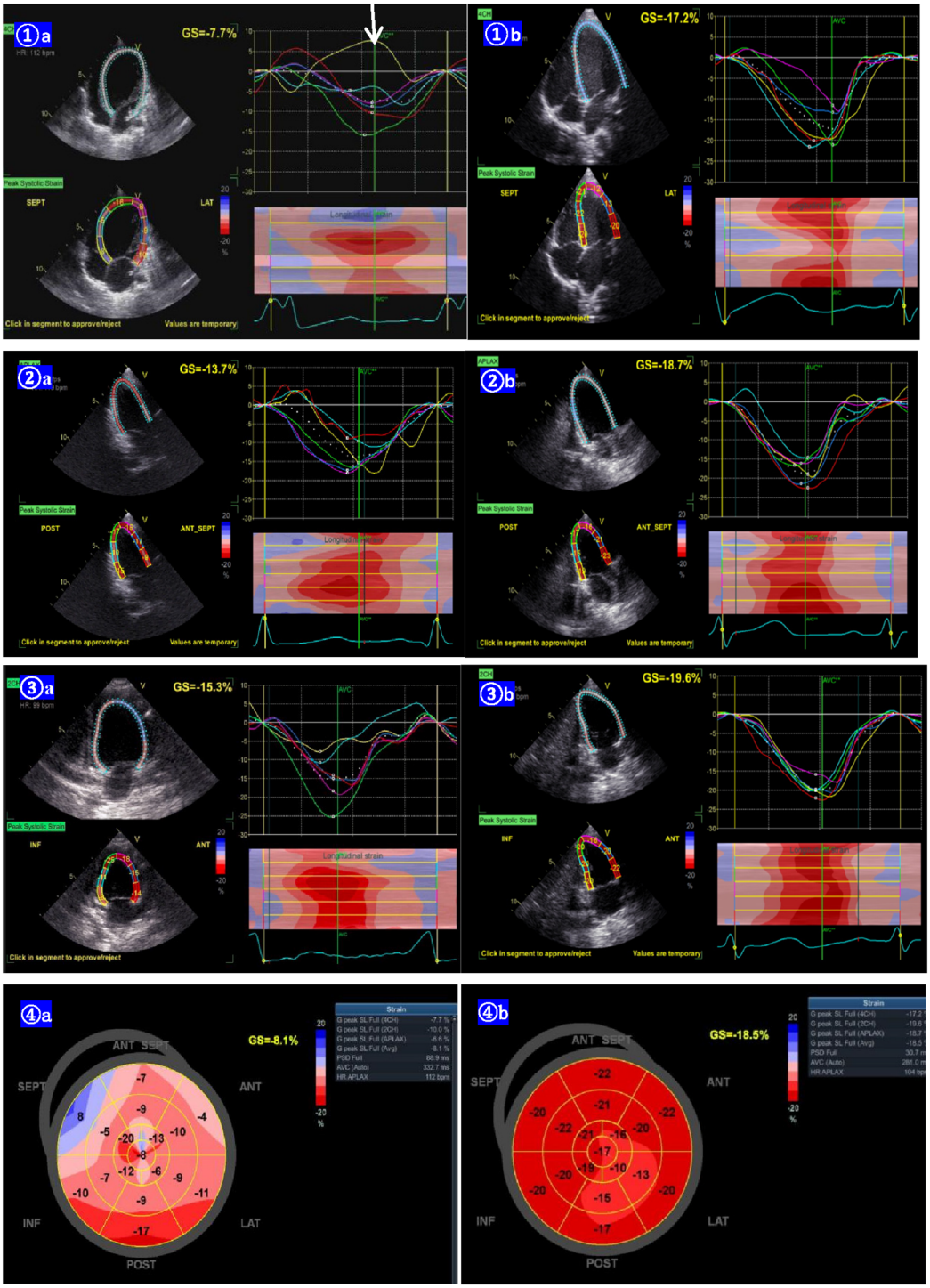


FIGURE 4
Lv longitudinal strain curves from the apical 4-chamber (1A), 2-chamber (2A), and 3-chamber (3A) view of case 2 before the pharmacotherapy of amiodarone, showing the basal segments of the interventricular septal paradoxical motion (arrow, positive strain). The LV longitudinal strain becomes normal 6 months post pharmacotherapy (1B,2B,3B). The bull's eye of the LV longitudinal strain before the pharmacotherapy, shows the segment of the post-interventricular septal wall paradoxical motion (positive strain). The bull's eye of the LV longitudinal strain changed to normal 6 months after the pharmacotherapy (4B).

discontinuation of amiodarone, she maintained normal heart function and was free from ventricular preexcitation. Amiodarone was also prescribed for intermittent ventricular preexcitation and mid septal AP in the following 2 cases and also gained satisfactory effects. Treated with the dosage of 5 mg/kg.d, case 3 still suffered from an episode of PSVT. Propafenone was added to control the onset of PSVT. Due to the combined effect, it just took 4.5 weeks for successful suppression of ventricular preexcitation.

Reports associated with pharmacologic therapy for cardiac resynchronization in infants with ventricular preexcitation-induced DCM were rare. There have been just seven cases reported (15–20) (Supplementary Table S2). Five cases used amiodarone and one case failed. One case chose propafenone and another chose flecainide. Cadrin Tourigny (15) reported that two infants with severe ventricular preexcitation-induced DCM were successfully treated with amiodarone to suppress the antegrade conduction of the AP, which obviated their need for heart transplantation. One case remained free from ventricular preexcitation and heart failure 10 years after withdrawal of amiodarone. Further ablation was still needed in another case. Suzuki Y (16) reported amiodarone was chosen for cardiac resynchronization after twice unsuccessful catheter ablations in a 6-month-old infant weighed 6.8 kg and attained satisfactory effect. However, amiodarone was not always effective (5). Besides amiodarone, flecainide and propafenone were also reported to be effective in such cases (17, 18). Since amiodarone had more positive evidence, we chose it as a preference. Long-term administration of amiodarone-related adverse effects such as interstitial lung disease, abnormal thyroid function, and corneal pigmentation should be paid attention to. In order to avoid the adverse effects, our maintenance dosage was 2–2.5 mg/kg.d.

Although it has been reported that catheter ablation may be a safe and effective treatment option in right free wall accessory pathways (21), catheter ablation for any reason is infrequently performed in infants less than 6 months of age considering the increased risks associated with the procedure. Of course, if small-size ablation catheters designed for children are available, catheter ablation can also be considered the first choice in centers with ample experience. Moreover, for infants with low body weight or anteroseptal/midseptal APs with a high risk of Ⅲ°atrioventricular block secondary to ablation, pharmacologic suppression of ventricular preexcitation is more sensible compared with ablation. In addition, the natural evolution of accessory pathways in infants, with a 36% rate of spontaneous resolution, favors a less aggressive approach (22). If antegrade conduction of the AP can not resolve spontaneously, amiodarone may postpone the need for ablation, so that the infants can grow and develop with normal cardiac function, and avoid the risks of ablation due to the low body weight.

Conclusions

Pharmacotherapy for cardiac resynchronization with oral amiodarone or in combination with propafenone for infants with ventricular preexcitation-induced dilated cardiomyopathy is effective and safe. Pharmacotherapy served as another therapeutic choice besides ablation for infants with low body weight, anteroseptal/midseptal APs, or intermittent ventricular preexcitation.

Data availability statement

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

Ethics statement

The studies involving humans were approved by Ethics Committee of Capital Medical University affiliated Beijing Anzhen Hospital. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin. Written informed consent was obtained from the individual(s), and minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article.

Author contributions

DL: Supervision, Writing – original draft, Writing – review & editing. CD: Data curation, Formal Analysis, Writing – original draft, Writing – review & editing. MZ: Data curation, Software, Writing – original draft. SW: Data curation, Methodology, Writing – original draft. WS: Data curation, Investigation, Writing – original draft. BG: Data curation, Writing – review & editing. XY: Data curation, Writing – original draft. LH: Supervision, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Dai CC, Guo BJ, Li WX, Xiao YY, Jin M, Han L, et al. Dyssynchronous ventricular contraction in Wolff-Parkinson-White syndrome: a risk factor for the development of dilated cardiomyopathy. *Eur J Pediatr*. (2013) 172(11):1491–500. doi: 10.1007/s00431-013-2070-z

2. Udink Ten Cate FE, Wiesner N, Trieschmann U, Khalil M, Sreeram N. Dyssynchronous ventricular activation in asymptomatic Wolff–Parkinson–White syndrome: a risk factor for development of dilated cardiomyopathy. *Indian Pacing Electrophysiol J*. (2010) 10:248–56. PMID: 20552060

3. Tomaske M, Janousek J, Razek V, Gebauer RA, Tomek V, Hindricks G, et al. Adverse effects of Wolff–Parkinson–White syndrome with right septal or posteroseptal accessory pathways on cardiac function. *Europace*. (2008) 10:181–9. doi: 10.1093/europace/eun005

4. Niu MC, Maskatia SA, Kim JJ. Marked septal dyskinesis from Wolff–Parkinson–White syndrome. *Circulation*. (2014) 130:e196–8. doi: 10.1161/CIRCULATIONAHA.114.012968

5. Kwon EN, Carter KA, Kanter RJ. Radiofrequency catheter ablation for dyssynchrony-induced dilated cardiomyopathy in an infant. *Congenit Heart Dis*. (2014) 9(6):E179–84. doi: 10.1111/chd.12124

6. Emmel M, Balaji S, Sreeram N. Ventricular preexcitation associated with dilated cardiomyopathy: a causal relationship? *Cardiol Young*. (2004) 14:594–9. doi: 10.1017/S1047951104006031

7. Dai C, Guo B, Li W, Xiao Y, Jin M, Han L, et al. The effect of ventricular pre-excitation on ventricular wall motion and left ventricular systolic function. *Europace*. (2018) 20(7):1175–81. doi: 10.1093/europace/eux242

8. Guo B, Dai C, Li Q, Li W, Han L. Hazards of ventricular pre-excitation to left ventricular systolic function and ventricular wall motion in children: analysis of 25 cases. *Cardiol Young*. (2019) 29(3):380–8. doi: 10.1017/S1047951118002500

9. Philip Saul J, Kanter RJ, Writing Committee, Abrams D, Asirvatham S, Bar-Cohen Y, et al. PACES/HRS expert consensus statement on the use of catheter ablation in children and patients with congenital heart disease: developed in partnership with the pediatric and congenital electrophysiology society (PACES) and the heart rhythm society (HRS). Endorsed by the governing bodies of PACES, HRS, the American academy of pediatrics (AAP), the American heart association (AHA), and the association for European pediatric and congenital cardiology (AEPC). *Heart Rhythm*. (2016) 13(6):e251–89. doi: 10.1016/j.hrthm.2016.02.009

10. Brugada J, Katritsis DG, Arbelo E, Arribas F, Bax JJ, Blomström-Lundqvist C, et al. 2019 ESC guidelines for the management of patients with supraventricular tachycardia the task force for the management of patients with supraventricular tachycardia of the European society of cardiology (ESC). *Eur Heart J*. (2020) 41(5):655–720. doi: 10.1093/eurheartj/ehz467

11. Friedman RA, Walsh EP, Silka MJ, Calkins H, Stevenson WG, Rhodes LA, et al. NAPSE expert consensus conference: radiofrequency catheter ablation in children with and without congenital heart disease: report of the writing committee. North American society of pacing and electrophysiology. *Pacing Clin Electrophysiol*. (2002) 25:1000–17. doi: 10.1046/j.1460-9592.2002.01000.x

12. Gorcsan J 3rd, Abraham T, Agler DA, Bax JJ, Derumeaux G, Grimm RA, et al. Echocardiography for cardiac resynchronization therapy: recommendations for performance and reporting–a report from the American society of echocardiography dyssynchrony writing group endorsed by the heart rhythm society. *J Am Soc Echocardiogr*. (2008) 21:191–213. doi: 10.1097/HCO.0b013e3282f2e260

13. Suffoletto MS, Dohi K, Cannesson M, Saba S, Gorcsan J 3rd. Novel speckle-tracking radial strain from routine black-and-white echocardiographic images to quantify dyssynchrony and predict response to cardiac resynchronization therapy. *Circulation*. (2006) 113:960–8. doi: 10.1161/CIRCULATIONAHA.105.571455

14. Modesto KM, Cauduro S, Dispenzieri A, Khandheria B, Belohlavek M, Lysyansky P, et al. Two-dimensional acoustic pattern derived strain parameters closely correlate with one-dimensional tissue Doppler derived strain measurements. *Eur J Echocardiogr*. (2006) 7:315–21. doi: 10.1016/j.euje.2005.07.003

15. Cadrin-Tourigny J, Fournier A, Andelfinger G, Khairy P. Severe left ventricular dysfunction in infants with ventricular preexcitation. *Heart Rhythm*. (2008) 5:1320–2. doi: 10.1016/j.hrthm.2008.05.022

16. Suzuki Y, Suzuki T, Imai Y, Inuzuka R, Suzuki T, Nakamura Y, et al. An infant with heart failure due to ventricular dyssynchrony and refractory tachycardia caused by a right anterolateral accessory pathway. *Cardiology*. (2012) 123(2):108–12. doi: 10.1159/000342052

17. Suzuki S, Hokosaki T, Iwamoto M. Pharmacologic therapy with flecainide for asymptomatic Wolff-Parkinson-White syndrome in an infant with severe left ventricular dyssynchrony. *Cardiol Young*. (2018) 28(7):970–3. doi: 10.1017/S1047951118000252

18. Ko J. Left ventricular dysfunction and dilated cardiomyopathy in infants and children with Wolff-Parkinson-White syndrome in the absence of tachyarrhythmias. *Korean Circ J*. (2012) 42(12):803–8. doi: 10.4070/kcj.2012.42.12.803

19. Paech C, Flosdorff P, Gebauer RA. Pharmacologic cardiac resynchronization of a 1-year-old boy with severe left ventricular dysfunction. *Pediatr Cardiol*. (2012) 33(7):1213–5. doi: 10.1007/s00246-012-0310-z

20. Kim SH, Jeong SI, Huh J, Kang IS, Lee HJ. Amiodarone and catheter ablation as cardiac resynchronization therapy for children with dilated cardiomyopathy and Wolff-Parkinson-White syndrome. *Korean Circ J*. (2013) 43:57–61. doi: 10.4070/kcj.2013.43.1.57

21. Zhang Y, Jiang H, Cui J, Li MT, Zhou HM, Li XM. Ablation of ventricular preexcitation to cure preexcitation-induced dilated cardiomyopathy in infants: diagnosis and outcome. *Circ Arrhythm Electrophysiol*. (2023) 16(4):e011569. doi: 10.1161/CIRCEP.122.011569

22. Deal BJ, Keane JF, Gillette PC, Garson Jr A. Wolff-Parkinson-White syndrome and supraventricular tachycardia during infancy: management and follow-up. *J Am Coll Cardiol*. (1985) 5:130–5. doi: 10.1016/S0735-1097(85)80095-4

frontiers | Frontiers in Public Health

TYPE Review
PUBLISHED 13 June 2024
DOI 10.3389/fpubh.2024.1298612

OPEN ACCESS

EDITED BY
Shikai Yu,
Tongji University, China

REVIEWED BY
Armando Caseiro,
Instituto Politécnico de Coimbra, Portugal
Zhen Zhou,
University of Tasmania, Australia

*CORRESPONDENCE
Lijie Ren
✉ renlijie72@126.com

RECEIVED 21 September 2023
ACCEPTED 29 April 2024
PUBLISHED 13 June 2024

CITATION
Huang Z, Li X, Liu X, Xu Y, Feng H and Ren L (2024) Exercise blood pressure, cardiorespiratory fitness, fatness and cardiovascular risk in children and adolescents.
Front. Public Health 12:1298612.
doi: 10.3389/fpubh.2024.1298612

Exercise blood pressure, cardiorespiratory fitness, fatness and cardiovascular risk in children and adolescents

Zhengzheng Huang[1,2], Xiuping Li[1,2], Xia Liu[3], Yayun Xu[2], Haixing Feng[12] and Lijie Ren[2]*

[1]Guangdong Key Laboratory for Biomedical Measurements and Ultrasound Imaging, National-Regional Key Technology Engineering Laboratory for Medical Ultrasound, School of Biomedical Engineering, Shenzhen University Medical School, Shenzhen, China, [2]Department of Neurology, The First Affiliated Hospital of Shenzhen University, Shenzhen Second People's Hospital, Shenzhen, China, [3]Department of Neurology, Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China

Cardiovascular disease remains the leading cause of mortality on a global scale. Individuals who possess risk factors for cardiovascular disease, such as high blood pressure (BP) and obesity, face an elevated risk of experiencing organ-specific pathophysiological changes. This damage includes pathophysiological changes in the heart and peripheral vascular systems, such as ventricular hypertrophy, arterial stiffening, and vascular narrowing and stenosis. Consequently, these damages are associated with an increased risk of developing severe cardiovascular outcomes including stroke, myocardial infarction, heart failure, and coronary heart disease. Among all the risk factors associated with cardiovascular disease, high blood pressure emerges as the most prominent. However, conventional resting BP measurement methods such as auscultatory or oscillometric methods may fail to identify many individuals with asymptomatic high BP. Recently, exercise BP has emerged as a valuable diagnostic tool for identifying real (high) blood pressure levels and assessing underlying cardiovascular risk, in addition to resting BP measurements in adults. Furthermore, numerous established factors, such as low cardiorespiratory fitness and high body fatness, have been confirmed to contribute to exercise BP and the associated cardiovascular risk. Modifying these factors may help reduce high exercise BP and, consequently, alleviate the burden of cardiovascular disease. A significant body of evidence has demonstrated cardiovascular disease in later life have their origins in early life. Children and adolescents with these cardiovascular risk factors also possess a greater propensity to develop cardiovascular diseases later in life. Nevertheless, the majority of previous studies on the clinical utility of exercise BP have been conducted in middle-to-older aged populations, often with pre-existing clinical conditions. Therefore, there is a need to investigate further of the factors influencing exercise BP in adolescence and its association with cardiovascular risk in early life. Our previously published work showed that exercise BP is a potential useful method to detect adolescents with increased cardiovascular risk. Children and adolescents with cardiovascular risk factors are more likely to develop cardiovascular diseases later in life. However, previous studies on the clinical utility of exercise BP have largely focused on middle-to-older aged populations with pre-existing clinical conditions. Therefore, there is a need to investigate further the factors influencing exercise BP in adolescence and its association with future cardiovascular risk. Our previous studies, which focused on exercise BP measured at submaximal intensity, have shown that exercise BP is a potentially useful method for identifying adolescents

at increased cardiovascular risk. Our previous findings suggest that improving cardio-respiratory fitness and reducing body fatness may help to reduce the risk of developing cardiovascular disease and improve overall cardiovascular health. These findings have important implications for the development of effective prevention and early detection strategies, which can contribute to improved public health outcomes.

KEYWORDS

exercise blood pressure, masked hypertension, adolescence, hypertension, cardiorespirarory fitness

Introduction

Cardiovascular disease is the leading cause of death worldwide, with individuals who have risk factors like high blood pressure (BP) and obesity being more likely to develop organ-specific pathophysiological changes that can lead to severe outcomes such as stroke, heart failure, and ischemic heart disease. High BP is identified as the most significant risk factor among all (1–3). Whilst this remains true, conventional resting BP measurement methods may fail to detect asymptomatic hypertension (4). Exercise BP has recently been proven useful in revealing high BP and underlying cardiovascular risk in complementary to resting BP in adults (5–7). Moreover, multiple factors such as cardiorespiratory fitness and fatness have also been revealed to contribute to exercise BP and related cardiovascular risk (8). Modifying these factors might lower high BP response to exercise and, as a result, alleviate the burden of cardiovascular disease. Of note, substantial evidence has shown that cardiovascular diseases in later life have an early life origin and children. Children and adolescents with these cardiovascular risk factors have a greater propensity to develop cardiovascular diseases in later life (9). Nonetheless, most of the previous studies on the clinical utility of exercise BP were conducted in the middle-to-older aged population often with pre-existing clinical conditions (8–10). Standardized exercise protocols are employed in specific clinical studies, as well as for evaluating the cardiorespiratory fitness. However, the limited availability of reference values for exercise BP in children and adolescents under various protocols complicates the interpretation of BP readings in these populations. Therefore, there is a need to gain deeper insights into the contribution of the factors on exercise BP in children and adolescence, and explore the association between exercise BP thresholds and long-term cardiovascular risk for developing effective prevention and early detection strategies.

The overarching aim was to summarize how these factors (such as cardio-respiratory fitness and fatness) contribute to exercise BP and its related potential cardiovascular risk in children and adolescence. We also want to provide an overview of the concept of exercise BP and related cardiovascular risk and to discuss essential literature on the clinical relevance of exercise BP, evidence of the early life origin of cardiovascular disease and rationale for utilising exercise BP in childhood and adolescence in revealing cardiovascular risk.

Cardiovascular disease risk factors

Many risk factors play an important role in contributing to the development of cardiovascular disease. These risk factors include modifiable factors such as high BP, diabetes, abnormal blood lipids, obesity, unhealthy diet, physical inactivity and socioeconomic status, and the non-modifiable risk factors of age and family history. Of all the identified risk factors, high BP stands out as the predominant risk factor for cardiovascular disease (11). A meta-analysis showed that for each 10 mm Hg reduction of SBP, the risk of major cardiovascular disease events including coronary heart disease (0.83, 0.78–0.88), stroke (0.73, 0.68–0.77), and heart failure (0.72, 0.67–0.78) are substantially reduced (12). The reduction of 10 mmHg of SBP has been shown to lead to a significant 13% reduction in all-cause mortality (0.87, 0.84–0.91) (12). Therefore, by managing high BP, the burden of cardiovascular disease can be significantly reduced.

Blood pressure – the greatest risk factor for cardiovascular disease

What is (high) blood pressure?

The heart provides tissues and organs of the human body with oxygenated blood for sustaining life (13). With each heartbeat, blood is pumped into the blood vessels of the circulatory system, the flow of which generates a perpendicular force against the endoluminal surface of the arterial walls (13). This force is termed arterial BP (13). BP is typically viewed as two numbers: the highest number being systolic pressure, representing the peak of pressure against the arterial wall during the contraction phase (14). Diastolic pressure is the BP in the arteries during the relaxation phase (14). In clinical practice, both systolic and diastolic BP are generally recorded with a unit of millimetres of mercury (mmHg) (14).

High BP, also known as hypertension, is a condition in which the pressure on the arterial walls (systolic and/or diastolic BP) is higher than normal (15). There is a continuum of risks related to BP, although high BP is classified according to a threshold level in clinical practice (16–19). Thresholds used to define high BP differ among regional clinical guidelines. For instance, the European guidelines define high BP as the average of more than two BP readings above 140 mmHg for SBP or above 90 mmHg for diastolic BP on more than two occasions (18). The same definitions are used

for the 'in-office' hypertension in the 2020 International Society of Hypertension global hypertension practice guidelines (17). However, the US guidelines propose a lower threshold of 130 for systolic and 80 mmHg for diastolic since 2017 (16). Despite the differences in thresholds for defining high BP, guidelines are in agreement on the necessity of taking multiple measurements and including the provision of out-of-office BP measurements such as ambulatory BP monitoring (ABPM) or home BP monitoring (HBPM) to confirm true BP level for clinical decisions (16–19). Diagnosing high BP/hypertension in pediatric and adolescent populations poses a significant challenge due to the complexity of standards and definitions during periods of rapid growth which makes it difficult to design outcome cardiovascular studies. Despite the heterogenity of definiton in different countries, high BP/hypertension in children and adolescents is usually defined as values exceeding the 95th percentile of age-specific and sex-specific distributions (20, 21).

How is BP measured and managed in clinical practice?

Despite the high prevalence of high BP and advancements in BP measurement and monitoring, there is still a lack of identification and control of high BP. According to WHO, approximately 46% of the adult population with high BP are unaware of their diagnosis (1). Given the significant role of high BP in contributing to cardiovascular risk, accurate measurement of BP in clinical practice is paramount (11, 22, 23). It is important to follow clinical guidelines for BP measurement to avoid misclassification of cardiovascular risk and potential adverse health consequences (23).

In real practice, health professionals typically measure BP in a clinic setting using a manual auscultatory or automatic oscillometric device that has been validated according to standardized protocols, known as "office BP" or "clinic BP" (24). Accurate measurement of BP in clinical practice is essential for assessing cardiovascular risk. To address the "white-coat effect, "where BP rises in the presence of health professionals, unobserved office BP measurements should be taken using an automatic device while patients sit alone in the doctor's office. These unobserved office BP readings are typically lower than conventional office BP readings, (25) but similar to or lower than average daytime BP readings measured by ambulatory blood pressure monitoring (ABPM), which is considered as the gold-standard BP measurement (26).

In addition to office BP measurements, out-of-office BP measurement is commonly performed in clinical practice. This refers to BP measurements taken outside of the doctor's office, such as at home or in the workplace, and is considered more reflective of daily life BP. Home BP monitoring (HBPM) is usually done by the patient using an automatic oscillometric device in a quiet environment at home in the morning. HBPM measurements are typically lower than office BP and showed higher reproducibility (27). HBPM has also been found to be more closely associated with targeted organ damage, such as left-ventricular hypertrophy, compared to office BP (27).

Another form of out-of-office BP measurement is ABPM, which is considered the gold-standard method to confirm high BP (27). ABPM records multiple BP readings over a 24-h period using a portable automatic oscillometric BP monitor. ABPM is more closely associated with hypertension-mediated organ damage and cardiovascular mortality than office BP (27, 28). Since the ABPM device is expensive and the side effects includs sleep interference, plan, skin irritation, noisy device, inconvenience with work, haematoma etc. for some patients (29). ABPM can not be performed without specialist equipment and clinical supervision. Thus, ABPM might not be appropriate for screening high BP in public health settings or in large population-based studies where there are time and budget constraints. Thus, there is a practical need to find other alternatives for population detection and screening for high BP.

In clinical practice, treatment decisions for high BP should consider factors beyond BP. Both US and European guidelines recommend considering coexisting risk factors to reduce underlying cardiovascular risk (16–18). High BP rarely exists alone, and risk factors that coexist with high BP have a multiplier effect on the risk of cardiovascular disease (30). Previous evidence suggests that cardiovascular risk calculator identifies patients at high risk who may not be identified through traditional BP measurement. Identification of individuals at high risk of developing cardiovascular risk based on algorithms which integrate several cardiovascular risk factors has been shown to be more effective than targeting BP alone (30, 31). Quantifying future cardiovascular risk in patients with hypertension is particularly important for healthcare service and disease prevention.

What are the current shortfalls in the current measurement and management of high BP?

Although the prevalence of high BP remains high worldwide, many asymptomatic individuals are unaware of their high BP diagnosis. Although office BP measurements are frequently utilized in clinical settings, they may not consistently provide an accurate representation of an individual's true BP status. White-coat hypertension is characterized by elevated BP readings obtained in a clinical setting that exceed the recommended thresholds, whereas measurements obtained through HBPM or ABPM demonstrate normotensive values. This observation indicates that the increased office BP may be a phenomenon triggered by the presence of a health professional. On the other hand, office BP measurements can also underestimate a person's true BP level, leading to a condition known as masked hypertension (18–20). This occurs when BP readings are normal in the clinic but elevated outside of the office on HBPM or ABPM. Individuals with masked hypertension have an increased cardiovascular risk compared to those with normal BP (30). Nevertheless, this risk is frequently overlooked due to the absence of a recommendation for ABPM when an individual's office BP falls within the normal range. For patients who are suspicious of masked hypertension, current guidelines recommend confirming BP levels with HBPM or ABPM rather than relying solely on a single clinical BP (16–19). Nevertheless, these individuals are frequently overlooked as a result of their "normal" clinic BP, and ABPM may not always be feasible for patients who struggle with wearing the monitoring device due to discomfort in the arm and disturbances in sleep (29). Therefore, other alternative methods are needed to identify masked hypertension and its associated risks.

Exercise BP

The acute BP response to exercise

Dynamic exercise increases the metabolic demand for skeletal muscles (32). Coordinated physiological responses to exercise fulfil this physiological need of the active musculature whilst maintaining sufficient blood supply to vital organs such as the heart and brain (33). Peripheral resistance reduces as a result of redistribution of blood flow from non-activated to activated circulatory beds and muscular arteriole dilates in order to supply skeletal muscle (34). Moreover, cardiac output increases due to upregulated sympathetic activity and accelerated heart rate as the workload of exercise increases (35). The increase in cardiac output predominates over the decrease in systemic vascular resistance, which can lead to as much as a 40% rise in mean arterial pressure (33). Regardless of the mode of the exercise test, systolic BP normally increases with exercise intensity and reaches its peak at maximal exercise intensity/capacity, (36) whilst diastolic BP remains largely unchanged (37). Although there is no unanimity on the definition of normal BP response to exercise, some studies used absolute value. For instance, according to Framingham criteria, a peak systolic BP reaching 210 mmHg for males and systolic BP reaching 190 mmHg for females was considered as the theoretical maximum values for treadmill testing according to standard protocols (often the Bruce protocol) (38, 39). In contrast, in other studies, maximal systolic BP below the 90th or 95th percentile of the studied population was considered normal (33, 34, 40). It is worth noticing that the peak exercise systolic BP, diastolic BP and the increase in systolic BP from rest to peak intensity were higher in men than in women in the same age group and the peak exercise systolic BP was shown to be positively associated with age (33, 41). Therefore, both gender and age should be taken into consideration when interpret BP responses to exercise.

Abnormal BP response to exercise

Despite the majority of people who undertake an exercise test presenting a normal BP response, some individuals may demonstrate an abnormal BP response to exercise, either a hypotensive response or a hypertensive response. Hypotensive response to exercise is a transient drop below the pre-test resting BP or failure of an increase of 10 mmHg in pre-test resting systolic BP as the exercise intensity progressively increases (42, 43). Currently there is no consensus on the magnitude of BP decrement or duration of the response (33, 42). Individuals with borderline hypertension have been reported as more likely to experience a greater drop in post-exercise BP than those without high BP (44, 45). A hypotensive response to exercise such as a decrease in systolic BP of 10 mmHg or more with the increased workload is an indication for termination of exercise testing (44, 46). The incidence of hypotensive response to exercise was previously reported 3 to 6% among those being referred to treadmill exercise testing (42, 47–49). Hypotensive response has been reported not only associated with a higher prevalence of coronary artery disease or left ventricular dysfunction but also a worse prognosis of cardiovascular events in those individuals with or without established cardiovascular diseases (42, 47–51). Hypotensive response to exercise was thought to be attributed to a decreased cardiac output and systemic vascular resistance, altered venous return and/or myocardial contractility, however, the underlying cause of abnormal haemodynamics has not yet been revealed and therefore warrants further investigation (44, 48, 52). Whilst hypotensive response is associated with cardiac dysfunction and subsequent cardiac events, it is not the focus of this review.

In contrast with hypotensive BP response, an excessive rise in exercise systolic BP is termed as a hypertensive response to exercise or exaggerated exercise BP (Figure 1), although the pathophysiological mechanism behind this rise remains unclear (48). Exaggerated BP response to exercise can occur at any stage or different intensity of exercise and in both a healthy population and patients on antihypertensive medications (38–41, 48). Exaggerated exercise BP measured at a fixed light or moderate intensity has been revealed to have higher prognostic value in predicting future cardiovascular risk than resting BP or exercise BP measured at maximal intensity, (37, 48) although currently there is no definitive threshold to define exaggerated exercise BP at either submaximal or maximal intensity of exercise. Some studies utilized specific BP thresholds to define an exaggerated exercise BP while others used the 90th to 95th percentile of the BP response in the studied population. For instance, a systolic BP of 210 mmHg in males or a systolic BP of 190 mmHg in females was adopted as the cut-off values for exaggerated exercise BP at a maximal intensity of exercise in several studies including the Framingham Heart Study (49–52). According to the ACSM guideline, a peak systolic BP greater than 250 mmHg or diastolic BP greater than 115 mm Hg with maximal exercise testing is defined as an exaggerated exercise BP (43). In addition to an exaggerated exercise BP at the peak or maximal exercise intensity, various thresholds ranging from 150 to 180 mmHg have been adopted at submaximal intensity in relation to different cardiovascular outcomes with different intensity and protocols of exercise tests (8). However, in the case of adults, the determination of elevated exercise BP is hindered by variations in testing methods and protocols, such as whether the exercise is conducted on a treadmill or bicycle, and whether BP is measured during moderate or maximum intensity. As mentioned in the hypertension guidelines, the definition of elevated BP in children is based on sex-and age-specific reference values rather than fixed cut-off points. The scarcity of studies investigating exercise BP in the children/adolescent population complicates the interpretation of

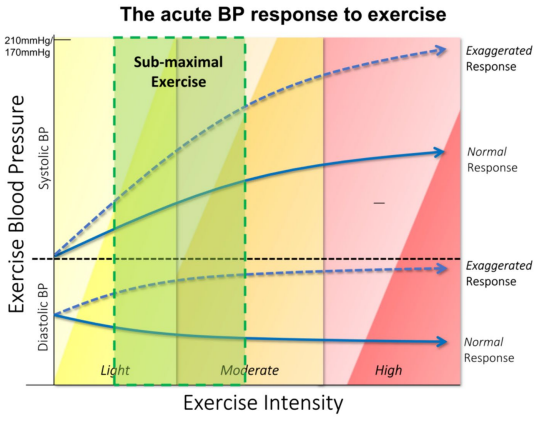


FIGURE 1
Exaggerated exercise BP or hypertensive BP response to exercise.

exercise BP in these groups. A recent published review advised that (1) the external exercise workload remain consistent when measuring exercise BP, and that (2) exercise BP should be assessed at a fixed submaximal exercise intensity (8). These aforementioned suggestions warrant a proper interpretation of exercise-induced BP changes in relation to cardiorespiratory fitness, and can be easily incorporated into practice. Further investigation is needed to establish standard reference values and assess the clinical relevance of indexing exercise systolic BP responses in diverse and extensive populations.

Whilst the mechanism behind exaggerated exercise BP remains to be elucidated, abnormal haemodynamics may be a key factor that contributes to the excessive rise in exercise BP. Previous studies suggested that impaired vascular function which includes increased arterial stiffness and impaired endothelial function is associated with exaggerated exercise BP (51, 53). This association between impaired vascular function and exaggerated exercise BP may explain the mechanism link between exercise BP and increased cardiovascular risk. A previous study also indicated that those with exaggerated exercise BP may have an underlying impaired vascular function (51). The vascular system with impaired vascular function fails to compensate for the increased cardiac output caused by daily normal physical activities and therefore leading to frequent rises in BP (35).

The dashed line in this figure depicts the excessive rise of the systolic BP in response to the increasing intensity with the progression of the exercise test. This abnormal rise which is called an exaggerated exercise BP or a hypertensive BP response to exercise occurs in some individuals, irrespective of their normal resting BP. The solid line represents the normal increase of exercise BP which is termed as a normal BP response.

Clinical relevance of abnormal exercise BP

Incident hypertension

Over the past four decades, increasing evidence has emerged suggesting that exaggerated BP response to exercise is complementary to conventional office BP in predicting incidents of hypertension among apparently healthy populations (54–57). For instance, the prognostic value of an exaggerated exercise BP measured at a graded treadmill test was reported higher in predicting the future incidence of hypertension than resting BP in general populations with normal resting BP (54). In a longitudinal study of 3,741 apparently healthy middle-aged men with normal office BP, those whose peak exercise systolic BP greater than 181 mmHg had a 1.54-fold higher risk of developing hypertension compared to those whose peak exercise BP was below the cut-off (50). This peak exercise systolic BP cut-off was also shown to be the strongest predictor of future hypertension (50). Similarly, another study of 1,534 middle-aged male participants with normal resting BP also showed that participants with peak exercise systolic BP greater than 200 mmHg would develop a higher resting BP after 10 years (58). Moreover, the baseline exercise systolic BP was confirmed a stronger predictor of future systolic BP than baseline resting BP after an average of a 10-year follow-up (58).

Due to the differences in mode of exercise and choice of protocol, different threshold values are used to define exaggerated exercise BP in adults, showing a notable variation. When exercising at maximum intensity, the 90th-95th percentiles of exercise BP specific to each gender (usually corresponding to 210/110 mmHg or higher for males and 190/110 mmHg or higher for females) are commonly employed to indicate exaggerated exercise BP (57, 59). Consistent with the aforementioned data, a peak exercise systolic BP of 210 mmHg for males or 190 mmHg for females was established as the cut-off to predict the incidence of hypertension 5 years later in individuals with normal resting BP (57). In addition to exercise BP measured at peak intensity, a submaximal exercise BP cut-off of 160 mmHg at 100 W workload of a symptom-limited cycle ergometry test for males was reported as the optimal cut-off value in predicting the incidence of hypertension independently of other established cardiovascular risk factors in normotensive males (59).

The utility of exaggerated exercise BP in predicting the development of hypertension has been confirmed in specific populations such as young athletes (60). For instance, a young athlete with an exaggerated BP response to exercise defined as peak exercise BP greater than 220/85 mmHg for males or 200/80 mmHg for females had a 3.6 times higher chance of developing into hypertension than an athlete with a normal exercise BP response (60). Several meta-analyses also demonstrated that an exaggerated exercise BP is associated with future cardiovascular risk irrespective of exercise mode/intensity (10, 54).

Underlying high BP/masked hypertension

Instead of staying in a resting state for an entire day, individuals spend substantial time each day in an ambulatory state. The major concern with only applying clinic (office) BP measurement is that it fails to capture high BP which occurs out of the office (masked hypertension) (7). For those with normal in-clinic BP but raised out-of-office BP, there is no indication for them to be referred to do an out-of-office BP measurement (ambulatory BP monitoring). Therefore, the hidden cardiovascular risk of masked hypertension can be easily missed if individuals are only provided with a conventional office BP measurement. Thus, there is a practical need to find other methods to detect those with underlying high BP such as masked hypertension. BP is measured during a submaximal (light-to-moderate) intensity exercise which is representative of the physiological response to daily life physical activity and it correlates well with ambulatory BP monitoring (51, 61). Thus, BP measured during submaximal exercise may be a more might be more reflective of the BP in daily life than BP measured in the resting state in the clinic.

Given the high prevalence of masked hypertension (58%) among those with a hypertensive response to exercise BP, many studies suggested that exercise BP might be a useful tool in revealing masked hypertension and related cardiovascular risk (5, 7, 61, 62). For instance, peak exercise systolic BP has been confirmed related to underlying high BP missed by office BP but also related to underlying high BP when measured by ABPM (63). Although most of the previous studies of exercise BP only focus on peak or maximal intensity exercise BP, submaximal intensity exercise is similar to daily physical activity. Therefore, various thresholds of BP response to submaximal intensity exercise have been revealed associated with masked hypertension in adults (5, 7, 61–63). For instance, a systolic BP above 150 mmHg at an early stage of exercise stress testing was

reported to reveal masked hypertension in individuals with apparent normal office BP (5). Similarly, an exercise systolic BP greater than 175 mmHg at low intensity was reported to reveal masked hypertension with high sensitivity (74%) and moderate specificity (67%) (7). These findings could be partially explained by the fact that the BP response to moderate-intensity exercise is more akin to the chronic BP load that people encounter in their daily physical activity and therefore more reflective of 'true BP' (8, 9). Taken together, all these results suggested that exaggerated exercise might be a warning signal of underlying high BP (masked hypertension) and related cardiovascular risk which is undetectable through conventional resting BP measurement.

Factors associated with exercise BP

Exercise BP has been shown associated with many factors such as increasing age, (30, 64) gender, (65) cardiorespiratory fitness (8, 48), and insulin sensitivity (55). Among all these factors, cardiorespiratory fitness is not only an important modifier of exercise BP but also a powerful predictor of future cardiovascular events and mortality (8, 57, 63, 66).

Cardiorespiratory fitness

Cardiorespiratory fitness is known as a clinical indicator to reveal the body's capacity for transport and consumption of oxygen during aerobic exercise and is traditionally represented by indices such as maximum oxygen uptake, physical work capacity, and resting heart rate. Cardiorespiratory fitness is considered an important cardiovascular risk factor since low cardiorespiratory fitness has been shown associated with higher all-cause and cardiovascular mortality (67–69). Moreover, high cardiorespiratory fitness has also been confirmed associated with a higher level of physical activity, which in turn creates more health benefits such as lower occurrence of coronary heart disease (39). Whilst numerous methods can be used to assess cardiorespiratory fitness either directly or indirectly, the gold standard or most objective measure of cardiorespiratory fitness is maximal oxygen uptake (VO_2 max). An individual's maximum capacity of oxygen utility (VO_2 max or peak VO_2 more appropriate) is normally assessed in a graded exercise treadmill or cycling test by wearing a ventilation mask and VO_2 max was generated by analysing the concentrations of oxygen and carbon dioxide of inspired and expired air (70–72). Other methods such as an indirect estimation of VO_2 max generated from validated metabolic equations are also acceptable under circumstances where a direct measure is not applicable (73–75).

The health benefits of improvement in cardiorespiratory fitness have been reported by many clinical studies. Substantial evidence showed that low cardiorespiratory fitness is associated with increased all-cause mortality from many causes, especially from cardiovascular disease (57, 63). Accordingly, improvement of cardiorespiratory fitness provides a variety of health benefits such as decreased incidence of cardiovascular diseases and mortality and better prognosis of cardiovascular events (51, 57, 63, 76). Cardiorespiratory fitness has been reported to modify exercise BP in different populations irrespective of resting BP. Previous studies indicated that exercise BP is negatively associated with cardiorespiratory fitness such that individuals with high fitness levels would exhibit a lower exercise BP compared to peers with lower fitness levels (76). Moreover, this negative linear association between exercise BP and cardiorespiratory fitness has been found in both normal, prehypertension, and hypertensive populations (72, 75). Furthermore, longitudinal studies have also shown that higher cardiorespiratory fitness at baseline was associated with lower submaximal systolic BP after years of follow-up in an apparently healthy middle-aged population (57).

Although the mechanism behind how cardiorespiratory fitness modifies exercise BP remains unclear, it can be speculated that exercise training improves the efficiency of oxygen delivery and consumption and therefore leads to an increase in fitness (63). For individuals with improved fitness, the cardiac work during exercise is much reduced as a result of a lower heart rate at a fixed cardiac output (51). As a result, a decrease in exercise BP was observed in adults who underwent lifestyle interventions such as exercise training (75).

Indeed, those with low cardiorespiratory fitness usually exhibited a high exercise systolic BP, however, a high exercise BP response could also be seen in those with high fitness. For instance, a reverse J-shape relationship between fitness and exercise systolic BP was reported in a cohort of young males such that a high exercise BP was found in those with low and high fitness (77). The high exercise BP exhibited in those with high fitness could be explained by the fact that cardiac output is the major determinant of fitness (78). Therefore, exercise BP increases due to high cardiac output associated with high fitness. Higher fitness has been shown conversely associated with a lower all-cause mortality rate due to the reduced rate of cardiovascular disease and cancer (51, 79). Thus, an elevation in exercise BP for those with high fitness might not share the same level of potential cardiovascular risk as those with low fitness. Moreover, an absolute value of exercise BP may not be adequate in assessing cardiovascular risk in the absence of cardiorespiratory fitness. Some recent studies suggested that indexing the increase in peak systolic BP to the increase in workload is more predictive of cardiovascular mortality than peak exercise systolic BP alone (80). These findings suggest the importance of combining fitness or workload with exercise BP in assessing exercise BP-related cardiovascular risk in practice.

Body composition

Body composition is often used to describe the different components of the human body such as lean body mass and body fat mass etc. Many aspects of body composition including quantity and distribution of body fat mass, and lean mass, are considered as critical outcomes in infant's and children's health research (81). Obesity and the proportion of body fat are well-established risk factors for chronic diseases, especially cardiovascular diseases. Some anthropometric indices of body composition such as body mass index (BMI), skinfold thickness, and the waist/hip circumference ratio (WHR) are conventionally used indicators of obesity or fatness level (82). These indices of body composition are widely used to quantify or monitor the change in obesity status and to assess related cardiovascular risk at either individual or population levels.

Whilst some factors such as gender, ethnicity and age were recognized to have a huge influence on these indices of body composition and sometimes it will lead to a misclassification of obesity. Other limitations still exist in using these indirect measures of body composition. For instance, BMI is a convenient measure of weight relative to height. BMI estimates body fatness level only on two

basic anthropometric components: height and weight (BMI = weight in kg/height^2 in m^2). BMI is widely used in epidemiological or clinical studies with a large population to assess the obesity level. However, there are some limitations in using BMI. It is not uncommon for individuals with well-developed muscles to be categorized as overweight according to their body mass index (BMI). However, this classification can be deceptive as it fails to account for the possibility that these individuals may possess minimal or no surplus body fat. Conversely, BMI has the potential to underestimate the level of adiposity in individuals with limited muscle mass, such as the older adults or those who are physically weak (83). What's more important than misdiagnosis is that the same level of BMI at different ages consists of different proportions of fat and fat-free mass. Therefore, differences in the body composition and components of fat and fat-free mass cannot be clearly distinguished using BMI. A more objective measure for different components of body composition is available with technological advances. Dual-energy x-ray absorptiometry (DXA) is a precise measurement method for body composition as it differentiates bone mass, fat mass and lean mass and thus, the proportion of each component can be easily calculated (84).

Data from prospective studies have shown that individuals with increased fatness characterised by an increase in waist circumference, waist/hip circumference ratio (WHR), or sum of skinfold were at heightened risk for developing cardiovascular diseases and had a higher incidence of cardiovascular mobility and mortality (73, 85). For instance, high BMI and fatness were associated with increased occurrence of cardiovascular diseases such as coronary heart disease, ischemic stroke, hypertension, and diabetes mellitus (79, 86–88). Due to lifestyle changes such as a poor diet and lack of exercise, the prevalence of fatness or obesity has increased in general. The prevalence of obesity has been reported to double and even quadrupled over the last three decades (85). An increase in body fatness or obesity as a result of the complexity of genetic, socioeconomic, environmental, and behavioral factors has become a major health and socioeconomic burden for individuals, health systems and society. Moreover, an unabated rise in the prevalence of obesity is expected to continue in the future with a higher incidence of cardiovascular diseases (89). Thus, monitoring and control of obesity remain a major public health problem worldwide that needs to be prioritized (1).

Body composition including body fatness and leanness are known risk factors for cardiovascular diseases in general. More specifically, body fatness is an important risk factor for both BP measured at rest and during exercise (86–88). High body fatness has been revealed positively associated with exercise BP in adults (70). A growing body of evidence also suggested that lifestyle interventions such as exercise training would lead to an attenuated exercise BP through a reduction in weight or body fat (70, 76). The Previous study also showed that reduced fatness through exercise training would lead to reduced exercise BP (75). Whilst the previous study was done in older adults with established cardiovascular diseases, the association between body composition (body fatness and leanness) and exercise BP has been seldom explored in a healthy adolescent population. By addressing these questions in the following sections, the influence of body composition on exercise BP and related cardiovascular risk can be better understood. Understanding these associations would enable the implementation of more appropriate treatment and management strategies which help to lower the incidence of cardiovascular morbidity and mortality caused by high fatness/obesity among these populations.

Exercise BP in adolescence

Given that high exercise BP appears to be associated with incident hypertension and cardiovascular disease in adults, it is crucial to detect underlying high BP using exercise BP and to identify the factors that modify exercise BP and its related cardiovascular risk. This could be especially important in early life such as childhood or adolescence since there is increasing evidence showing that high BP is established at an early time point in life as indicated in a meta-analysis where BP tracking from childhood to adulthood was strong (68).

While the association between exercise BP and the well-established cardiovascular risk factors has been confirmed in adult populations, (51) studies on these associations in early life in adolescence are scarce. For instance, decreased adiposity or body fatness through exercise training has been reported as related to a reduction in exercise BP in adults (75). Obese hypertensive adolescents have higher BP than lean hypertensives during exercise (90). Whilst lower submaximal exercise BP has been shown associated with higher cardiorespiratory fitness in the older adult population, (75) a reverse J shape association between exercise BP and fitness has also been reported in a cohort of young men (77). However, the mechanism or reason behind the J shape relationship between fitness and exercise BP in youth remains to be elucidated. Thus, more studies are needed to explore the association between exercise BP and fitness in adolescents.

Although it has been revealed that exercise BP is associated with altered cardiovascular structure and function in adults, (48) exercise BP in adolescence has also been shown associated with cardiovascular structure in adolescence (91). Moreover, less is known about whether exercise BP in adolescence is associated with an adapted cardiovascular structure or future cardiovascular risk. Currently, few large population-based studies have examined the long-term association between exercise BP and cardiovascular structure and future cardiovascular risk in healthy adolescents.

Our previous studies focused on the clinical importance of exercise BP in detecting high BP and the factors that contribute to exercise BP (fitness and fatness) and the influence of exercise BP on cardiovascular risk (high BP and altered cardiovascular structure) in adolescents (92–94). One of our previous studies first demonstrated that exercise BP might be a useful tool to rule out underlying high BP or "masked hypertension" in adolescence (Specificity: 86.9%, NPV: 95.5%) (92). Adolescents with exercise BP above the thresholds are more likely to have a worse left ventricular mass index and aortic PWV (92). Moreover, the influence of fitness on the association between post-exercise BP and LV mass index was 'U shaped', suggesting that both those with low and high cardiorespiratory fitness shared a similar association which highlights the importance of considering fitness as a factor that contributes to both exercise BP and its relationship with the cardiac structure in adolescence (93). In addition to cardiorespiratory fitness, fatness was also associated with post-exercise systolic BP and might have a relatively more important role in exercise BP in adolescence (94). Furthermore, three distinctive trajectories of fatness and leanness from childhood to early adulthood were identified (unpublished work). Those in trajectory with the consistently highest level of fatness or lowest level of leanness had higher post-exercise systolic SBP. However, these associations were largely attenuated after adjustment for adult measures of fatness or leanness, which suggested that modelling trajectories of fatness and leanness from childhood to adulthood does not provide additional information about exercise BP than a

single concurrent measurement in adulthood. Taken together, this review has discussed the potential importance of fitness and to a greater extent, fatness in contributing to exercise BP in adolescence. Higher exercise BP appears to be associated with high BP and altered cardiovascular structure, (49) highlighting the potential clinical implications of assessing exercise BP in adolescents for the identification of current and future cardiovascular disease risks.

Although this review provided some new insights into the understanding of the role of exercise BP and its association with fitness and fatness in adolescents, there are important issues to be addressed in future research. Our previous study showed that specific thresholds derived from exercise BP from a submaximal exercise step-test has a high specificity and negative predictive value in predicting masked hypertension in adolescence (92). This result suggested that exercise BP may serve as a useful screening tool in complementary to clinic BP for ruling out masked hypertension and potential cardiovascular risk. For example, BP measurements can be incorporated as a customary examination in educational institutions during children's physical education classes. This may involve conducting pre-and post-exercise tests at sub-maximal intensity levels. The measurement of BP prior to and following exercise can provide valuable insights into the presence of underlying hypertension, warranting further investigation through specialized examinations to confirm the diagnosis. Furthermore, it is worth noting that the sensitivity and positive predictive value exhibit relatively low values. Consequently, a persisting challenge lies in the identification of readily available BP measures that can effectively detect masked hypertension.

Apart from this, exercise systolic BP above these thresholds was associated with greater cardiovascular risk in adolescence. To extend the clinical value of these findings, these thresholds should be tested in further large-scale population-based studies to validate the prognostic efficiency for predicting future cardiovascular risk/events. Also, future studies should focus on specifying prognostic/diagnostic thresholds of exercise BP in children and adolescents (different gender/age at a (fix) external workload) to predict future clinical outcomes or cardiovascular events. Notwithstanding the constraints of the preceding investigations, the aforementioned findings emphasize the pragmatic efficacy of exercise BP as a complementary tool for identifying and promptly detecting latent hypertension and its correlated cardiovascular hazards among children/adolescents.

Summary/conclusion

In summary, high exercise BP seems to be associated with underlying high BP and altered cardiovascular structure and increased cardiovascular risk, emphasizing the potential clinical utility of exercise BP in the assessment or identification of existing and future cardiovascular disease risk in adolescence.

High BP and related cardiovascular diseases add a huge social and economic burden to society as many individuals with asymptomatic high BP remained undiagnosed and uncontrolled. Thus, there is an urgent and practical need to find other alternatives to detect underlying high BP and cardiovascular risk. Despite previous evidence showing that exercise BP is useful in revealing underlying cardiovascular risk, underlying high BP or masked hypertension which was often overlooked by the conventional resting BP method prompts the high cardiovascular risk in adults (7). However, thresholds of exercise BP that could reveal high BP or underlying cardiovascular risk in childhood and adolescence remains unclear. In addition to revealing underlying high BP and cardiovascular risk, many factors such as cardiorespiratory fitness and body composition (fatness) have been demonstrated associated with exercise BP and could modify its association with the cardiovascular structure in adulthood. However, it is unknown whether this is the case in childhood and adolescence. By reviewing the current knowledge/literature, this review aims to achieve a better understanding of the factors that contribute to exercise BP (including fitness and fatness), and the association between exercise BP in childhood and adolescence and potential future cardiovascular risk (high BP and altered cardiovascular structure).

Although we have performed a series of studies to explore these associations in adolescence, (92–94) the existing literature on exercise BP in pediatric and adolescent populations is still scarce, lacking precise and valuable reference data for evaluating BP following various exercise protocols, as well as identifying potential clinical conditions that may contribute to an exaggerated BP response. Therefore, a deeper understanding the implications of such exaggerated BP responses is crucial in clinical practice.

Fitness and fatness and other factors is crucial in contributing to exercise BP and its association with the cardiovascular risk in childhood and adolescence. Deeper exploration into early-life exercise BP and its clinical utility in detecting future cardiovascular risk should be encouraged.

Author contributions

ZH: Conceptualization, Writing – original draft, Writing – review & editing. XiuL: Writing – review & editing. XiaL: Writing – review & editing. YX: Writing – review & editing. HF: Writing – review & editing. LR: Writing – review & editing.

Funding

The author(s) declare that financial support was received for the research, authorship, and/or publication of this article. This work was supported by the Guangdong Innovation Platform of Translational Research for Cerebrovascular Diseases and grants from Guangdong Basic and Applied Basic Research Foundation (2022A1515220100); Science and Technology Innovation Commission of Shenzhen (ZDSYS20200811142600003); Natural Science Foundation of Guangdong Province (2023A1515010169) and Provincial Clinical Prominent Specialty Training Project - Neurology supported by Shenzhen High-level Hospital Construction Fund (4004038).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated

organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. World Health Organization. Hypertension. (2019). Available at: https://www.who.int/news-room/fact-sheets/detail/hypertension

2. Juhola J, Oikonen M, Magnussen CG, Mikkilä V, Siitonen N, Jokinen E, et al. Childhood physical, environmental, and genetic predictors of adult hypertension: the cardiovascular risk in young Finns study. *Circulation*. (2012) 126:402–9. doi: 10.1161/CIRCULATIONAHA.111.085977

3. Tracy RE, Newman WP, Wattigney WA, Srinivasan SR, Strong JP, Berenson GS. Histologic features of atherosclerosis and hypertension from autopsies of young individuals in a defined geographic population: the Bogalusa heart study. *Atherosclerosis*. (1995) 116:163–79. doi: 10.1016/0021-9150(95)05525-2

4. Schutte AE, Kollias A, Stergiou GS. Blood pressure and its variability: classic and novel measurement techniques. *Nat Rev Cardiol*. (2022) 19:643–54. doi: 10.1038/s41569-022-00690-0

5. Schultz MG, Picone DS, Nikolic SB, Williams AD, Sharman JE. Exaggerated blood pressure response to early stages of exercise stress testing and presence of hypertension. *J Sci Med Sport*. (2016) 19:1039–42. doi: 10.1016/j.jsams.2016.04.004

6. Sharman JE, Hare JL, Thomas S, Davies JE, Leano R, Jenkins C, et al. Association of masked hypertension and left ventricular remodeling with the hypertensive response to exercise. *Am J Hypertens*. (2011) 24:898–903. doi: 10.1038/ajh.2011.75

7. Schultz MG, Hare JL, Marwick TH, Stowasser M, Sharman JE. Masked hypertension is "unmasked" by low-intensity exercise blood pressure. *Blood Press*. (2011) 20:284–9. doi: 10.3109/08037051.2011.566251

8. Schultz MG, La Gerche A, Sharman JE. Cardiorespiratory fitness, workload, and the blood pressure response to exercise testing. *Exerc Sport Sci Rev*. (2022) 50:25–30. doi: 10.1249/JES.0000000000000276

9. Holzemer NF, Silveira LJ, Kay J, Khanna AD, Jacobsen RM. Submaximal exercise response is associated with future hypertension in patients with Coarctation of the aorta. *Pediatr Cardiol*. (2023) 44:1209–16. doi: 10.1007/s00246-023-03176-z

10. Schultz MG, Otahal P, Picone DS, Sharman JE. Clinical relevance of exaggerated exercise blood pressure. *J Am Coll Cardiol*. (2015) 66:1843–5. doi: 10.1016/j.jacc.2015.08.015

11. Yusuf S, Joseph P, Rangarajan S, Islam S, Mente A, Hystad P, et al. Modifiable risk factors, cardiovascular disease, and mortality in 155 722 individuals from 21 high-income, middle-income, and low-income countries (PURE): a prospective cohort study. *Lancet*. (2020) 395:795–808. doi: 10.1016/S0140-6736(19)32008-2

12. Ettehad D, Emdin CA, Kiran A, Anderson SG, Callender T, Emberson J, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. *Lancet*. (2016) 387:957–67. doi: 10.1016/S0140-6736(15)01225-8

13. Loscalzo J, Fauci AS, Kasper DL, Hauser SL, Longo DL, Jameson JL. *Harrison's principles of internal medicine*. New York, NY: Mcgraw-hill (2012).

14. American Heart Association. What is high blood pressure, (2016). Available at: https://www.heart.org/en/health-topics/high-blood-pressure/the-facts-about-high-blood-pressure/what-is-high-blood-pressure (Accessed September 12, 2023).

15. Institute for Quality and Efficiency in Health Care. What is blood pressure and how is it measured? Cologne, Germany: InformedHealth.org; (2006). Available at: https://www.ncbi.nlm.nih.gov/books/NBK279251/ (Accessed September 12, 2023).

16. Whelton PK, Carey RM, Aronow WS, Casey DE, Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. *J Am Coll Cardiol*. (2018) 71:e127–248. doi: 10.1016/j.jacc.2017.11.006

17. Unger T, Borghi C, Charchar F, Khan NA, Poulter NR, Prabhakaran D, et al. 2020 International Society of Hypertension global hypertension practice guidelines. *J Hypertens*. (2020) 38:982–1004. doi: 10.1097/hjh.0000000000002453

18. Mancia G, Kreutz R, Brunström M, Burnier M, Grassi G, Januszewicz A, et al. 2023 ESH guidelines for the management of arterial hypertension the task force for the management of arterial hypertension of the European Society of Hypertension: endorsed by the International Society of Hypertension (ISH) and the European renal association (ERA). *J Hypertens*. (2023) 41:1874–2071. doi: 10.1097/HJH.0000000000003480

19. Stergiou GS, Palatini P, Parati G, O'Brien E, Januszewicz A, Lurbe E, et al. European Society of Hypertension Council and the European Society of Hypertension Working Group on blood pressure monitoring and cardiovascular variability. 2021 European Society of Hypertension practice guidelines for office and out-of-office blood pressure measurement. *J Hypertens*. (2021) 39:1293–302. doi: 10.1097/HJH.0000000000002843

20. Flynn JT, Kaelber DC, Baker-Smith CM, Blowey D, Carroll AE, Daniels SR, et al. Clinical practice guideline for screening and management of high blood pressure in children and adolescents. *Pediatrics*. (2017) 140:e20171904. doi: 10.1542/peds.2017-1904

21. de Simone G, Mancusi C, Hanssen H, Genovesi S, Lurbe E, Parati G, et al. Hypertension in children and adolescents. *Eur Heart J*. (2022) 43:3290–301. doi: 10.1093/eurheartj/ehac328

22. Handler J. The importance of accurate blood pressure measurement. *Perm J*. (2009) 13:51–4. doi: 10.7812/TPP/09-054

23. Cheung AK, Whelton PK, Muntner P, Schutte AE, Moran AE, Williams B, et al. International consensus on standardized clinic blood pressure measurement - a call to action. *Am J Med*. (2023) 136:438–445.e1. doi: 10.1016/j.amjmed.2022.12.015

24. Stergiou GS, Alpert B, Mieke S, Asmar R, Atkins N, Eckert S, et al. A universal standard for the validation of blood pressure measuring devices: Association for the Advancement of medical instrumentation/European Society of Hypertension/International Organization for Standardization (AAMI/ESH/ISO) collaboration statement. *Hypertension*. (2018) 71:368–74. doi: 10.1161/HYPERTENSIONAHA.117.10237

25. Myers MG, Godwin M, Dawes M, Kiss A, Tobe SW, Kaczorowski J. Measurement of blood pressure in the office: recognizing the problem and proposing the solution. *Hypertension*. (2010) 55:195–200. doi: 10.1161/HYPERTENSIONAHA.109.141879

26. Verdecchia P. Prognostic value of ambulatory blood pressure: current evidence and clinical implications. *Hypertension*. (2000) 35:844–51. doi: 10.1161/01.HYP.35.3.844

27. Parati G, Stergiou GS, Bilo G, Kollias A, Pengo M, Ochoa JE, et al. Working group on blood pressure monitoring and cardiovascular variability of the European Society of Hypertension. Home blood pressure monitoring: methodology, clinical relevance and practical application: a 2021 position paper by the working group on blood pressure monitoring and cardiovascular variability of the European Society of Hypertension. *J Hypertens*. (2021) 39:1742–67. doi: 10.1097/HJH.0000000000002922

28. Bliziotis IA, Destounis A, Stergiou GS. Home versus ambulatory and office blood pressure in predicting target organ damage in hypertension: a systematic review and meta-analysis. *J Hypertens*. (2012) 30:1289–99. doi: 10.1097/HJH.0b013e3283531eaf

29. Beltman F, Heesen W, Smit A, May JF, Lie KI, Meyboom-de Jong B. Acceptance and side effects of ambulatory blood pressure monitoring: evaluation of a new technology. *J Hum Hypertens*. (1996) 10 Suppl 3:S39–42.

30. Berry JD, Dyer A, Cai X, Garside DB, Ning H, Thomas A, et al. Lifetime risks of cardiovascular disease. *N Engl J Med*. (2012) 366:321–9. doi: 10.1056/NEJMoa1012848

31. SCORE2 working group and ESC Cardiovascular risk collaboration. SCORE2 risk prediction algorithms: new models to estimate 10-year risk of cardiovascular disease in Europe. *Eur Heart J*. (2021) 42:2439–54. doi: 10.1093/eurheartj/ehab309

32. Hoppeler H, Kayar SR, Claasen H, Uhlmann E, Karas RH. Adaptive variation in the mammalian respiratory system in relation to energetic demand: III. Skeletal muscles: setting the demand for oxygen. *Respir Physiol*. (1987) 69:27–46. doi: 10.1016/0034-5687(87)90099-5

33. le VV, Mitiku T, Sungar G, Myers J, Froelicher V. The blood pressure response to dynamic exercise testing: a systematic review. *Prog Cardiovasc Dis*. (2008) 51:135–60. doi: 10.1016/j.pcad.2008.07.001

34. Munir S, Jiang B, Guilcher A, Brett S, Redwood S, Marber M, et al. Exercise reduces arterial pressure augmentation through vasodilation of muscular arteries in humans. *Am J Phys Heart Circ Phys*. (2008) 294:H1645–50. doi: 10.1152/ajpheart.01171.2007

35. Klabunde R. *Cardiovascular physiology concepts*. Waltham, Massachusetts: Lippincott Williams & Wilkins (2011).

36. Daida H, Allison TG, Squires RW, Miller TD, Gau GT. Peak exercise blood pressure stratified by age and gender in apparently healthy subjects. *Mayo Clin Proc*. (1996) 71:445–52. doi: 10.4065/71.5.445

37. Schultz MG. The clinical importance of exercise blood pressure. *Artery Res*. (2018) 21:58–62. doi: 10.1016/j.artres.2017.11.004

38. Campbell L, Marwick TH, Pashkow FJ, Snader CE, Lauer MS. Usefulness of an exaggerated systolic blood pressure response to exercise in predicting myocardial perfusion defects in known or suspected coronary artery disease. *Am J Cardiol*. (1999) 84:1304–10. doi: 10.1016/S0002-9149(99)00562-7

39. Lauer MS, Levy D, Anderson KM, Plehn JF. Is there a relationship between exercise systolic blood pressure response and left ventricular mass? The Framingham heart study. *Ann Intern Med*. (1992) 116:203–10. doi: 10.7326/0003-4819-116-3-203

40. Schultz MG, La Gerche A, Sharman JE. Blood pressure response to exercise and cardiovascular disease. *Curr Hypertens Rep*. (2017) 19:89. doi: 10.1007/s11906-017-0787-1

41. Michelsen S, Otterstad J. Blood pressure response during maximal exercise in apparently healthy men and women. *J Intern Med*. (1990) 227:157–63. doi: 10.1111/j.1365-2796.1990.tb00137.x

42. MacDonald JR. Potential causes, mechanisms, and implications of post exercise hypotension. *J Hum Hypertens*. (2002) 16:225–36. doi: 10.1038/sj.jhh.1001377

43. American College of Sports Medicine. *ACSM's guidelines for exercise testing and prescription*. Waltham, Massachusetts: Lippincott Williams & Wilkins (2013).

44. Bruce RA, Cobb LA, Katsura S, Morledge JH, Andrus WW, Fuller TJ. Exertional hypotension in cardiac patients. *Circulation*. (1959) 19:543–51. doi: 10.1161/01.CIR.19.4.543

45. Barlow PA, Otahal P, Schultz MG, Shing CM, Sharman JE. Low exercise blood pressure and risk of cardiovascular events and all-cause mortality: systematic review and meta-analysis. *Atherosclerosis*. (2014) 237:13–22. doi: 10.1016/j.atherosclerosis.2014.08.029

46. Hagberg JM, Montain SJ, Martin W 3rd. Blood pressure and hemodynamic responses after exercise in older hypertensives. *J Appl Physiol*. (1987) 63:270–6. doi: 10.1152/jappl.1987.63.1.270

47. Floras JS, Sinkey CA, Aylward PE, Seals DR, Thoren PN, Mark AL. Postexercise hypotension and sympathoinhibition in borderline hypertensive men. *Hypertension*. (1989) 14:28–35. doi: 10.1161/01.HYP.14.1.28

48. Schultz MG, Otahal P, Cleland VJ, Blizzard L, Marwick TH, Sharman JE. Exercise-induced hypertension, cardiovascular events, and mortality in patients undergoing exercise stress testing: a systematic review and meta-analysis. *Am J Hypertens*. (2013) 26:357–66. doi: 10.1093/ajh/hps053

49. Xia B, Cao P, Zhang L, Huang H, Li R, Yin X. Exercise-induced excessive blood pressure elevation is associated with cardiac dysfunction in male patients with essential hypertension. *Int J Hypertens*. (2022) 2022:8910453–11. doi: 10.1155/2022/8910453

50. Jae SY, Franklin BA, Choo J, Choi YH, Fernhall B. Exaggerated exercise blood pressure response during treadmill testing as a predictor of future hypertension in men: a longitudinal study. *Am J Hypertens*. (2015) 28:1362–7. doi: 10.1093/ajh/hpv036

51. Thanassoulis G, Lyass A, Benjamin EJ, Larson MG, Vita JA, Levy D, et al. Relations of exercise blood pressure response to cardiovascular risk factors and vascular function in the Framingham heart study. *Circulation*. (2012) 125:2836–43. doi: 10.1161/CIRCULATIONAHA.111.063933

52. Michishita R, Ohta M, Ikeda M, Jiang Y, Yamato H. An exaggerated blood pressure response to exercise is associated with nitric oxide bioavailability and inflammatory markers in normotensive females. *Hypertens Res*. (2016) 39:792–8. doi: 10.1038/hr.2016.75

53. Starling MR, Crawford MH, Kennedy GT, O'Rourke RA. Exercise testing early after myocardial infarction: predictive value for subsequent unstable angina and death. *Am J Cardiol*. (1980) 46:909–14. doi: 10.1016/0002-9149(80)90344-6

54. Kjeldsen SE, Mundal R, Sandvik L, Erikssen G, Thaulow E, Erikssen J. Supine and exercise systolic blood pressure predict cardiovascular death in middle-aged men. *J Hypertens*. (2001) 19:1343–8. doi: 10.1097/00004872-200108000-00001

55. Møller NC, Grøntved A, Wedderkopp N, Ried-Larsen M, Kristensen PL, Andersen LB, et al. Cardiovascular disease risk factors and blood pressure response during exercise in healthy children and adolescents: the European youth heart study. *J Appl Physiol*. (2010) 109:1125–32. doi: 10.1152/japplphysiol.00316.2010

56. Miyai N, Arita M, Miyashita K, Morioka I, Shiraishi T, Nishio I. Blood pressure response to heart rate during exercise test and risk of future hypertension. *Hypertension*. (2002) 39:761–6. doi: 10.1161/hy0302.105777

57. Manolio TA, Burke GL, Savage PJ, Sidney S, Gardin JM, Oberman A. Exercise blood pressure response and 5-year risk of elevated blood pressure in a cohort of young adults: the CARDIA study. *Am J Hypertens*. (1994) 7:234–41. doi: 10.1093/ajh/7.3.234

58. Ito K, Iwane M, Miyai N, Uchikawa Y, Mugitani K, Mohara O, et al. Exaggerated exercise blood pressure response in middle-aged men as a predictor of future blood pressure: a 10-year follow-up. *Clin Exp Hypertens*. (2016) 38:696–700. doi: 10.1080/10641963.2016.1200597

59. Lorbeer R, Ittermann T, Völzke H, Gläser S, Ewert R, Felix SB, et al. Assessing cutoff values for increased exercise blood pressure to predict incident hypertension in a general population. *J Hypertens*. (2015) 33:1386–93. doi: 10.1097/HJH.0000000000000568

60. Caselli S, Serdoz A, Mango F, Lemme E, Vaquer Seguì A, Milan A, et al. High blood pressure response to exercise predicts future development of hypertension in young athletes. *Eur Heart J*. (2019) 40:62–8. doi: 10.1093/eurheartj/ehy810

61. Lim P, Donnan P, MacDonald T. Blood pressure determinants of left ventricular wall thickness and mass index in hypertension: comparing office, ambulatory and exercise blood pressures. *J Hum Hypertens*. (2001) 15:627–33. doi: 10.1038/sj.jhh.1001229

62. Kramer C, Leitão CB, Canani L, Ricardo ED, Pinto LC, Gross JL. Blood pressure responses to exercise in type II diabetes mellitus patients with masked hypertension. *J Hum Hypertens*. (2009) 23:620–2. doi: 10.1038/jhh.2009.24

63. Kayrak M, Bacaksiz A, Vatankulu MA, Ayhan SS, Kaya Z, Ari H, et al. Exaggerated blood pressure response to exercise–a new portent of masked hypertension. *Clin Exp Hypertens*. (2011) 32:560–8. doi: 10.3109/10641963.2010.503298

64. Kokkinos PF, Andreas PE, Coutoulakis E, Colleran JA, Narayan P, Dotson CO, et al. Determinants of exercise blood pressure response in normotensive and hypertensive women: role of cardiorespiratory fitness. *J Cardpulm Rehabil*. (2002) 22:178–83. doi: 10.1097/00008483-200205000-00009

65. Howard BV, Lee ET, Cowan LD, Fabsitz RR, Howard WJ, Oopik AJ, et al. Coronary heart disease prevalence and its relation to risk factors in American Indians: the Strong heart study. *Am J Epidemiol*. (1995) 142:254–68. doi: 10.1093/oxfordjournals.aje.a117632

66. Banegas JR, Ruilope LM, de la Sierra A, Vinyoles E, Gorostidi M, de la Cruz JJ, et al. Relationship between clinic and ambulatory blood-pressure measurements and mortality. *N Engl J Med*. (2018) 378:1509–20. doi: 10.1056/NEJMoa1712231

67. Theodore RF, Broadbent J, Nagin D, Ambler A, Hogan S, Ramrakha S, et al. Childhood to early-midlife systolic blood pressure trajectories: early-life predictors, effect modifiers, and adult cardiovascular outcomes. *Hypertension*. (2015) 66:1108–15. doi: 10.1161/hypertensionaha.115.05831

68. Chen X, Wang Y. Tracking of blood pressure from childhood to adulthood: a systematic review and meta-regression analysis. *Circulation*. (2008) 117:3171–80. doi: 10.1161/circulationaha.107.730366

69. Lurbe E, Thijs L, Torro MI, Alvarez J, Staessen JA, Redon J. Sexual dimorphism in the transition from masked to sustained hypertension in healthy youths. *Hypertension*. (2013) 62:410–4. doi: 10.1161/hypertensionaha.113.01549

70. Kokkinos P. Cardiorespiratory fitness, exercise, and blood pressure. *Hypertension*. (2014) 64:1160–4. doi: 10.1161/HYPERTENSIONAHA.114.03616

71. Gulati M, Black HR, Shaw LJ, Arnsdorf MF, Merz CNB, Lauer MS, et al. The prognostic value of a nomogram for exercise capacity in women. *N Engl J Med*. (2005) 353:468–75. doi: 10.1056/NEJMoa044154

72. Liu J, Sui X, Lavie CJ, Zhou H, Mark Park YM, Cai B, et al. Effects of cardiorespiratory fitness on blood pressure trajectory with aging in a cohort of healthy men. *J Am Coll Cardiol*. (2014) 64:1245–53. doi: 10.1016/j.jacc.2014.06.1184

73. Lee DC, Sui X, Artero EG, Lee IM, Church TS, McAuley PA, et al. Long-term effects of changes in cardiorespiratory fitness and body mass index on all-cause and cardiovascular disease mortality in men: the aerobics Center longitudinal study. *Circulation*. (2011) 124:2483–90. doi: 10.1161/circulationaha.111.038422

74. Lakka TA, Venalainen JM, Rauramaa R, Salonen R, Tuomilehto J, Salonen JT. Relation of leisure-time physical activity and cardiorespiratory fitness to the risk of acute myocardial infarction in men. *N Engl J Med*. (1994) 330:1549–54. doi: 10.1056/NEJM199406023302201

75. Barone BB, Wang N-Y, Bacher AC, Stewart KJ. Decreased exercise blood pressure in older adults after exercise training: contributions of increased fitness and decreased fatness. *Br J Sports Med*. (2009) 43:52–6. doi: 10.1136/bjsm.2008.050906

76. Malina RM, Beunen GP, Claessens AL, Lefevre J, Eynde BV, Renson R, et al. Fatness and physical fitness of girls 7 to 17 years. *Obes Res*. (1995) 3:221–31. doi: 10.1002/j.1550-8528.1995.tb00142.x

77. Prasad VK, Drenowatz C, Hand GA, Lavie CJ, Sui X, Demello M, et al. Association between cardiorespiratory fitness and submaximal systolic blood pressure among young adult men: a reversed J-curve pattern relationship. *J Hypertens*. (2015) 33:2239–44. doi: 10.1097/HJH.0000000000000715

78. Park C, Fraser A, Howe LD, Jones S, Davey Smith G, Lawlor DA, et al. Elevated blood pressure in adolescence is attributable to a combination of elevated cardiac output and Total peripheral resistance: evidence against a hyperkinetic state. *Hypertension*. (2018) 72:1103–8. doi: 10.1161/HYPERTENSIONAHA.118.11925

79. Ortega FB, Ruiz JR, Castillo MJ, Sjöström M. Physical fitness in childhood and adolescence: a powerful marker of health. *Int J Obes*. (2008) 32:1–11. doi: 10.1038/sj.ijo.0803774

80. Hedman K, Cauwenberghs N, Christle JW, Kuznetsova T, Haddad F, Myers J. Workload-indexed blood pressure response is superior to peak systolic blood pressure in predicting all-cause mortality. *Eur J Prev Cardiol*. (2020) 27:978–87. doi: 10.1177/2047487319877268

81. Currie KD, Sless RT, Notarius CF, Thomas SG, Goodman JM. Absence of resting cardiovascular dysfunction in middle-aged endurance-trained athletes with exaggerated exercise blood pressure responses. *J Hypertens*. (2017) 35:1586–93. doi: 10.1097/HJH.0000000000001365

82. Mintjens S, Menting MD, Daams JG, van Poppel MNM, Roseboom TJ, Gemke RJBJ. Cardiorespiratory fitness in childhood and adolescence affects future cardiovascular risk factors: a systematic review of longitudinal studies. *Sports Med*. (2018) 48:2577–605. doi: 10.1007/s40279-018-0974-5

83. Nutrition: Science and Everyday Application, v. 1.0 Indicators of Health: BMI, Body Composition, and Metabolic Health Available at: https://openoregon.pressbooks.pub/nutritionscience/chapter/7b-bmi-body-comp-metabolic-health/ (Accessed September 20, 2023).

84. Lemos T, Gallagher D. Current body composition measurement techniques. *Curr Opin Endocrinol Diabetes Obes*. (2017) 24:310–4. doi: 10.1097/MED.0000000000000360

85. Chooi YC, Ding C, Magkos F. The epidemiology of obesity. *Metabolism*. (2019) 92:6–10. doi: 10.1016/j.metabol.2018.09.005

86. Steele RM, Brage S, Corder K, Wareham NJ, Ekelund U. Physical activity, cardiorespiratory fitness, and the metabolic syndrome in youth. *J Appl Physiol*. (2008) 105:342–51. doi: 10.1152/japplphysiol.00072.2008

87. Ruiz JR, Cavero-Redondo I, Ortega FB, Welk GJ, Andersen LB, Martinez-Vizcaino V. Cardiorespiratory fitness cut points to avoid cardiovascular disease risk in children and adolescents; what level of fitness should raise a red flag? A systematic review and meta-analysis. *Br J Sports Med*. (2016) 50:1451–8. doi: 10.1136/bjsports-2015-095903

88. García-Hermoso A, Ramírez-Vélez R, García-Alonso Y, Alonso-Martínez AM, Izquierdo M. Association of Cardiorespiratory Fitness Levels during Youth with Health Risk Later in life: a systematic review and meta-analysis. *JAMA Pediatr*. (2020) 174:952–60. doi: 10.1001/jamapediatrics.2020.2400

89. Finkelstein EA, Khavjou OA, Thompson H, Trogdon JG, Pan L, Sherry B, et al. Obesity and severe obesity forecasts through 2030. *Am J Prev Med*. (2012) 42:563–70. doi: 10.1016/j.amepre.2011.10.026

90. Tulio S, Eglé S, Greily B. Blood pressure response to exercise of obese and lean hypertensive and normotensive male adolescents. *J Hum Hypertens*. (1995) 9:953–8.

91. Schultz MG, Park C, Fraser A, Howe LD, Jones S, Rapala A, et al. Submaximal exercise blood pressure and cardiovascular structure in adolescence. *Int J Cardiol*. (2019) 275:152–7. doi: 10.1016/j.ijcard.2018.10.060

92. Huang Z, Sharman JE, Fonseca R, Park C, Chaturvedi N, Davey Smith G, et al. Masked hypertension and submaximal exercise blood pressure among adolescents from the Avon longitudinal study of parents and children (ALSPAC). *Scand J Med Sci Sports*. (2020) 30:25–30. doi: 10.1111/sms.13525

93. Huang Z, Fonseca R, Sharman JE, Park C, Chaturvedi N, Howe LD, et al. The influence of fitness on exercise blood pressure and its association with cardiac structure in adolescence. *Scand J Med Sci Sports*. (2020) 30:1033–9. doi: 10.1111/sms.13645

94. Huang Z, Park C, Chaturvedi N, Howe LD, Sharman JE, Hughes AD, et al. Cardiorespiratory fitness, fatness, and the acute blood pressure response to exercise in adolescence. *Scand J Med Sci Sports*. (2021) 31:1693–8. doi: 10.1111/sms.13976

frontiers | Frontiers in Pediatrics

TYPE Original Research
PUBLISHED 25 October 2024
DOI 10.3389/fped.2024.1371286

OPEN ACCESS

EDITED BY
Shikai Yu,
Tongji University, China

REVIEWED BY
Meixian Zhang,
Taizhou Hospital of Zhejiang Province Affiliated to Wenzhou Medical University, China
Feitong Wu,
Baker Heart and Diabetes Institute, Australia

*CORRESPONDENCE
Bo Xi
xibo2010@sdu.edu.cn

RECEIVED 22 January 2024
ACCEPTED 10 October 2024
PUBLISHED 25 October 2024

CITATION
Liu Q, Li C, Yang L, Gong Z, Zhao M, Bovet P and Xi B (2024) Weight status change during four years and left ventricular hypertrophy in Chinese children.
Front. Pediatr. 12:1371286.
doi: 10.3389/fped.2024.1371286

Weight status change during four years and left ventricular hypertrophy in Chinese children

Qin Liu[1], Cheng Li[2], Lili Yang[2], Zhuo Gong[3], Min Zhao[4], Pascal Bovet[5] and Bo Xi[2]*

[1]Department of Ultrasound, Children's Hospital of the Capital Institute of Pediatrics, Beijing, China, [2]Department of Epidemiology, School of Public Health, Qilu Hospital, Cheeloo College of Medicine, Shandong University, Jinan, China, [3]School of Public Health, Changsha Medical University, Changsha, China, [4]Department of Nutrition and Food Hygiene, School of Public Health, Cheeloo College of Medicine, Shandong University, Jinan, China, [5]Center for Primary Care and Public Health (Unisanté), University of Lausanne, Lausanne, Switzerland

Objective: It is well-established that overweight/obesity is a major risk factor for left ventricular hypertrophy (LVH) in childhood. However, it is still unclear if reversing from overweight/obesity to normal weight is associated with decreased LVH in children. This study aimed to examine the association between weight status change during four years and LVH among Chinese children based on a prospective cohort study.

Methods: Data were obtained from the Huantai Childhood Cardiovascular Health Cohort Study in China. A total of 1,178 children without LVH at baseline (mean age: 8.3 years) were included in this study. According to weight status [normal weight or overweight (including obesity)] at baseline (2017) and follow-up (2021), children were divided, based on sex- and age-adjusted body mass index (BMI), into four groups: persistent normal weight (normal weight at both baseline and follow-up), incident overweight (normal weight at baseline but overweight at follow-up), reversal to normal weight (overweight at baseline but normal weight at follow-up), persistent overweight (overweight at both baseline and follow-up).

Results: After adjustment for potential confounding factors, children with incident overweight ($n = 114$, 30.63 ± 4.74 g/m$^{2.7}$) and those with persistent overweight ($n = 363$, 31.56 ± 6.24 g/m$^{2.7}$) had higher left ventricular mass index (LVMI) at the end of the follow-up period than those with persistent normal weight ($n = 632$, 28.46 ± 7.64 g/m$^{2.7}$), while those who reversed from overweight to normal weight had a non-significantly lower LVMI ($n = 69$, 28.51 ± 4.28 g/m$^{2.7}$). Compared to children with persistent normal weight, those with persistent overweight [odds ratio (*OR*) = 5.14, 95% confidence interval (*CI*) = 3.33–7.95] and those with incident overweight (*OR* = 3.34, 95% *CI* = 1.77–6.30) had an increased risk of LVH. The risk of LVH tended to decrease, although not significantly, in those who reversed from overweight to normal weight (*OR* = 0.76, 95% *CI* = 0.22–2.55).

Conclusion: Our findings demonstrate a positive association between overweight and left ventricular mass in children and suggest that LVH in childhood could be attenuated by weight loss.

KEYWORDS

children, overweight, weight status change, left ventricular hypertrophy, Chinese

Introduction

Childhood overweight/obesity is a severe public health issue globally. The prevalence of overweight (including obesity) among children aged 6–17 years increased from 6.7% in 1991 to 24.4% in 2015 in China (1), and it was estimated that the total number of children with overweight would reach 50 million in China by 2030 (2). It is well-established that overweight is associated with a range of chronic diseases, such as cardiovascular diseases (CVD), several cancers, hypertension, type 2 diabetes, and several other diseases (3, 4), and overweight is also considered as a main driver of a decline in life quality and expectancy (5).

Left ventricular mass index (LVMI) and left ventricular hypertrophy (LVH) are important risk factors of cardiovascular events (6). Recent studies showed that most children with obesity are suffering from early impairment of the cardiac structure, including increased LVMI and LVH (7, 8), but evidence is mainly based on cross-sectional studies (9–11). Recently, using a longitudinal study, we described that, compared with children who had normal waist circumstance (WC) at both baseline and follow-up, those with a WC gain or with persistently elevated WC had an increased risk of LVH in childhood. However, children who reversed from abdominal obesity to normal WC did not have an increased risk of LVH (12). To our knowledge, no study has examined the effect of weight status change based on body mass index (BMI) during childhood on LVMI and the risk of LVH among Chinese children. It is still unclear whether reversal from overweight to normal weight during childhood could lower the incidence of childhood LVH. Although several studies have found that WC had better predictive effect on cardiovascular outcomes than BMI due to its ability to distinguish between fat mass and fat-free mass (13, 14), others have shown no significant difference (15). BMI is more widely used globally and has a more standardized calculation formula and classification, which may benefit more the development of child health policies. Therefore, based on a prospective cohort study of Chinese children conducted in 2017 and 2021, we examined the association between weight status change over four years and LVH among Chinese children aged 8.3 years on average at baseline.

Methods

Study populations

Data were from the Huantai Childhood Cardiovascular Health Cohort Study, which was conducted in one primary school from Huantai County, Zibo City, Shandong Province, China (16). The cohort is a prospective study using a convenient cluster sampling method to select eligible participants. A total of 1,516 children aged 6–11 years were recruited to participate in the baseline survey (November 2017 to January 2018), and 1,353 children of them were followed up (October to December 2021). Among them, 225 children were excluded due to loss of follow-up or missing information on anthropometric indices, ultrasound measurements, or questionnaires. We also excluded the children who had LVH at baseline ($n = 113$). Finally, 1,178 children in total were included in this study to examine the association between weight status change from 2017 to 2021 and LVMI and incident LVH. This study was approved by the Ethics Committee of School of Public Health, Shandong University (No. 20160308), and informed consent was signed by each participant and their parents/guardians.

Physical examination

Height (cm) and weight (kg) were measured with children wearing light clothing without shoes and with 0.1 cm and 0.1 kg precision, respectively. BMI (kg/m^2) was calculated as the ratio of weight (kg) and the square of height (m^2).

Cardiac ultrasound measurements

According to the Pediatric Cardiometry Guidelines of the American Society of Echocardiography (17), the structure of the left ventricle was measured by an experienced sonographer using a color Doppler ultrasound machine (S4-2, CX30; Royal Philips, Amsterdam, The Netherlands). Measurements were available on the left ventricular end-diastolic internal dimension (LVID), interventricular septal wall thickness (IVST), and left ventricular posterior wall thickness (LVPWT), and left ventricular mass (LVM) and LVMI were calculated using the following formulas: LVM (g) = $0.8 \times [1.04 \times (\text{IVST} + \text{LVID} + \text{LVPWT})^3 - (\text{LVID})^3] + 0.6$ (18), LVMI (g/m$^{2.7}$) = LVM (g)/height$^{2.7}$ (m) (19).

Definitions of weight status change and LVH

Childhood overweight (including obesity) was defined according to the sex- and age-specific BMI percentile reference for Chinese children (20). According to the weight status (normal weight vs. overweight) at baseline and follow-up, all participants were divided into four groups: persistent normal weight (normal weight at both baseline and follow-up), reversal to normal weight (overweight at baseline but normal weight at follow-up), incident overweight (normal weight at baseline but overweight at follow-up), and persistent overweight (overweight at both baseline and follow-up). In this study, LVH was defined as the LVMI ≥ the sex- and age- specific 90th percentile values based on this population (12).

Covariates

A self-reported structured questionnaire was used to collect demographic and lifestyle information of the participants, including age, sex, parental education, dietary habits (intake of

fruits/vegetables and intake of carbonated drinks), sleep duration, and physical activity. Wake-up time and bedtime were obtained by self-report, and sleep duration was calculated by subtracting bedtime from wake-up time. Physical activity (<1 vs. ≥1 h per day) and dietary intake of fruits/vegetables (<5 vs. ≥5 servings per day) were categorized according to the recommendations of World Health Organization (21, 22). We defined intake of carbonated drinks as <1 times/week vs. ≥1 times/week (23). Parental education was classified as junior high school and below vs. high school vs. college and above.

Statistical analysis

Data on the characteristics of the participants are presented as means ± standard deviations for continuous variables and frequencies (proportions) for categorical variables. Differences in characteristics according to the four weight status groups (persistent normal weight, reversal to normal weight, incident overweight, and persistent overweight) were tested using variance analysis for continuous variables and chi-square test for categorical variables. Covariance analysis was used to assess the association between weight status change and LVMI measured at follow-up. Association between weight status change and LVH was examined using multivariate logistic regression models, and odds ratios (*OR*s) with their 95% confidence intervals (95% *CI*s) were calculated. Three models were performed to assess the confounding effects of the included covariates. Model 1 was adjusted for sex and age at baseline, and model 2 was additionally adjusted for parental education, intake of fruits/vegetables, intake of carbonated drinks, physical activity, and sleep duration at baseline. Model 3 was then additionally adjusted for intake of fruits/vegetables, intake of carbonated drinks, physical activity, and sleep duration at follow-up. All statistical analyses were conducted using SAS version 9.4 and a two-sided *P*-value <0.05 was considered to be statistically significant.

Results

Basic characteristics of the participants

1,178 children (males: 52.9%) were included in this study (children with LVH at baseline were not included in this study). Among them, 53.7% (632/1,178) had persistent normal weight; 5.8% (69/1,178) had overweight at baseline but normal weight at follow-up (reversal to normal weight); 9.7% (114/1,178) had normal weight at baseline but overweight at follow-up (incident overweight), and 30.8% (363/1,178) had persistent overweight at both baseline and follow-up (persistent overweight). There were significant differences in sex, age, BMI, and LVMI at baseline across the four groups. Children in the persistent overweight group tended to have a higher LVMI than those in the persistent normal weight group. Similar differences in age, BMI and LVMI across the four groups at follow-up were also observed (Table 1).

Weight status change and the levels of childhood LVMI

After adjustment for all potential confounding factors, LVMI (at follow-up) of children in the incident overweight group ($n = 114$, 30.63 ± 4.74 g/m$^{2.7}$) and persistent overweight group ($n = 363$, 31.56 ± 6.24 g/m$^{2.7}$) were significantly higher than those in persistent normal weight group ($n = 632$, 28.46 ± 7.64 g/m$^{2.7}$), whereas LVMI of children who reversed from overweight to normal weight ($n = 69$, 28.51 ± 4.28 g/m$^{2.7}$) was not statistically different from the persistent normal weight group, recognizing that the sample size in this group is very small (Table 2).

Weight status change and childhood LVH

The incidence rates of LVH over the 4-year follow-up period were higher in the persistent overweight group (22.0%) and the incident overweight group (14.9%) than those in the persistent normal weight group (5.2%) and reversal to normal weight group (4.4%) (Figure 1). Compared with children who had persistent normal weight, those who had persistent overweight (*OR* = 5.14, 95% *CI* = 3.33–7.95) and incident overweight (*OR* = 3.34, 95% *CI* = 1.77–6.30) had higher odds of LVH. In contrast, the few children ($n = 69$) who reversed from overweight to normal weight had lower but statistically non-significant odds of LVH (*OR* = 0.76, 95% *CI* = 0.22–2.55) (Table 3).

Discussion

To our knowledge, this is the first study that assessed the association between weight status change during childhood and childhood LVH. Our study showed that children who developed overweight during a four-year period or maintained overweight had an increased risk of LVH compared with those who had persistent normal weight. In addition, children who reversed from overweight to normal weight status had a slightly smaller, although not significant, risk of LVH.

Previous studies had assessed the association between weight change from childhood to adulthood and left ventricular structure in adulthood (24, 25). For instance, the data from the Beijing Blood Pressure Cohort Study showed that the cumulative burden of overweight from childhood to adulthood was independently associated with the risk of LVH and abnormal left ventricular geometric patterns (including concentric remodeling, eccentric hypertrophy, and concentric hypertrophy) (25). Another multiethnic longitudinal cohort study with a mean follow-up of 28 years showed that increasing BMI from childhood to adulthood was associated with the LVMI and risk of LVH in middle-aged adulthood (24). More importantly, some studies showed that reversing weight status from overweight to normal from childhood to adulthood can reduce the risk of LVH in adulthood (5, 12), which is consistent with our findings. One longitudinal study with a 22.9-year follow-up in China showed

10.3389/fped.2024.1371286

TABLE 1 Characteristics of the participants across four groups of weight status change from baseline to follow-up.

Characteristics	*N* (%)/(*M* ± *SD*)	Change of weight status				*P*
		Persistent normal weight	Reversal to normal weight	Incident overweight	Persistent overweight	
Baseline (2017)						
Age (years)	8.3 ± 1.5	8.4 ± 1.6	8.9 ± 1.3	7.8 ± 1.5*	8.2 ± 1.6	<0.001
Sleep duration (h/day)	9.3 ± 0.5	9.3 ± 0.5	9.3 ± 0.5	9.4 ± 0.5	9.3 ± 0.5	0.723
BMI (kg/m^2)	17.7 ± 1.7	15.7 ± 1.3	19.7 ± 1.7*	16.8 ± 1.1*	20.9 ± 2.4*	<0.001
LVMI (g/m$^{2.7}$)	27.4 ± 3.4	26.7 ± 3.3	27.1 ± 3.7	27.4 ± 3.0	28.9 ± 3.8*	<0.001
Sex						
Male	623 (52.9)	311 (49.2)	35 (50.7)	65 (57.0)	212 (58.4)	0.033
Female	555 (47.1)	321 (50.8)	34 (49.3)	49 (43.0)	151 (41.6)	
Physical activity						
<1 h/day	974 (82.7)	522 (82.6)	50 (72.5)	99 (86.8)	303 (83.5)	0.087
≥1 h/day	204 (17.3)	110 (17.4)	19 (27.5)	15 (13.2)	60 (16.5)	
Intake of fruits/vegetables						
<5 times/day	354 (30.1)	189 (29.9)	30 (43.5)	29 (25.4)	106 (29.2)	0.066
≥5 times/day	824 (69.9)	443 (70.1)	39 (56.5)	85 (74.6)	257 (70.8)	
Intake of carbonated drinks						
<1 time/week	1,109 (94.1)	597 (94.5)	63 (91.3)	109 (95.6)	340 (93.7)	0.632
≥1 times/week	69 (5.9)	35 (5.5)	6 (8.7)	5 (4.4)	23 (6.3)	
Father's education						
Junior high and below	259 (22.0)	132 (20.9)	15 (21.8)	27 (23.7)	85 (23.4)	0.677
High school	385 (32.7)	221 (35.0)	19 (27.5)	36 (31.6)	109 (30.0)	
College and above	534 (45.3)	279 (44.1)	35 (50.7)	51 (44.7)	169 (46.6)	
Mother's education						
Junior high and below	328 (27.8)	172 (27.2)	21 (30.4)	34 (29.8)	101 (27.8)	0.426
High school	353 (30.0)	203 (32.1)	17 (24.7)	25 (21.9)	108 (29.8)	
College and above	497 (42.2)	257 (40.7)	31 (44.9)	55 (48.3)	154 (42.4)	
Follow-up (2021)						
Age (years)	12.2 ± 1.5	12.3 ± 1.5	12.8 ± 1.3	11.7 ± 1.4*	12.1 ± 1.5	<0.001
Sleep duration (h/day)	8.5 ± 1.0	8.5 ± 1.0	8.1 ± 1.0*	8.7 ± 0.9	8.5 ± 1.0	0.001
BMI (kg/m^2)	20.8 ± 2.2	18.0 ± 1.9	20.2 ± 1.2*	22.2 ± 1.6*	25.3 ± 2.9*	<0.001
LVMI (g/m$^{2.7}$)	29.5 ± 3.8	28.3 ± 3.5	28.6 ± 3.3	30.4 ± 3.2*	31.5 ± 4.5*	<0.001
Physical activity						
<1 h/day	362 (30.7)	212 (33.5)	17 (24.6)	38 (33.3)	95 (26.2)	0.059
≥1 h/day	816 (69.3)	420 (66.5)	52 (75.4)	76 (66.7)	268 (73.8)	
Intake of fruits/vegetables						
<5 times/day	268 (22.8)	144 (22.8)	24 (34.8)	19 (16.7)	81 (22.3)	0.044
≥5 times/day	910 (77.2)	488 (77.2)	45 (65.2)	95 (83.3)	282 (77.7)	
Intake of carbonated drinks						
<1 time/week	991 (84.1)	543 (85.9)	59 (85.5)	94 (82.5)	295 (81.3)	0.253
≥1 times/week	187 (15.9)	89 (14.1)	10 (14.5)	20 (17.5)	68 (18.7)	

*$P < 0.05$ vs. persistent normal weight.

TABLE 2 Association between the change in weight status and LVMI (g/m$^{2.7}$) among Chinese children.

Weight status change	Model 1		Model 2		Model 3	
	M ± *SD*	*P*[b]	*M* ± *SD*	*P*[b]	*M* ± *SD*	*P*[b]
Persistent normal weight (*n* = 632)	28.33 ± 3.74	Reference	28.41 ± 7.02	Reference	28.46 ± 7.64	Reference
Reversal to normal weight (*n* = 69)	28.41 ± 3.75	0.860	28.44 ± 4.14	0.933	28.51 ± 4.28	0.912
Incident overweight (*n* = 114)	30.47 ± 3.75	<0.001	30.57 ± 4.59	<0.001	30.63 ± 4.74	<0.001
Persistent overweight (*n* = 363)	31.43 ± 3.75	<0.001	31.49 ± 5.83	<0.001	31.56 ± 6.24	<0.001
P[a]	<0.001		<0.001		<0.001	

Model 1: Adjusted for sex, age at baseline.
Model 2: Model 1 + additionally adjusted for sleep duration, physical activity, intake of fruit/vegetables, intake of carbonated drinks and parental education levels at baseline.
Model 3: Model 2 + additionally adjusted for sleep duration, physical activity, intake of fruit/vegetables, and intake of carbonated drinks at follow-up.
[a]*P*-value for difference in LVMI levels across four groups of weight status change.
[b]*P*-value for difference in LVMI levels between the persistent normal weight group and the specific group.

that compared with participants who had persistent normal weight from childhood to adulthood, those who had persistent overweight (*OR* = 9.58, 95% *CI* = 5.92–15.49) and those who had incident overweight (*OR* = 5.96, 95% *CI* = 4.01–8.86) had a higher risk of LVH in adulthood. However, the few individuals ($n = 22$) who were overweight in childhood but had a normal weight in adulthood did not seem to have a markedly increased risk of LVH (*OR* = 2.43, 95% *CI* = 0.85–6.95) (26). Those findings above underscore the importance of maintaining a normal weight throughout the life course and suggest that individuals who were overweight in childhood but reversed to a normal weight later can decrease their risk of LVH, although likely not to levels as low as those who maintained a normal weight at all times.

LVH is usually regarded as a robust predictor of CVD events (27). Previous studies suggested that the relationship between weight status change and CVD events showed similar features as discussed above, which further support our findings. For example, a pooled analysis of four cohort studies reported that compared with individuals who had a normal weight from childhood to adulthood, those who were overweight in adulthood irrespective of their weight status in childhood had a higher risk of CVD in adulthood, whereas those who were overweight in childhood but non-overweight in adulthood did not have a higher risk of CVD (4). As for other risk factors of CVD in adulthood used for outcomes, a meta-analysis showed that those who had a normal weight in childhood but were overweight in adulthood or those with persistent overweight from childhood to adulthood had an increased risk of high carotid intima-median thickness, type 2 diabetes, dyslipidemia, and hypertension in adulthood (5). However, those who were overweight in childhood but not in adulthood had largely decreased risk. Those data suggest a large potential to reduce CVD risk when controlling reversing from overweight to normal weight.

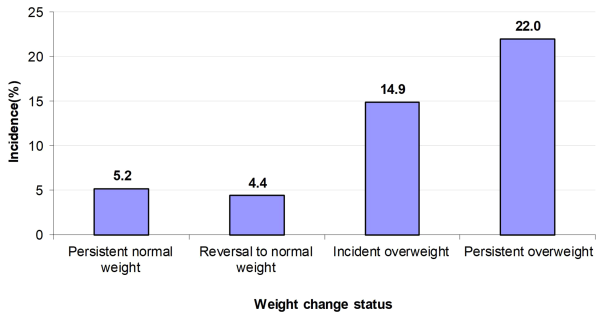


FIGURE 1
Incident rates of LVH across four groups of weight change status.

All these studies above, including ours, indicated the adverse influence of overweight/obesity on childhood cardiovascular health and highlighted the importance of losing weight for individuals who were currently overweight/obese. Yet, only very few children ($n = 69$, 5.8%) managed to lose weight in our study, which is consistent with the well-known challenge for individuals to lose weight without intensive behavioral therapy or treatment (28). In contrast, a relatively great number ($n = 114$, 9.7%) of individuals changed from normal weight to overweight/obesity, which poses a great challenge to the prevention of cardiovascular outcomes. Therefore, the government and families are encouraged to strengthen the management of children's body weight to decrease the potential cardiovascular burden.

Usually, children with overweight/obesity tend to choose the healthy way of changing their lifestyle habits when they are asked to lose weight. Previous studies found that adopting healthy lifestyles (e.g., eating healthy diets and doing more exercise) among individuals with overweight/obesity can significantly improve their heart structure and function (29–31). This may explain the reasons why children who reverse from overweight/obesity to normal weight have a lower risk of LVH. A meta-analysis that included 1,022 obese adults who underwent bariatric surgery showed that this therapeutic approach can contribute to the regression of LVH and improvement of diastolic function (32). Another study of 38 morbidly obese adolescents aged 13–19 years showed that weight loss was significantly correlated with a decrease in LVMI after bariatric surgery (33). Despite there are a variety of approaches to losing weight, ultimately all the results suggest that weight loss has a beneficial effect on cardiovascular health in childhood. Those results remind children who are overweight or obese to lose weight and try to reverse to a normal weight as soon as possible for the prevention of cardiovascular damage.

Although this study is among the first to convincingly report the association between weight status change and LVH among children, several limitations of this study should be mentioned. First, all children were selected from one primary school, so the

TABLE 3 Association between the change in weight status and LVH among Chinese children.

Weight status change	Incident rate of LVH (%)	Model 1		Model 2		Model 3	
		OR (95% *CI*)	*P*	*OR* (95% *CI*)	*P*	*OR* (95% *CI*)	*P*
Persistent normal weight ($n = 632$)	5.22	Reference		Reference		Reference	
Reversal to normal weight ($n = 69$)	4.35	0.82 (0.25, 2.76)	0.751	0.78 (0.23, 2.62)	0.686	0.76 (0.22, 2.55)	0.651
Incident overweight ($n = 114$)	14.91	3.22 (1.72, 6.04)	<0.001	3.31 (1.76, 6.23)	<0.001	3.34 (1.77, 6.30)	<0.001
Persistent overweight ($n = 363$)	22.04	5.18 (3.37, 7.99)	<0.001	5.21 (3.38, 8.04)	<0.001	5.14 (3.33, 7.95)	<0.001

CI, confidence interval; OR, odds ratio.
Model 1: Adjusted for sex, age at baseline.
Model 2: Model 1 + additionally adjusted for sleep duration, physical activity, intake of fruit/vegetables, intake of carbonated drinks and parental education levels at baseline.
Model 3: Model 2 + additionally adjusted for sleep duration, physical activity, intake of fruit/vegetables, and intake of carbonated drinks at follow-up.

generalizability of our findings should be cautious. Second, all the participants were followed up for only four years, further studies with longer duration are needed to confirm our findings. Third, the sample size of this study is not large, particularly in the group of children who were overweight/obesity at baseline and lost weight later, and the low statistical power impeded us from performing further subgroup analysis by participants' characteristics (e.g., sex, age, etc.). Fourth, we combined the overweight and obesity due to the relatively small sample sizes in the subgroups, which may interfere with the consolidated conclusion. Therefore, a longitudinal cohort design with a larger sample size to assess the specific effect of overweight and obesity is needed to further validate our conclusions.

Conclusions

In summary, we found that children who had persistent overweight or incident overweight over a four-year period had an increased risk of LVH in childhood. Conversely, the risk of acquiring LVH was lower among the few children who reversed from overweight to normal weight. These findings highlight the importance of maintaining a normal weight over the life course but also suggest a reduced risk of LVH for those who are overweight or obese but succeed in normalizing their weight.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Ethics Committee of School of Public Health, Shandong University. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

QL: Conceptualization, Funding acquisition, Writing – original draft, Writing – review & editing. CL: Data curation, Formal Analysis, Writing – review & editing. LY: Investigation, Validation, Visualization, Writing – review & editing. ZG: Investigation, Visualization, Writing – review & editing. MZ: Conceptualization, Investigation, Supervision, Writing – review & editing. PB: Project administration, Supervision, Visualization, Writing – review & editing. BX: Conceptualization, Funding acquisition, Supervision, Writing – review & editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This work was supported by the Research Foundation of Capital Institute of Pediatrics (ERB-2023-05).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Ma S, Zhang Y, Yang L, Zhao M, Xi B. Analysis on the trend of overweight and obesity of children and adolescents in 9 provinces of China from 1991 to 2015. *Chin J Prev Med*. (2020) 54(2):133–8. doi: 10.3760/cma.j.issn.0253-9624.2020.02.004

2. Ma GMJ, Ma J, et al. *Report on Childhood Obesity in China*. Beijing: People's Medical Publishing House (2017).

3. Simmonds M, Burch J, Llewellyn A, Griffiths C, Woolacott N. The use of measures of obesity in childhood for predicting obesity and the development of obesity-related diseases in adulthood: a systematic review and meta-analysis. *Health Technol Assess*. (2015) 19(43):1–336. doi: 10.3310/hta19430

4. Juonala M, Magnussen CG, Berenson GS, Venn A, Burns TL, Sabin MA, et al. Childhood adiposity, adult adiposity, and cardiovascular risk factors. *N Engl J Med*. (2011) 365(20):1876–885. doi: 10.1056/NEJMoa1010112

5. Sun J, Xi B, Yang L, Zhao M, Magnussen CG. Weight change from childhood to adulthood and cardiovascular risk factors and outcomes in adulthood: a systematic review of the literature. *Obes Rev*. (2020) 22(3):e13138. doi: 10.1111/obr.13138

6. Gosse P. Left ventricular hypertrophy as a predictor of cardiovascular risk. *J Hypertens*. (2005) 23:S27–33. doi: 10.1097/01.hjh.0000165625.79933.9a

7. Jing LY, Nevius CD, Friday CM, Suever JD, Pulenthiran A, Mejia-Spiegeler A, et al. Ambulatory systolic blood pressure and obesity are independently associated with left ventricular hypertrophic remodeling in children. *J Cardiovasc Magn Reson*. (2017) 19(1):86. doi: 10.1186/s12968-017-0401-3

8. Xi B. Children obesity and short-term subclinical cardiovascular damage. *Chin J Sch Health*. (2019) 40(06):803–4. doi: 10.16835/j.cnki.1000-9817.2019.06.002

9. Bartkowiak J, Spitzer E, Kurmann R, Zurcher F, Krahenmann P, Garcia-Ruiz V, et al. The impact of obesity on left ventricular hypertrophy and diastolic dysfunction in children and adolescents. *Sci Rep*. (2021) 11(1):13022. doi: 10.1038/s41598-021-92463-x

10. Brady TM. The role of obesity in the development of left ventricular hypertrophy among children and adolescents. *Curr Hypertens Rep*. (2016) 18(1):3. doi: 10.1007/s11906-015-0608-3

11. Wang H, Zhao M, Magnussen CG, Xi B. Utility of three adiposity indices for identifying left ventricular hypertrophy and geometric remodeling in Chinese children. *Front Endocrinol*. (2021) 12:762250. doi: 10.3389/fendo.2021.762250

12. Wang H, Zhao M, Magnussen CG, Xi B. Change in waist circumference over 2 years and the odds of left ventricular hypertrophy among Chinese children. *Nutr Metab Cardiovasc Dis*. (2021) 31(8):2484–9. doi: 10.1016/j.numecd.2021.04.027

13. Savva SC, Tornaritis M, Savva ME, Kourides Y, Panagi A, Silikiotou N, et al. Waist circumference and waist-to-height ratio are better predictors of cardiovascular disease risk factors in children than body mass index. *Int J Obes*. (2000) 24(11):1453–8. doi: 10.1038/sj.ijo.0801401

14. Ma L, Cai L, Deng L, Zhu YN, Ma J, Jing J, et al. Waist circumference is better than other anthropometric indices for predicting cardiovascular disease risk factors in Chinese children-a cross-sectional study in Guangzhou. *J Atheroscler Thromb*. (2016) 23(3):320–9. doi: 10.5551/jat.31302

15. Lo K, Wong M, Khalechelvam P, Tam W. Waist-to-height ratio, body mass index and waist circumference for screening paediatric cardio-metabolic risk factors: a meta-analysis. *Obes Rev*. (2016) 17(12):1258–75. doi: 10.1111/obr.12456

16. Yang L, Zhang Q, Zhang Y, Sun J, Zhao M, Xi B. Design of Huantai childhood cardiovascular health cohort study. *Chin J Prev Med*. (2020) 54(12):1461–4. doi: 10.3760/cma.j.cn112150-20200610-00857

17. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, et al. Recommendations for chamber quantification: a report from the American society of echocardiography's guidelines and standards committee and the chamber quantification writing group, developed in conjunction with the European association of echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr*. (2005) 18(12):1440–63. doi: 10.1016/j.echo.2005.10.005

18. Devereux RB, Alonso DR, Lutas EM, Gottlieb GJ, Campo E, Sachs I, et al. Echocardiographic assessment of left-ventricular hypertrophy—comparison to necropsy findings. *Am J Cardiol*. (1986) 57(6):450–8. doi: 10.1016/0002-9149(86)90771-x

19. Desimone G, Daniels SR, Devereux RB, Meyer RA, Roman MJ, Dedivitiis O, et al. Left-ventricular mass and body size in normotensive children and adults—assessment of allometric relations and impact of overweight. *J Am Coll Cardiol*. (1992) 20(5):1251–60. doi: 10.1016/0735-1097(92)90385-z

20. Li H, Zong X-n, Ji C-y, Mi J. Body mass index cut-offs for overweight and obesity in Chinese children and adolescents aged 2–18 years. *Chin J Epide*. (2010) 31(6):616–20. doi: 10.3760/cma.j.issn.0254-6450.2010.06.004

21. Non-communicable Diseases Alliance. Non-Communicable Diseases Facts: the Global Epidemic, 2017. Available online at: https://ncdalliance.org/the-global-epidemic-In (accessed November 14, 2022)

22. World Health Organization. Effectiveness of Interventions and Programmes Promoting Fruit and Vegetable Intake. Available online at: https://www.who.int/dietphysicalactivity/publications/f&v_promotion_effectiveness.pdf?ua=1 (accessed November 14, 2022)

23. Holstein BE, Damsgaard MT, Due P, Krolner RF, Pedersen TP, Rasmussen M. Intake of sugar sweetened soft drinks among adolescents: trends and social inequality in Denmark 2002–2018. *Nutr Health (Bicester)*. (2020) 26(1):3–8. doi: 10.1177/0260106019900742

24. Lai CC, Sun D, Cen RQ, Wang J, Li SX, Fernandez-Alonso C, et al. Impact of long-term burden of excessive adiposity and elevated blood pressure from childhood on adulthood left ventricular remodeling patterns the Bogalusa heart study. *J Am Coll Cardiol*. (2014) 64(15):1580–7. doi: 10.1016/j.jacc.2014.05.072

25. Yan YK, Liu JT, Wang LA, Hou DQ, Zhao XY, Cheng H, et al. Independent influences of excessive body weight and elevated blood pressure from childhood on left ventricular geometric remodeling in adulthood. *Int J Cardiol*. (2017) 243:492–6. doi: 10.1016/j.ijcard.2017.05.085

26. Yan YK, Hou DQ, Liang YJ, Zhao XY, Hu YH, Liu JT, et al. Tracking body mass Index from childhood to adulthood for subclinical cardiovascular diseases at adulthood. *J Am Coll Cardiol*. (2016) 67(8):1006–7. doi: 10.1016/j.jacc.2015.12.013

27. Brown DW, Giles WH, Croft JB. Left ventricular hypertrophy as a predictor of coronary heart disease mortality and the effect of hypertension. *Am Heart J*. (2000) 140(6):848–56. doi: 10.1067/mhj.2000.111112

28. Rosen CJ, Ingelfinger JR. Shifting tides offer new hope for obesity. *N Engl J Med*. (2022) 387(3):271–3. doi: 10.1056/NEJMe2206939

29. Wang HT, Liu CF, Tsai TH, Chen YL, Chang HW, Tsai CY, et al. Effect of obesity reduction on preservation of heart function and attenuation of left ventricular remodeling, oxidative stress and inflammation in obese mice. *J Transl Med*. (2012) 10(145):1–13. doi: 10.1186/1479-5876-10-145

30. Lascaris B, Pouwels S, Houthuizen P, Dekker LR, Nienhuijs SW, Bouwman RA, et al. Cardiac structure and function before and after bariatric surgery: a clinical overview. *Clin Obes*. (2018) 8(6):434–43. doi: 10.1111/cob.12278

31. Karimian S, Stein J, Bauer B, Teupe C. Improvement of impaired diastolic left ventricular function after diet-induced weight reduction in severe obesity. *Diabetes Metab Syndr Obes*. (2017) 10:19–25. doi: 10.2147/dmso.S124541

32. Cuspidi C, Rescaldani M, Tadic M, Sala C, Grassi G. Effects of bariatric surgery on cardiac structure and function: a systematic review and meta-analysis. *Am J Hypertens*. (2014) 27(2):146–56. doi: 10.1093/ajh/hpt215

33. Ippisch HM, Inge TH, Daniels SR, Wang BY, Khoury PR, Witt SA, et al. Reversibility of cardiac abnormalities in morbidly obese adolescents. *J Am Coll Cardiol*. (2008) 51(14):1342–8. doi: 10.1016/j.jacc.2007.12.029

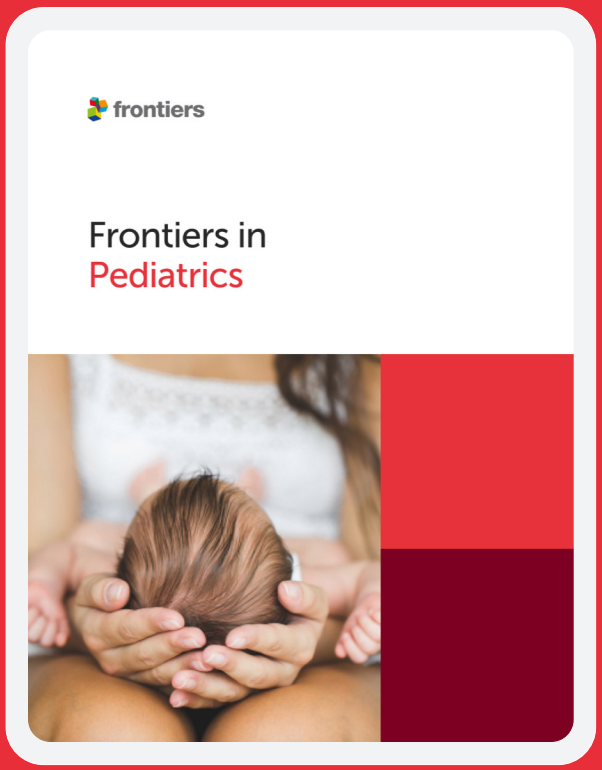
Frontiers in Pediatrics

Addresses ongoing challenges in child health and patient care

Explores research that meets ongoing challenges in pediatric patient care and child health, from neonatal screening to adolescent development.

Discover the latest Research Topics

See more →



Frontiers

Avenue du Tribunal-Fédéral 34
1005 Lausanne, Switzerland
frontiersin.org

Contact us

+41 (0)21 510 17 00
frontiersin.org/about/contact