

Early maternal and child health management and the impact of living environment

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Early maternal and child health management and the impact of living environment

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Editorial: Early maternal and child health management and the impact of living environment

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Editorial on the Research Topic

[Early maternal and child health management and the impact of living environment](#)

Advancing maternal and newborn health: a call to action

Maternal and newborn health remains a fundamental pillar of global public health, reflecting broader imperatives of health equity, social justice, and sustainable development. As emphasized in the United Nations Sustainable Development Goals (SDGs) and particularly SDG 3, which aims to ensure healthy lives and promote wellbeing for all at all ages, improving outcomes during pregnancy, childbirth, and early childhood is not only a medical concern, but also a societal and ethical imperative. This special edition of *Frontiers in Public Health* brings together emerging research at the intersection of early maternal and child health management and the environmental contexts in which these lives begin and evolve. This edition comprises of 10 original research articles, one methods paper, one systematic review, and one study protocol. Collectively, these contributions reflect a broad thematic coherence centered on maternal and child health, while drawing from diverse geographic contexts including Africa, Asia, South America, and Europe.

Maternal and child health in context

Growing evidence underscores the profound influence of environmental determinants—such as air and water quality, housing conditions, sanitation, and exposure to toxicants—on pregnancy outcomes and early childhood development. Despite increasing recognition, these environmental risks remain underrepresented in clinical protocols and public health strategies. This Research Topic addresses this critical gap, advocating for a more holistic, systems-based understanding of maternal and child health that acknowledges the intricate connections between ecological exposures and health trajectories. Articles in this submission which focus on this topic include.

A global and multidisciplinary perspective

The articles featured in this Research Topic provide a rich and diverse examination of maternal and child health across continents—from the public hospitals of Ethiopia (Wondifraw et al.) to urban centers in China (Zhu et al.), Brazil (Lima-Soares et al.), and Malta (Battista et al.). They explore multifactorial influences on health outcomes, including biomedical, environmental, socioeconomic, and behavioral determinants. A consistent theme is the vulnerability of mothers and infants to systemic and environmental risks.

Studies investigating the impact of polycyclic aromatic hydrocarbons (Cheng et al.) and environmental tobacco smoke (Zhang et al.) on pregnant women and newborns reveal urgent concerns about prenatal environmental exposures and their metabolic consequences. Meanwhile, a mechanistic study (Jia et al.) on parental exposure to Nd₂O₃ demonstrates how intergenerational toxicity mediated through the brain-gut axis can impair neurodevelopment and cognition in offspring—adding new depth to our understanding of inherited environmental burdens.

Barriers and innovations in care delivery

Access to timely and appropriate care is another crucial dimension. Research from East Africa (Terefe et al.) and Ethiopia (Wondifraw et al.) reveals systemic barriers to postnatal care and challenges in pediatric antiretroviral therapy adherence, calling for community-driven solutions and policy reform. In China, qualitative studies (Cai et al.) on kangaroo mother care provide insight into provider attitudes and implementation challenges, humanizing the complexities of neonatal care delivery in intensive care settings.

Predictive models, preventive strategies, and mental health

Other studies focus on early risk detection and long-term health planning. These include predictive models for low birth weight in the context of gestational diabetes (Pan et al.), as well as the socioeconomic roots of birth outcomes and their link to peripubertal obesity (Lima-Soares et al.). Such findings reinforce the importance of health equity, social determinants, and proactive care models. A longitudinal analysis of perinatal outcomes in Malta (Battista et al.) over 15 years offers a historical perspective on progress and areas for improvement.

Notably, the Research Topic also highlights the mental health needs of obstetric and gynecological providers. As the demand for perinatal mental health screening grows, supporting healthcare professionals with knowledge, training, and systemic backing is essential for sustainable implementation.

Toward an integrated, global approach

Together, these contributions form a compelling call for a multidisciplinary, evidence-based, and culturally responsive approach to maternal and child health. They underscore the urgency and global significance of this field, which lies at the intersection of medicine, public health, environmental science, and social policy. As maternal and child health remains a central focus of global health agendas, these studies highlight the need for integrated strategies that are adaptable across diverse settings and responsive to both emerging and persistent health inequities worldwide.

This Research Topic not only deepens our understanding of the early-life health landscape but also serves as a pivotal rallying point for continued research, collaboration, and innovation. The findings presented here underscore the pressing need for further investigation into the complex interplay of biomedical, environmental, and social factors that shape maternal and child health outcomes. We call on the global research and public health communities to expand upon this work, fostering interdisciplinary partnerships that explore the transgenerational impact of early-life health. By addressing persistent disparities, advancing evidence-based interventions, and understanding the long-term effects on future generations, we can ensure that every mother and child has the opportunity to thrive in a safe, supportive, and health-promoting environment. Ultimately, these efforts will contribute to the realization of global health goals and the wellbeing of future generations.

Author contributions

KB: Writing – review & editing. HL: Writing – review & editing, Writing – original draft. LR: Writing – original draft, Writing – review & editing. JY: Writing – review & editing. WL: Writing – review & editing. YH: Writing – review & editing.

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Healthcare providers' perceptions and experiences of kangaroo mother care for preterm infants in four neonatal intensive care units in China: a qualitative descriptive study

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Background: Kangaroo mother care (KMC) is an evidence-based intervention that can effectively reduce morbidity and mortality in preterm infants, but it has yet to be widely implemented in health systems in China. Most qualitative studies on KMC for preterm infants focused on the experiences and influencing factors from the perspective of preterm infant parents, while neglecting the perspective of healthcare providers, who played a critical role in guiding KMC practice. Therefore, this study aimed to explore the perceptions and experiences of healthcare providers regarding their involvement in KMC implementation for preterm infants to promote the contextualized implementation of KMC.

Methods: A descriptive qualitative approach was adopted. A purposive sampling was used to select healthcare providers involved in KMC implementation in the neonatal intensive care units (NICUs) as participants from four tertiary hospitals across four cities in Zhejiang Province, China. Face-to-face semi-structured interviews were conducted to collect information. Thematic analysis was employed to analyze the data.

Results: Seventeen healthcare professionals were recruited, including thirteen nurses and four doctors in the NICUs. Four themes and twelve subthemes emerged: different cognitions based on different perspectives (acknowledged effects and benefits, not profitable economically), ambivalent emotions regarding KMC implementation (gaining understanding, gratitude and trust from parents, not used to working under parental presence, and concerning nursing safety issues), barriers to KMC implementation (lack of unified norms and standards, lack of systematic training and communication platform, insufficient human resources, and inadequate parental compliance) and suggestions for KMC implementation (improving equipment and environment, strengthening collaboration between nurses and doctors, and support from hospital managers).

Conclusions: Despite acknowledging the clinical benefits of KMC, the lack of economic incentives, concerns about potential risks, and various barriers hindered healthcare providers' intrinsic motivation to implement KMC in NICUs in China. To facilitate the effective implementation of KMC, hospital managers

should provide bonuses and training programs for healthcare providers, while giving them recognition and encouragement to enhance their motivation to implement KMC.

KEYWORDS

kangaroo care, neonatal intensive care unit, preterm, healthcare providers, qualitative study

1 Introduction

According to the World Health Organization (WHO), an estimated 13.4 million preterm babies were born globally in 2020, accounting for 9.9% of total newborns (1, 2). In China, the overall incidence of preterm birth increased from 5.9% in 2012 to 6.4% in 2018 (3), and the rate of low birth weight also rose from 2.34% in 2010 to 3.70% in 2021 (4). Notably, in 2021, the low birth weight rate in Zhejiang Province was 4.48% (4), higher than the national average. It was indicated that the neonatal mortality rate in China had declined from 22.8% in 2000 to 3.1% in 2021 (4). Furthermore, the neonatal mortality rate in Zhejiang Province had dropped from 2.75% in 2010 to 1.16% in 2020 (5). From 2009 to 2018, the proportion of preterm births among newborn deaths in China increased from around 42.6–49.8% (6). Immaturity, asphyxia, and congenital abnormalities accounted for approximately 80% of preterm infant deaths (6). Preterm birth complications remained a leading cause of neonatal mortality in China (7), indicating that clinical care for preterm infants was still insufficient (8). Many survivors faced lifelong disabilities, including learning disabilities, sensory impairments, and motor disorders (9–11). In 2022, WHO updated its recommendations for preterm care, suggesting that Kangaroo mother care (KMC) should be initiated immediately after birth, which could significantly improve preterm infants' survival and health outcomes (12).

KMC refers to a clinical care approach in which the mother (or the father) of a preterm infant holds the naked baby against her (or his) bare chest in the same way as kangaroo parenting (13). This method allows for early, continuous, and prolonged skin-to-skin contact between the preterm infant and the parent, while also promoting exclusive breastfeeding and measures such as early discharge and post-discharge follow-up (14, 15). Compared to traditional care, KMC has numerous short-term and long-term benefits for newborns, such as stabilizing physiological status, promoting neurobehavioral development, enhancing immune function, increasing exclusive breastfeeding rates, and fostering attachment between the newborn and caregivers (16–19). Despite extensive research reporting on the benefits and effectiveness of KMC, this intervention has not been fully integrated into healthcare systems globally (20, 21).

China is confronted with one of the highest rates of preterm birth, a trend that continues to escalate annually (1, 3). In 2014, the National Health Commission of China's Department of Maternal and Child Health initiated the Premature Birth and Preterm Infants Intervention program, enlisting ten hospitals to pioneer the implementation of KMC (22). In 2017, the commission issued the

"Guidelines for Health Care Services for Premature Infants," which catalyzed the broader adoption of KMC within the country (23). Building on this momentum, the "Action Plan for Healthy Children (2021–2025)" (24), published by the National Health Commission, underscored the importance of promoting kangaroo care as a means to enhance the quality of life for premature infants. Despite these concerted efforts and significant strides, the practice of KMC has yet to achieve widespread adoption in China. Specifically, while the neonatal intensive care units (NICUs) of tertiary referral hospitals related to maternal and child health in China all provide level III of neonatal care (25), a survey revealed that the current adoption rate of KMC in these NICUs was mere 21.2% (22). This figure indicated that although some hospitals in China had piloted KMC in their NICUs to varying degrees, it did not become routine practice (26), and the scale-up of KMC implementation remained sub-optimal. Factors influencing KMC implementation primarily included environmental factors, parent/family factors, access factors, cultural factors, and professional factors (27). Among these factors, for healthcare providers, support from leadership, training programs on KMC, and adequate staffing were key to KMC implementation. Feucht et al. pointed out that healthcare providers played an important role in KMC (28). To some extent, they were the supporters and supervisors in KMC practice, requiring them to have the knowledge, experience, and willingness to implement KMC (29).

Previous qualitative studies on KMC for preterm infants primarily focused on parents' experiences of participation and the influencing factors to its implementation from their perspective (30–32). However, participants in these studies indicated that the information provided by healthcare professionals significantly influenced their experiences of engaging in KMC with their preterm infants. Therefore, it was crucial for healthcare providers to recognize the value of KMC and to establish strong relationships with parents to effectively explain the necessity and effectiveness of KMC, which would potentially enhance parents' adherence to KMC implementation (33). A study on the barriers and facilitators to KMC revealed that KMC implementation was not running optimally due to inconsistent local leadership, heavy workload, and the knowledge and attitudes of health workers (34). Feng et al. directly pointed out the importance of research conducted from the perspective of healthcare professionals and recommended exploring their views and suggestions on KMC to facilitate its implementation (35). It was evident that gaining insights into healthcare providers' cognitive and practical experiences of KMC, using a qualitative approach, was crucial in advancing the implementation of KMC.

However, research exploring the perceptions and experiences of healthcare providers regarding KMC was relatively limited. A qualitative study by Pratomio et al. indicated that due to the lack of systematic and formal KMC training, healthcare providers had misconceptions about certain aspects of KMC, which could impact the successful implementation of KMC (36). Some nursing staff mentioned in a study that despite improving their knowledge about KMC, they were still confused about its safety and appropriate application (37). On the other hand, Rahmatika et al. indicated that healthcare providers held positive perceptions of KMC and believed that this positive attitude was crucial for providing KMC education to facilitate its implementation (38). Only one study in China conducted a preliminary exploration of NICU nurses' participation in KMC, highlighting the shortage of nursing resources as a barrier to KMC implementation and emphasizing the importance of standardized language in communication, operational homogenization, and standardized training (39). However, the study was conducted in only one hospital and was limited to the real feelings and experiences of nurses without exploring their views and cognition on KMC implementation. Overall, there was a notable gap in research concerning the perceptions and experiences of NICU healthcare providers regarding implementing KMC.

This study aimed to conduct interviews with healthcare providers who implemented KMC for preterm infants in the NICUs of four tertiary hospitals across four cities in Zhejiang Province, China, in order to deeply explore their feelings and experiences in guiding parents of preterm infants to practice KMC, as well as their perceptions of KMC and the challenges they faced. This helped us comprehend the current situation of KMC practice in China from the healthcare perspective, enabling us to better promote the customized implementation of KMC in the future and providing a reference for KMC application in NICUs with similar restricted visitation policies in other developing countries.

2 Materials and methods

2.1 Study design

A descriptive qualitative design was adopted. This approach is appropriate for research questions that aim to provide the most direct and essential answers to the concerns of practitioners or policymakers, which enable new insights to emerge that provide a richer understanding of the phenomenon (40). This study is reported in accordance with the consolidated criteria for reporting qualitative research (COREQ) guideline (41).

2.2 Setting and participants

This study was carried out in the NICUs of four tertiary hospitals in Hangzhou, Shaoxing, Jiaxing, and Huzhou in Zhejiang Province, China, all of which had previously implemented KMC. These hospitals were chosen for the study based on their high utilization of KMC and accessibility. Initially, the first author directly contacted the head nurses of the NICUs in each hospital,

explaining the research objectives and obtaining their consent to participate in the study. In each ward, the head nurse was assigned as the study coordinator for that site and assisted in recruiting a mix of doctors and nurses who had experience with KMC for interview. There had been no prior relationships between the researcher and these participants. However, we faced several challenges during recruitment, primarily due to the time constraints of the healthcare providers and their initial hesitancy to participate in research activities. To overcome these challenges, we established open communication with the healthcare providers in the NICUs, providing clear information about the study's aims and ensuring confidentiality. Additionally, we offered flexible scheduling for interviews to accommodate the participants' availability.

This study employed a purposive sampling method to select participants. The method effectively targets individuals with similar experiences based on predetermined criteria within a specific environment, thereby gathering comprehensive data for the study (42). Moreover, the selection process aimed to ensure the representation and diversity of participants by considering various factors like age and years of professional experience. All participants had to meet the following inclusion criteria: ① nurses and doctors both needed to be licensed; ② NICU working experience ≥ 5 years; ③ having experience in KMC; ④ proficiency in expression abilities. Exclusion criteria for healthcare providers included individuals in rotating, internship, trainee, or residency positions.

2.3 Data collection

Qualitative data were collected using face-to-face, semi-structured individual interviews conducted in four of the NICU wards from January to April 2023. Demographic details of participants were collected prior to the interview using self-designed questionnaires. The first author designed the initial interview outline, and after two pilot interviews and internal discussions, the semi-structured interview guide was revised and adjusted (43), mainly to ensure the questions could be easily understood by the interviewees (Supplementary Tables S1, S2).

Interviews were conducted in private and calm rooms within the healthcare facilities so that the participants would be more comfortable expressing themselves. At the outset of each interview, the primary researcher introduced herself and asked introductory questions to establish rapport and put participants at ease. Each interview lasted ~ 40 –70 min, and all the interviews were conducted in Chinese and audio-recorded with the participant's consent. There were no repeat interviews. Field notes were taken and used to capture interview details, including non-verbal communication.

2.4 Data analysis

Data analysis occurred concurrently with data collection. All audio recordings were transcribed verbatim for the initial transcripts. These initial transcripts were manually verified

against the recording for fidelity by the first two authors, and then managed using NVivo 12 software (QSR International, Melbourne, Australia). Participants were assigned codes to maintain confidentiality.

Data analysis was conducted using thematic analysis guided by Braun and Clarke's approach (44). The analysis process comprised the following six steps: ① initial codes were developed by two researchers after independently reading the first four transcribed interviews multiple times; ② through in-depth analysis of the remaining 13 interview transcripts, initial sub-themes and themes were developed; ③ the researchers continued to enhance the sub-themes and themes through iterative refinement; ④ the research team collaborated to refine the representation of sub-themes and themes, ensuring alignment with the research question and establishing the final thematic framework; ⑤ all sub-themes and themes were subjected to review by the research team in order to establish consensus on clear definitions and names; ⑥ the data analysis findings were presented in a narrative format by the first author, and subsequently confirmed by the research team.

The data analysis was conducted in Chinese, and selected thematic codes were translated into English for presentation in the Section 3. In order to avoid any misinterpretation or inaccurate translation, a rigorous process involving forward translation, back-translation and reconciliation of discrepancies was employed. The initial forward translation and the back-translation were conducted by the first author interviewer (QC), a female PhD candidate fluent in Chinese and English. Any differences that emerged during the back-translation were carefully reviewed and reconciled by the first co-author (YZ), who obtained her PhD degree in Australia and currently serves as a doctoral supervisor at a university in China. Quotations connected with each of these themes were selected and utilized to highlight the various fashions in which these participants described themes. Saturation was achieved when new information from interviews became limited, indicating the identification of all relevant themes and concepts (45). Specifically, after the 15th interview, there were no new themes generated from the interviews in our study. To ensure that we achieved data saturation, we proceeded with two additional interviews to ensure and confirm that no new themes were emerging. The pilot interview data were not included in the analysis.

2.5 Rigor

A qualitative study is commonly evaluated by trustworthiness, including credibility, transferability, dependability, and confirmability (46). In this study, credibility was established through peer debriefing, in which the researchers consulted with one another to address any ambiguities or disagreements on methodological issues or data analysis. Transferability was attained by the transparent method, which might allow auditing and replicating to occur in other settings. Dependability was obtained using verbatim transcriptions, detailed field notes, and a record of analytical decisions, as it provided an audit trail that could be reviewed and verified. Confirmability was obtained using interview quotations to illustrate the informants' voices in the results section.

2.6 Ethical considerations

Ethical approval was obtained from the Ethics Committee of the Women's Hospital, School of Medicine, Zhejiang University (Approval No. IRB-20220219-R) before the start of the study. Written informed consent was provided by each participant before the interviews. All participants could withdraw from the study at any stage without disclosing the reason. The audio recordings and transcripts were tagged with pseudonyms so that confidentiality and anonymity were assured and data were safely archived in files protected by passwords.

3 Results

A total of 17 healthcare providers in the NICUs were interviewed in this study, including four doctors and 13 nurses, with four nurses being head nurses. Among them, two doctors were male, while the rest of the participants were female. The participants ranged from 33 to 52 years old, with an average age of 41.2 years, and they had an average work experience of 19.7 years (11–33 years), with an average of 14.5 years of experience working in the NICUs (9–24 years). All participants held a bachelor's degree or higher and possessed intermediate or higher professional titles. The detailed characteristics of the participants are presented in Table 1. The analysis yielded four main themes and twelve subthemes, as outlined in Table 2.

3.1 Theme 1: different cognitions based on different perspectives

Differences in cognition on KMC were observed among healthcare providers. The majority of the participants believed that KMC could benefit preterm infants and their parents, including improving and stabilizing the infants' conditions, shortening their hospital stays, and alleviating family members' emotions. However, most healthcare providers also believed that, from the perspective of hospital revenue, the relatively low fees for KMC were essentially non-profitable compared to the time and effort they dedicated.

3.1.1 Acknowledged effects and benefits

The majority of healthcare providers [13 participants (76%)] endorsed the significant benefits of KMC for preterm infants. They pointed out that KMC could enhance and stabilize the physiological wellbeing of preterm infants, including breathing, heart rate, and body temperature. Moreover, KMC was observed to facilitate weight gain in preterm infants and better promote their health and development by providing a sense of security and close contact with their parents.

Many of the preterm infants with underdeveloped lung development experienced desaturation and respiratory distress. However, when they were placed on their mother's chest, they did not need oxygen. (H6)

TABLE 1 Characteristics of the healthcare providers interviewed (N = 17).

No.	Gender	Age (years)	Working experience (years)	Working experience in NICU (years)	Education level	Professional title	Position
H1	Female	46	28	12	Bachelor	Senior title	Head nurse
H2	Female	35	12	12	Master	Medium-grade title	Staff nurse
H3	Female	40	19	19	Bachelor	Medium-grade title	Nurse team leader
H4	Female	43	25	24	Bachelor	Medium-grade title	Staff nurse
H5	Male	35	12	12	Bachelor	Medium-grade title	Medical team leader
H6	Female	46	27	10	Bachelor	Senior title	Head nurse
H7	Female	40	17	15	Master	Medium-grade title	Staff nurse
H8	Female	38	12	11	Master	Medium-grade title	Staff doctor
H9	Female	35	13	12	Bachelor	Medium-grade title	Staff nurse
H10	Female	44	26	21	Bachelor	Medium-grade title	Nurse team leader
H11	Female	52	33	15	Bachelor	Senior title	Head nurse
H12	Female	47	26	12	Bachelor	Senior title	Staff doctor
H13	Male	40	11	11	PhD	Senior title	Medical team leader
H14	Female	41	21	21	Bachelor	Medium-grade title	Nurse team leader
H15	Female	40	19	12	Bachelor	Medium-grade title	Head nurse
H16	Female	33	13	9	Bachelor	Medium-grade title	Staff nurse
H17	Female	45	20	18	Master	Medium-grade title	Nurse team leader

NICU, neonatal intensive care unit; PhD, doctor of philosophy.

Some healthcare providers [five participants (29%)] also mentioned a notable association between the KMC and reduced hospitalization time for preterm infants. The adoption of KMC promoted the turnover of NICU beds to free up valuable bed resources to care for other preterm infants in need, which was particularly crucial in NICUs experiencing bed shortages or in hospitals undergoing diagnosis-related group system (DRGs) assessment. Moreover, by shortening the duration of hospitalization, KMC decreased the risk of nosocomial infection among preterm infants.

Especially for now, there is also an assessment based on DRGs. If the length of hospital stay is too long, the costs will be higher, resulting in a loss... KMC can shorten the hospital stay of preterm infants, reducing bed occupancy and thereby increasing bed utilization rates, indirectly promoting the revenue of the NICU... There is a heightened risk of infection for a preterm infant who is unable to be discharged for a prolonged period. (H3)

Moreover, some healthcare providers [three participants (18%)] highlighted that KMC had additional effects on parents of preterm infants and hospitals. During KMC, parents actively participated in caring for their preterm infants and observed their infants' condition and changes firsthand, which could alleviate their negative emotions, foster communication between parents and healthcare providers, and potentially enhance the hospital's reputation positively.

Enabling parents to witness their preterm infants visually helps alleviate their anxiety and pressure. It can also minimize complaints, promote the hospital's reputation, and reduce potential disputes and conflicts. (H13)

3.1.2 Not profitable economically

Despite the benefits KMC brought to families of preterm infants and hospitals, the economic revenue it could gain was a consideration. As an emerging nursing care practice, the fees for KMC needed regulation by the Price Bureau, that is the fees should be set according to specific standards rather than arbitrarily based on costs incurred. Some healthcare providers [six participants (35%)] believed that the fees for KMC were relatively low, and the current charge standards did not reflect the actual costs of the services and resources provided by healthcare workers.

It's really cheap, not covering the costs because our KMC is priced at just 120 RMB per session, but as far as I know, the effort our nurses put in far exceeds the value of this amount. (H17)

In contrast to low fees, department costs for KMC implementation were high. Many healthcare providers [nine participants (53%)] mentioned that implementing KMC was basically a financial loss compared to the substantial time and effort dedicated by medical staff. Despite KMC being predominantly

TABLE 2 Themes and subthemes.

Themes	Subthemes
Different cognitions based on different perspectives	Acknowledged effects and benefits
	Not profitable economically
Ambivalent emotions regarding KMC implementation	Gaining understanding, gratitude and trust from parents
	Not used to working under parental presence
	Concerning nursing safety issues
Barriers to KMC implementation	Lack of unified norms and standards
	Lack of systematic training and communication platform
	Insufficient human resources
	Inadequate parental compliance
Suggestions for KMC implementation	Improving equipment and environment
	Strengthening collaboration between nurses and doctors
	Support from hospital managers

KMC, kangaroo mother care.

carried out by parents of preterm infants, medical staff’s guidance, collaboration, and support were deemed crucial, thereby further increasing their workload. For NICUs, the extra costs incurred by the devotion of medical staff may not have been fully compensated through KMC charges.

Basically, the nurse spends almost two hours for each session. The income generated is very little. In terms of the labor costs, doing KMC is actually a loss. Spending the entire morning there only earns a few tens of yuan for the department. That’s why many hospitals are reluctant to do it. (H1)

3.2 Theme 2: ambivalent emotions regarding KMC implementation

The emotional experience of healthcare providers involved in KMC was ambivalent. They mentioned that receiving positive feedback from parents made them feel their efforts were acknowledged and appreciated, which brought them a sense of accomplishment and fulfillment. However, they still felt uncomfortable and uneasy about the working pattern with parents present, and they also worried about potential risks or adverse effects that might arise from KMC. This sense of contradiction permeated their involvement in implementing KMC.

3.2.1 Gaining understanding, gratitude and trust from parents

During their participation in KMC, parents could direct skin-to-skin contact with their preterm infants and receive guidance on caring for infants from healthcare professionals, such as feeding. Some healthcare providers [five participants (29%)]

expressed that they could sense the increasing satisfaction from parents and the gradual improvement in cooperation with each other. Gradually, a strong emotional connection was established, further enhancing the relationship between healthcare providers and parents. They mentioned that while supporting parents participating in KMC, they received positive emotional feedback from parents occasionally. The most important aspect of these gains was the understanding, gratitude, and trust, which made them feel their work was acknowledged and recognized.

Tears welled in her eyes at the moment of skin-to-skin contact, feeling truly touched as she held her infant close. She was very grateful to us... If we assist her effectively, she will be extremely thankful. (H10)

When parents witness firsthand and perceive the dedication you put into ensuring the well-being of their babies during this process, their sensation is profoundly intuitive, and then they will have a deeper level of trust. Many relationships are built in this way. (H11)

3.2.2 Not used to working under parental presence

With the restricted visitation system in NICUs, healthcare professionals had adapted to working without parents present. Implementing KMC meant that their procedures and communications were exposed to the parents. Some healthcare providers [seven participants (41%)] expressed feeling anxious and stressed due to the perceived scrutiny and monitoring by parents. They were concerned that parents might question their professional competencies or the quality of care, causing them to be highly vigilant in their words and actions to avoid criticism or reproach.

Our nurses were used to working without the presence of parents. Having parents involved in KMC definitely adds pressure on us because they would observe all our behaviors. We all know that our operations are not always perfect, which is impossible, but parents may not think it that way. (H2)

Moreover, in the era of highly advanced modern information technology and networking, parents present at the scene might take photos, record audio or videos to document specific medical procedures or even detailed conversations among healthcare providers. Some healthcare providers [five participants (29%)] mentioned that once these recordings were disseminated and magnified, they could pose hidden risks of medical disputes. Even inadvertent errors or negligence could be scrutinized and distorted later, potentially damaging their reputation and professional careers.

Parents may misunderstand if healthcare workers deviate slightly from standardized procedures in some operations or even the things mentioned in our casual conversations. This information might be exposed online or shared in other ways, so we need to be very cautious. It makes us feel nervous internally. (H4)

3.2.3 Concerning nursing safety issues

Parents' involvement in KMC entailed their entry into the NICU. Many healthcare providers [eight participants (47%)] were concerned that some parents might be in the latent period of infection or carry pathogens. Additionally, parents typically did not undergo strict disinfection procedures before entering the NICU. Some items that had not been disinfected, such as phones, keys or wallets, could also have carried pathogens, thereby increasing the risk of infection for preterm infants.

There are still some risks in the entire process, and we fear the possibility of hospital-acquired infections. This is actually our biggest concern. (H3)

Some healthcare providers [four participants (24%)] expressed that inadequate observation and delayed responses in the process of KMC could potentially result in adverse events. This was particularly concerning when there was a shortage of nursing staff and lapses in care. For instance, preterm infants might experience a drop in oxygen saturation during feeding. If nurses do not notice this promptly, it could lead to complications. Similarly, during skin-to-skin contact, preterm infants could accidentally suffocate due to their immature respiratory systems.

Especially those infants who require oxygen therapy are inherently unstable. If their condition suddenly changes during this process, even if we come over to deal with it immediately, it may still cause harm to the infant. (H11)

3.3.2 Lack of systematic training and communication platform

Some healthcare providers [six participants (35%)] mentioned that hospitals generally lack systematic training on KMC. If KMC was not regularly implemented, some details might be overlooked. However, some NICU departments believed they had been conducting KMC for a long time and were already proficient without encountering adverse events during implementation. Consequently, they underestimated the importance of regular, systematic KMC training.

There is no specialized training available for KMC. In reality, it is needed. Everyone is very busy with their work, and if something is posted in the DingTalk work group, they may not pay much attention to it. (H12)

Some healthcare providers [five participants (29%)] also mentioned the absence of synchronous experience-sharing and learning channels. Currently, there is no specialized platform or website for KMC communication, making it difficult for them to exchange experiences and engage in online learning activities. This hindered the improvement of KMC implementation quality and the timely adoption and application of the latest advancements and progress.

Training and communication regarding KMC for preterm infants are still relatively scarce. We are not quite sure about the current situation and how well-established hospitals are approaching this. (H16)

3.3 Theme 3: barriers to KMC implementation

Healthcare providers indicated that they faced some practical obstacles in implementing KMC. The lack of standardized protocols might affect its effectiveness and safety. The absence of systematic training for them could impact the quality of KMC implementation. Additionally, insufficient manpower and parental compliance might affect its successful implementation.

3.3.1 Lack of unified norms and standards

Many healthcare providers [10 participants (59%)] indicated that hospitals in China had not established unified, standardized KMC implementation protocols, leading to variations in operational norms or execution standards among hospitals. Due to the lack of standardization, the implementation process of KMC could easily become a more subjective care-giving behavior, making it challenging to ensure the quality and safety of KMC and bringing about confusion and uncertainty for healthcare providers.

Currently, KMC may have its own standards in each hospital, but it has not formed a relatively unified operational process like many other procedures, so there is no clear execution standard. (H9)

3.3.3 Insufficient human resources

The majority of healthcare providers [12 participants (71%)] indicated that participating in KMC directly increased their workload, which emerged as a primary challenge. Consequently, effective implementation became difficult when the departments were busy or under circumstances of limited nursing staff. The low nurse-to-patient ratio imposed a heavy workload on healthcare providers, constraining their ability to allocate the necessary time and energy for the high-quality implementation of KMC. This scarcity of personnel not only hindered the effective execution of KMC but also potentially influenced healthcare providers' attitudes toward and willingness to implement KMC.

The nurse-to-patient ratio is insufficient. One nurse has to care for 10 infants or even more, and we really don't have enough time to spare. We can't even complete our daily tasks, so how can we do it? That's why we have to assign additional nurses specifically for KMC. (H15)

Furthermore, some healthcare providers [five participants (29%)] highlighted that implementing KMC required a high level of nursing competence. It frequently needed the support of nurses with extensive experience, as younger nurses might lack the requisite professional knowledge and skills. Particularly in terms of communication with parents and providing guidance, younger nurses often felt inadequate, which exacerbated the issue of insufficient human resources.

Nurses with limited experience cannot independently implement KMC. It requires nurses with a certain level of clinical experience and expertise, as the scope of communication and guidance involved is highly flexible. Younger nurses may only provide mechanical responses when communicating with parents, and they are unable to offer effective education or address queries. Handling unexpected situations is even more challenging for them. (H1)

3.3.4 Inadequate parental compliance

The acceptance and compliance of parents were also mentioned as another barrier during the implementation of KMC. On the one hand, some healthcare providers [five participants (29%)] noted a lack of understanding coupled with misconceptions and cognitive dissonance regarding KMC among preterm infant parents. For instance, some parents did not grasp the necessity and benefits of KMC, mistakenly believing that hospitals offered KMC solely for profit-making purposes. These biases and misunderstandings brought psychological discomfort, leading to their resistance toward KMC.

Many parents may not fully understand the importance of KMC. Some mothers may even think it's just a way for the hospital to charge them; they think that such little infants know nothing. These cognitive biases make it difficult for them to persist with it. (H2)

On the other hand, healthcare providers [three participants (18%)] mentioned that some parents might discontinue their participation or inconsistently engage in it after the initial trial for various reasons, including feelings of fatigue, time conflicts, or the perception of no significant effects. These factors diminished the acceptance and involvement of parents in KMC, ultimately resulting in challenges in maintaining long-term commitment or deeming it unnecessary to continue.

Some parents come for the first time but don't want to return for the second time. They come today, but feel it's unnecessary to come tomorrow. In this way, the care plan is disrupted. (H7)

3.4 Theme 4: suggestions for KMC implementation

To promote and optimize the implementation of KMC, healthcare providers proposed a range of suggestions and improvement needs, hoping to comprehensively improve it through a multi-pronged approach. These included enhancing the equipment and environment, fostering collaboration and communication among healthcare providers, and acquiring support from hospital managers.

3.4.1 Improving equipment and environment

Many healthcare providers [nine participants (53%)] highlighted that engaging in KMC was a hard and laborious

task for parents, especially when faced with sub-optimal facilities or uncomfortable environments, which would directly influence their experiences. Therefore, it was recommended that the KMC implementation environment and equipment should be optimized, such as providing better privacy protection and adjustable reclining chairs, to create a more cozy, homely, and family-oriented KMC implementation space, thereby enhancing parental compliance and satisfaction.

The equipment for KMC needs to be improved anyway; the more comfortable, the better. Our KMC chairs should be both easy to disinfect and comfortable. (H15)

It's definitely better to have one private room per family and then optimize its environment. The layout should be warmer, more daily, and more family-friendly, and it would be great to play some music, creating a relaxed atmosphere. (H8)

3.4.2 Strengthening collaboration between nurses and doctors

Apart from the above, some healthcare providers [six participants (35%)] highlighted the significant impact of the close collaboration between medical and nursing staff in KMC practice. Nurses observed that parents trusted doctors more and recommended that doctors should engage in KMC advocacy together with them to enhance parental compliance. Furthermore, cooperation among healthcare providers ensured the smooth delivery of information and coordinated KMC implementation plan, thereby improving the effectiveness and quality of KMC.

No matter how well we nurses do it, parents may not appreciate it. However, they all listen to doctors very attentively, so it's essential for doctors to be involved and convey this information to the families. (H14)

Doctors may need to participate in the KMC, either providing guidance or updating on the infants' condition. Some doctors may need a prompting reminder to be more proactive and involved. There is potential for further deepening their engagement in this aspect. (H9)

3.4.3 Support from hospital managers

The majority of healthcare providers [11 participants (65%)] emphasized that support from hospital managers played a pivotal role in driving the practice of KMC. It was crucial for managers to acknowledge the significance of healthcare professionals in KMC and provide appropriate incentives for those involved in the practice. Among various incentive measures, performance bonuses were considered one of the most practical and effective ways, especially in the current shortage of human resources in NICUs. By integrating the KMC implementation into performance evaluations and providing bonuses, more nurses would be motivated to engage in KMC during their rest time, thereby alleviating the issue of manpower shortage to some extent.

If there are rewards, nurses will be more willing to do it, even on their rest days. So, the hospital should emphasize the labor value, and a performance bonus is the most realistic and tangible. (H5)

In addition to the material rewards, some healthcare providers [four participants (24%)] agreed that spiritual incentives were also crucial. These non-monetary incentives are mainly manifested in the praise and recognition of individuals involved in KMC to enhance their sense of honor and achievement. By publicly acknowledging and commending, managers could make healthcare professionals feel the importance and value of their contributions to KMC, thereby inspiring greater enthusiasm and dedication in their work.

The managers have praised our team's efforts at hospital weekly meetings several times. And they also extended invitations to staff from other medical facilities to visit us and learn about KMC practice. Such positive feedback serves as a strong source of encouragement for us. (H6)

Moreover, over half of the healthcare providers [nine participants (53%)] mentioned the vital importance of policy and institutional support from the hospital leadership level for KMC. They stated that if the medical and nursing departments jointly emphasized and actively promoted the implementation of KMC, it would undoubtedly be carried out effectively. This was because only with the top-down attention and comprehensive support from hospital managers could the hardware facilities and staffing keep up more smoothly, and the high execution ability of clinical nurses could be fully leveraged.

In Chinese hospitals, as long as the managers are willing to do and support it, it can definitely be implemented...When it comes to implementing KMC, from hospital managers to department managers to nurses, I think everyone should have the mindset to carry it out. (H17)

4 Discussion

Although healthcare providers generally acknowledged the significant benefits of KMC for preterm infants and their parents, there remained a lack of intrinsic motivation to implement KMC, mainly due to the lack of economic profitability. Moreover, other potential concerns arose in the process of KMC, such as worries about nursing risks, potential pressures and disputes stemming from parents' presence, and various obstacles to KMC implementation, such as inadequate human resources. These factors indicated that promoting the implementation of KMC in China faced significant challenges. Therefore, there was a pressing need to enhance collaboration among healthcare providers and gain support from hospital managers to facilitate the implementation of KMC in China.

This study showed that the lack of motivation among healthcare providers to implement KMC mainly stemmed from the economic unprofitability of departments and hospitals. In the market-oriented healthcare environment in China, hospitals need to be

responsible for their own profits and losses, which means they are financially self-sufficient (47, 48). When deciding whether to implement a program or procedure, they needed to conduct a cost-benefit analysis. Healthcare providers perceived KMC charges as relatively low. Compared with the corresponding space, equipment, and manpower input, the expenses for KMC could not make ends meet. Moreover, healthcare providers' bonuses were directly tied to hospital income (49, 50), and the lack of economic incentives made them feel insufficiently motivated to implement KMC. This viewpoint represented the personal and subjective cognition of the healthcare providers we interviewed, reflecting their concerns and experiences related to the economic aspects of KMC implementation. Actually, some studies indicated that in environments with limited medical resources, KMC was recognized as the most straightforward and cost-effective method for managing preterm infants, especially when compared to the financial losses that may result from not providing KMC (51, 52). However, the extent to which KMC aligns with the long-term interests of hospitals in China, particularly in Zhejiang Province with relatively abundant medical resources (e.g., incubators) but high human resource costs, necessitates further research and validation. The core reason why hospital managers were reluctant to carry out KMC was not due to a lack of awareness of its clinical benefits but because KMC was not profitable in Chinese hospitals under the current pricing system. At present, with the gradual promotion of DRGs in major hospitals in China, hospitals might be more motivated and willing to provide nursing services such as KMC, which could shorten the average hospital stay (53). With the full roll-out of DRGs, hospitals would receive reasonable compensation for the costs associated with implementing KMC (54, 55), which is likely to be an opportunity for the future promotion of KMC.

Our study emphasized that insufficient human resources was a significant barrier that affected the implementation of KMC, which is similar to previous findings. A review on KMC in the sub-Saharan African region indicated that the shortage of healthcare workers limited the support available to parents, hindering the implementation of KMC (34). In countries such as Malawi and Indonesia, challenges related to human resources and concerns about increased workloads were reported as obstacles to implementing KMC (56, 57). The financial self-sufficiency attribute of Chinese hospitals meant that when allocating healthcare staff, hospitals needed to consider not only whether they could meet the medical workload but also the human efficiency, which was likely the underlying reason for the shortage of doctors and nurses in China. Compared to high-income countries like the United States, the ratio of nurses to preterm infants in China was relatively low (58, 59). However, a study indicated that while an initial increase in workload during the early stages of KMC implementation, continuous KMC implementation thereafter could reduce the nurse workload (56), which deserved further attention and exploration in future research. Additionally, if KMC were included in medical insurance, hospitals would be relieved of the burden of economic considerations when implementing KMC but rather focus on whether it was beneficial for preterm infants (60). Therefore, it is necessary to call on policymakers to include KMC in medical insurance, providing the necessary institutional guarantee and support for NICUs to carry out KMC.

In the absence of economic incentives, the key to successfully integrating KMC into routine practice laid in the support of hospital managers. This involved motivating healthcare staff, particularly nurses, to engage more effectively in KMC through enhancing their intrinsic drive and external support. Research showed that a lack of leadership's spiritual motivation or support could make healthcare workers more susceptible to wavering, which affects the implementation and participation in clinical operations (61). Their intrinsic motivation could be enhanced through hospital managers' recognition and reinforcement of their values (62). Therefore, managers should demonstrate the significance of KMC in the recovery of preterm infants and the wellbeing of parents to nurses, enabling them to perceive their contributions as valuable and appreciated. This internal cognition and motivation should have been considered a key part of healthcare personnel management and should have been taken into account when assessing staffing and implementation (27, 38). Studies on the introduction of KMC found that many nurses and doctors attributed their enthusiasm for KMC to the leadership and support of hospital managers (26, 60). Moreover, it was found in our study that the performance bonus was the most practical and effective support measure currently available, as evidenced in previous research (63). Therefore, incorporating the KMC implementation into performance appraisal could enhance the enthusiasm and involvement of healthcare workers in KMC.

Our findings indicated that there were differences in the perceptions of KMC between healthcare providers and parents of preterm infants. According to the literature, parents' cognition and evaluation of KMC directly influenced their decisions and behaviors, including their willingness to accept KMC and their degree of involvement in the implementation process (31). Although healthcare providers believed that KMC charges were relatively low and even resulted in department losses, it was purely for the benefit of preterm infants and parents; on the other hand, many parents failed to realize the significance and benefits of KMC and misunderstood medical staff implementing KMC to make a profit. To some extent, this was also related to the fact that KMC was not included in the medical insurance; non-insured medical procedures were easy to be regarded as unnecessary by parents and provided by hospitals solely for profit-driven purposes (64). The cognitive gap in KMC between healthcare providers and parents of preterm infants stemmed from information asymmetry between the two parties. Breaking down these cognitive barriers to achieve better understanding was crucial (32). This also highlighted the inadequacy of healthcare providers' early KMC education efforts. A study suggested to introduce the concept of KMC during prenatal care or immediately after delivery (65). Meanwhile, healthcare providers should enhance KMC advocacy and education to promote long-term parental engagement and compliance.

Our study also found that some healthcare providers harbored negative emotional experiences of KMC, believing that the presence of parents would increase the risk of nursing safety and medical disputes. This negative attitude hindered staff from actively engaging in KMC. However, previous research showed that parental involvement in KMC could promote the recovery of preterm infants, enhance parental understanding of preterm infant-related knowledge, and teach them some care-giving skills (66, 67), while KMC did not increase the incidence of infants' infections

in NICUs (68). In our study, some healthcare providers perceived parental involvement in KMC as a burden, which was obviously one-sided and biased. This perception might be related to the fact that Chinese NICUs traditionally operated as unaccompanied wards, with staff having limited contact with parents and being unaccustomed to working in front of parents (69). To some extent, healthcare providers' concerns about the potential risks of medical disputes when operating under parental supervision or monitoring confirmed the tense doctor-patient relationship in China (70). While excluding parents may have mitigated certain risks for healthcare providers, it also meant missing an opportunity to establish a trusting relationship with parents, which could have posed obstacles to specific tasks later on (71). Therefore, it is of great significance to shift the mindset of healthcare providers, enhance communication and trust with parents, and alleviate concerns about the presence of parents.

On the other hand, some healthcare providers in our study expressed that they could sense the increasing satisfaction from parents and the gradual improvement in cooperation with each other, which in turn strengthened their intrinsic motivation to carry out KMC. In other words, some medical staff had also become aware of the positive aspects from parents of preterm infants. It is indeed natural for healthcare providers to hold conflicting feelings or attitudes about the parent's presence during KMC, given their differing perspectives and experiences. Therefore, in promoting KMC, healthcare providers should not solely concentrate on the potential risks associated with parental involvement, but rather raise awareness of the positive aspects of parental involvement. Studies showed that healthcare providers' knowledge, beliefs, and attitudes toward KMC were crucial for its implementation (37, 72). When staff in NICUs feel that they are assisting preterm infants and their parents in resolving issues through KMC, they would not perceive parental presence as a nuisance or a disadvantage. Conversely, if healthcare providers are merely going through the motions of their tasks, they may view the presence of parents as disruptive and inconvenient. Studies involving healthcare providers and parents participating in KMC demonstrated that as parents became more familiar with daily nursing, both parties experienced reduced anxiety, leading to an improvement in the doctor-patient relationship and a closer bond (73, 74). As mentioned by the interviewees in our study, they sensed the trust and recognition from parents being elevated, the cooperation between staff and patients gradually being improved, and a solid emotional connection was established between them. Therefore, healthcare providers need to recognize the positive significance and value behind parental involvement, viewing it as an essential way to promote the recovery of preterm infants and enhance relationships with parents. This positive feedback will further enhance their motivation to implement KMC.

Understanding the barriers and challenges to implementing KMC in specific settings is the foundation for successful implementation. In our study, some participants pointed out that the current training related to KMC was insufficient, and the standardization still needed further improvement and uniformity. Considering that the personnel implementing KMC in China were relatively not fixed, the unified operations could not only make the entire KMC process more standardized, systematic, and comprehensive but also avoid the waste of manpower and

resources (26, 64). Therefore, it is necessary to localize the existing KMC guidelines based on evidence-based methods and establish standardized practices for KMC implementation that are suitable for the Chinese context. Furthermore, through systematic training and policy support, healthcare providers can acquire the necessary knowledge and skills, creating a more conducive environment for KMC implementation, reducing their concerns, and boosting the team's confidence in KMC practice (75). Existing studies indicated that these standards and training programs should at least cover aspects such as how to properly implement KMC, how to deal with potential risks, and how to communicate with parents effectively (76–78). In this way, tailored support strategies should be developed from the perspective of healthcare providers to promote the implementation of KMC and expand the scale of KMC practice in China.

4.1 Limitations

This study used a qualitative research method to explore the perceptions and experiences of Chinese healthcare providers in caring for parents' KMC of preterm infants in four NICUs in China. However, the study had several limitations. First, although the researchers and participants were in a quiet and undisturbed office during the interview, it was inevitable that participants would be interrupted by calls they needed to answer or other tasks requiring urgent handling, which may have impacted their thinking during the interview. Second, all hospitals included in the study are tertiary hospitals, including general teaching hospitals and maternal and child healthcare hospitals located in major urban cities in Zhejiang. The experience and practice of KMC in lower-level healthcare facilities may be different.

5 Conclusions

Our study showed that although healthcare providers generally agreed on the importance and benefits of KMC for infants and parents, after considering multiple factors, they believed that implementing KMC was not cost-effective and lacked intrinsic motivation for implementation. These factors included the fact that KMC was not profitable at the economic level, concerns about potential risks due to the presence and participation of parents, and obstacles such as insufficient human resources and lack of norms in the implementation. It is recommended that hospital managers provide policy support in performance appraisal and recognize and encourage healthcare professionals so as to enhance their motivation to implement KMC. Promoting parental compliance with KMC also requires collaboration between medical and nursing staff. Moreover, it is also necessary to improve the training of staff and standardize the KMC program so as to form a more conducive and supportive KMC implementation environment.

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 the Women's Hospital, School of Medicine, Zhejiang 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

QC: Writing – original draft. YZ: Writing – review & editing. MH: Writing – review & editing. DC: Writing – review & editing. XX: Writing – review & editing.

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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.

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Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fpubh.2024.1419828/full#supplementary-material>

References

- Ohuma E, Moller AB, Bradley E, Chakwera S, Hussain-Alkhateeb L, Lewin A, et al. National, regional, and worldwide estimates of preterm birth in 2020, with trends from 2010: a systematic analysis. *Lancet*. (2023) 402:1261–71. doi: 10.1016/S0140-6736(23)00878-4
- World Health Organization. *Preterm Birth*. (2023). Available online: <https://www.who.int/news-room/fact-sheets/detail/preterm-birth> (accessed April 3, 2024).
- Deng K, Liang J, Mu Y, Liu Z, Wang Y, Li M, et al. Preterm births in China between 2012 and 2018: an observational study of more than 9 million women. *Lancet Glob Health*. (2021) 9:e1226–41. doi: 10.1016/S2214-109X(21)00298-9
- National Health Commission. *China Health Statistics Yearbook*. (2023). Available online at: <http://www.nhc.gov.cn/mohwsbwstjxxzx/tjtnj/202305/6ef68aac6bd14c1eb9375e01a0faa1fb.shtml> (accessed May 27, 2024).
- Zhejiang Provincial Bureau of Statistics. *End-term Statistical Monitoring Report on the Implementation of the “China Children’s Development Outline (2011–2020)” and the “Zhejiang Province Children’s Development Plan (2016–2020)”*. (2021). Available online at: https://tjj.zj.gov.cn/art/2021/6/7/art_1229129214_4653541.html (accessed May 27, 2024).
- Yu X, He C, Wang Y, Kang L, Miao L, Chen J, et al. Preterm neonatal mortality in China during 2009–2018: A retrospective study. *PLoS ONE*. (2021) 16:e0260611. doi: 10.1371/journal.pone.0260611
- Liu Y, Kang L, He C, Miao L, Qiu X, Xia W, et al. Neonatal mortality and leading causes of deaths: a descriptive study in China, 2014–2018. *BMJ Open*. (2021) 11:e042654. doi: 10.1136/bmjopen-2020-042654
- Mason E, Mathai M, Silvestre MA. Time of transition: lessons from China’s progress in reproductive, maternal, newborn, child, and adolescent health. *Lancet*. (2021) 397:2444–7. doi: 10.1016/S0140-6736(21)01159-4
- Dean B, Ginnell L, Ledsham V, Tsanas A, Telford E, Sparrow S, et al. Eye-tracking for longitudinal assessment of social cognition in children born preterm. *J Child Psychol Psychiatry*. (2021) 62:470–80. doi: 10.1111/jcpp.13304
- Allotey J, Zamora J, Cheong-See F, Kalidindi M, Arroyo-Manzano D, Asztalos E, et al. Cognitive, motor, behavioural and academic performances of children born preterm: a meta-analysis and systematic review involving 64 061 children. *BJOG*. (2018) 125:16–25. doi: 10.1111/1471-0528.14832
- Ream MA, Lehwald L. Neurologic consequences of preterm birth. *Curr Neurol Neurosci Rep*. (2018) 18:48. doi: 10.1007/s11910-018-0862-2
- World Health Organization. *Launch of the WHO Recommendations for Care of the Preterm or Low Birth Weight Infant*. (2022). Available online at: <https://www.who.int/news-room/events/detail/2022/11/17/default-calendar/launch-of-the-who-recommendations-for-care-of-the-preterm-or-low-birth-weight-infant> (accessed April 3, 2024).
- World Health Organization. *Kangaroo Mother Care: A Practical Guide*. Geneva: World Health Organization (2003). Available online at: <https://www.who.int/publications/i/item/9241590351> (accessed April 1, 2024).
- Chan GJ, Valsangkar B, Kajeepeta S, Boundy EO, Wall S. What is kangaroo mother care? Systematic review of the literature. *J Glob Health*. (2016) 6:010701. doi: 10.7189/jogh.06.010701
- World Health Organization. *WHO Recommendations on Interventions to Improve Preterm Birth Outcomes*. Geneva: World Health Organization (2015). Available online at: <https://www.who.int/publications/i/item/9789241508988> (accessed April 1, 2024).
- Furman L. Kangaroo mother care 20 years later: connecting infants and families. *Pediatrics*. (2017) 139:e20163332. doi: 10.1542/peds.2016-3332
- Cho ES, Kim SJ, Kwon MS, Cho H, Kim EH, Jun EM, et al. The effects of kangaroo care in the neonatal intensive care unit on the physiological functions of preterm infants, maternal-infant attachment, and maternal stress. *J Pediatr Nurs*. (2016) 31:430–8. doi: 10.1016/j.pedn.2016.02.007
- Zhu Z, Wang X, Chen W, Pei S, Wang Q, Guan H, et al. The efficacy of Kangaroo-Mother care to the clinical outcomes of LBW and premature infants in the first 28 days: a meta-analysis of randomized clinical trials. *Front Pediatr*. (2023) 11:1067183. doi: 10.3389/fped.2023.1067183
- Sharma D, Farahbakhsh N, Sharma S, Sharma P, Sharma A. Role of kangaroo mother care in growth and breast feeding rates in very low birth weight (VLBW) neonates: a systematic review. *J Matern Fetal Neonatal Med*. (2019) 32:129–42. doi: 10.1080/14767058.2017.1304535
- Salim N, Shabani J, Peven K, Rahman QS, Kc A, Shamba D, et al. Kangaroo mother care: EN-BIRTH multi-country validation study. *BMC Pregn Childb*. (2021) 21:231. doi: 10.1186/s12884-020-03423-8
- Stefani G, Skopec M, Battersby C, Matthew H. Why is Kangaroo Mother Care not yet scaled in the UK? A systematic review and realist synthesis of a frugal innovation for newborn care. *BMJ Innov*. (2022) 8:9–20. doi: 10.1136/bmjinnov-2021-000828
- Liu X, Li Z, Chen X, Cao B, Yue S, Yang C, et al. Utilization pattern of kangaroo mother care after introduction in eight selected neonatal intensive care units in China. *BMC Pediatr*. (2020) 20:260. doi: 10.1186/s12887-020-02153-2
- General Office of the National Health and Family Planning Commission. *Guideline for health care services for premature infants*. (2017). Available online: <http://www.nhc.gov.cn/fys/s3585/201703/d5656db4e43a49f9d14470864b0fb16.shtml> (accessed May 27, 2024).
- National Health Commission. *The Action Plan for Healthy Children (2018–2020)*. (2018). Available online at: <http://www.nhc.gov.cn/fys/s3585/202111/554a64ff0eff4971a37db413a00083a6.shtml> (accessed May 27, 2024).
- Chinese Society of Neonatology. Proposal on the grading and management of neonatal wards in China. *J Dev Med*. (2015) 3:193–202.
- Wang W, Wang Y, Zhang H, Yang G, Lin Y, Wang C, et al. A pilot study of Kangaroo mother care in early essential newborn care in resource-limited areas of China: the facilitators and barriers to implementation. *BMC Pregn Childb*. (2023) 23:451. doi: 10.1186/s12884-023-05720-4
- Cai Q, Chen DQ, Wang H, Zhang Y, Yang R, Xu WL, et al. What influences the implementation of kangaroo mother care? An umbrella review. *BMC Pregn Childb*. (2022) 22:851. doi: 10.1186/s12884-022-05163-3
- Feucht UD, van Rooyen E, Skhosana R, Bergh AM. Taking kangaroo mother care forward in South Africa: the role of district clinical specialist teams. *S Afr Med J*. (2015) 106:49–52. doi: 10.7196/SAMJ.2016.v106i1.10149
- Günay U, Coşkun D. Observations, opinions and experiences of the newborn team in a newborn intensive care unit that implemented the kangaroo care: a qualitative research. *Cocuk Acil ve Yogun Bakim*. (2019) 6:85–90. doi: 10.4274/cayd.galenos.2018.96967
- Sjömar J, Ottesen H, Banik G, Rahman AE, Thernström Blomqvist Y, Rahman SM, et al. Exploring caregivers’ experiences of Kangaroo Mother Care in Bangladesh: a descriptive qualitative study. *PLoS One*. (2023) 18:e0280254. doi: 10.1371/journal.pone.0280254
- Foong WC, Foong SC, Ho JJ, Gautam D, Leong JJ, Tan PY, et al. Exploring factors influencing the uptake of kangaroo mother care: key informant interviews with parents. *BMC Pregn Childb*. (2023) 23:706. doi: 10.1186/s12884-023-06021-6
- Bilal SM, Tadele H, Abebo TA, Tadesse BT, Muleta M. W/Gebriel F, et al. Barriers for kangaroo mother care (KMC) acceptance, and practices in southern Ethiopia: a model for scaling up uptake and adherence using qualitative study. *BMC Pregn Childb*. (2021) 21:25. doi: 10.1186/s12884-020-03409-6
- Kampekete GSM, Ngoma C, Masumo M. Acceptance of kangaroo mother care by mothers of premature babies. *Afr J Midwif Womens Health*. (2018) 12:178–88. doi: 10.12968/ajmw.2018.12.4.178
- Kinshella MW, Hiwa T, Pickerill K, Vidler M, Dube Q, Goldfarb D, et al. Barriers and facilitators of facility-based kangaroo mother care in sub-Saharan Africa: a systematic review. *BMC Pregn Childb*. (2021) 21:176. doi: 10.1186/s12884-021-03646-3
- Feng CL, Li YM, Zhou L, Yuan L, Yuan L, Wang L, et al. Qualitative studies on parents’ experience of skin to skin contact for newborns: a meta synthesis. *J Nurs*. (2021) 28:27–32. doi: 10.16460/j.issn1008-9969.2021.11.027
- Pratomo H, Amelia T, Nurlin F, Adisasmita AC. Knowledge and perceptions of kangaroo mother care among health providers: a qualitative study. *Clin Exp Pediatr*. (2020) 63:433–7. doi: 10.3345/cep.2018.06506
- Adisasmita A, Izati Y, Choirunisa S, Pratomo H, Adriyanti L. Kangaroo mother care knowledge, attitude, and practice among nursing staff in a hospital in Jakarta, Indonesia. *PLoS ONE*. (2021) 16:e0252704. doi: 10.1371/journal.pone.0252704
- Rahmatika QT, Aditya RS, Yusuf A, Almutairi RL, Al Razeeni DM, Kotijah S, et al. We are facing some barriers: a qualitative study on the implementation of kangaroo mother care from the perspectives of healthcare providers. *J Public Health Afr*. (2022) 13:2412. doi: 10.4081/jphia.2022.2412
- Lin Y, Zheng YY, Yu XR, Fan YF, Cheng XX. Nurses participated in the qualitative study of kangaroo nursing experience. *China Health Std Manag*. (2018) 9:195–7. doi: 10.3969/j.issn.1674-9316.2018.19.088
- Doyle L, McCabe C, Keogh B, Brady A, McCann M. An overview of the qualitative descriptive design within nursing research. *J Res Nurs*. (2020) 25:443–55. doi: 10.1177/1744987119880234
- Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. *Int J Qual Health Care*. (2007) 19:349–57. doi: 10.1093/intqhc/mzm042
- Yunxian Z. *Quality of Nursing Research: Theory and Cases*. Zhejiang: Zhejiang University Press (2017). (Chinese book).
- Kallio H, Pietilä AM, Johnson M, Kangasniemi M. Systematic methodological review: developing a framework for a qualitative semi-structured interview guide. *J Adv Nurs*. (2016) 72:2954–65. doi: 10.1111/jan.13031

44. Braun V, Clarke V. Using thematic analysis in psychology. *Qual Res Psychol*. (2006) 3:77–101. doi: 10.1191/1478088706qp0630a
45. Bowen GA. Naturalistic inquiry and the saturation concept: a research note. *Qual Res*. (2008) 8:137–52. doi: 10.1177/1468794107085301
46. Guba E, Lincoln Y. *Competing Paradigms in Qualitative Research, Handbook of Qualitative Research*. Vol. 2. Thousand Oaks, CA: Sage (1994).
47. Jakovljevic M, Chang H, Pan J, Guo C, Hui J, Hu H, et al. Successes and challenges of China's health care reform: a four-decade perspective spanning 1985–2023. *Cost Eff Resour Alloc*. (2023) 21:59. doi: 10.1186/s12962-023-00461-9
48. Sahoo PM, Rout HS, Jakovljevic M. Dynamics of health financing among the BRICS: a literature review. *Sustainability*. (2023) 15:12385. doi: 10.3390/su151612385
49. Zhang C, Liu Y. The salary of physicians in Chinese public tertiary hospitals: a national cross-sectional and follow-up study. *BMC Health Serv Res*. (2018) 18:661. doi: 10.1186/s12913-018-3461-7
50. Wang Y, Castelli A, Cao Q, Liu D. Assessing the design of China's complex health system - concerns on equity and efficiency. *Health Policy Open*. (2020) 1:100021. doi: 10.1016/j.hpopen.2020.100021
51. Ruiz JG, Charpak N, Castillo M, Bernal A, Ríos J, Trujillo T, et al. Latin American Clinical Epidemiology Network Series - Paper 4: economic evaluation of Kangaroo Mother Care: cost utility analysis of results from a randomized controlled trial conducted in Bogotá. *J Clin Epidemiol*. (2017) 86:91–100. doi: 10.1016/j.jclinepi.2016.10.007
52. Uwaezuoke S N. Kangaroo mother care in resource-limited settings: implementation, health benefits, and cost-effectiveness. *Res Rep Neonatol*. (2017) 7:11–8. doi: 10.2147/RRN.S138773
53. Zhao C, Wang C, Shen C, Wang Q. Diagnosis-related group (DRG)-based case-mix funding system, a promising alternative for fee for service payment in China. *Biosci Trends*. (2018) 12:109–15. doi: 10.5582/bst.2017.01289
54. Aragón MJ, Chalkley M, Kreif N. The long-run effects of diagnosis related group payment on hospital lengths of stay in a publicly funded health care system: evidence from 15 years of micro data. *Health Econ*. (2022) 31:956–72. doi: 10.1002/hec.4479
55. Zhu T, Chen C, Zhang X, Yang Q, Hu Y, Liu R, et al. Differences in inpatient performance of public general hospitals following implementation of a points-counting payment based on diagnosis-related group: a robust multiple interrupted time series study in Wenzhou, China. *BMJ Open*. (2024) 14:e073913. doi: 10.1136/bmjopen-2023-073913
56. Pratomo H, Uhudiyah U, Sidi IPS, Rustina Y, Suradi R, Bergh AM, et al. Supporting factors and barriers in implementing kangaroo mother care in Indonesia. *Paediatr Indones*. (2012) 52:43–50. doi: 10.14238/pi52.1.2012.43-50
57. Maniago JD, Almazan JU, Albougami AS. Nurses' Kangaroo Mother Care practice implementation and future challenges: an integrative review. *Scand J Caring Sci*. (2020) 34:293–304. doi: 10.1111/scs.12755
58. Rogowski JA, Staiger DO, Patrick TE, Horbar JD, Kenny MJ, Lake ET. Nurse staffing in neonatal intensive care units in the United States. *Res Nurs Health*. (2015) 38:333–41. doi: 10.1002/nur.21674
59. Shen Y, Jian W, Zhu Q, Li W, Shang W, Yao L. Nurse staffing in large general hospitals in China: an observational study. *Hum Resour Health*. (2020) 18:3. doi: 10.1186/s12960-020-0446-5
60. Yue J, Liu J, Williams S, Zhang B, Zhao Y, Zhang Q, et al. Barriers and facilitators of kangaroo mother care adoption in five Chinese hospitals: a qualitative study. *BMC Public Health*. (2020) 20:1234. doi: 10.1186/s12889-020-09337-6
61. Wu WL, Lee YC. How spiritual leadership boosts nurses' work engagement: the mediating roles of calling and psychological capital. *Int J Environ Res Public Health*. (2020) 17:6364. doi: 10.3390/ijerph17176364
62. Tokumasu K, Obika M, Obara H, Kikukawa M, Nishimura Y, Otsuka F. Processes of increasing medical residents' intrinsic motivation: a qualitative study. *Int J Med Educ*. (2022) 13:115–23. doi: 10.5116/ijme.6250.1017
63. Li H, Yuan B, Wang D, Meng Q. Motivating factors on performance of primary care workers in China: a systematic review and meta-analysis. *BMJ Open*. (2019) 9:e028619. doi: 10.1136/bmjopen-2018-028619
64. Liu K, Liu W, Frank R, Lu C. Assessing the long-term effects of Basic Medical Insurance on catastrophic health spending in China. *Health Policy Plan*. (2022) 37:747–59. doi: 10.1093/heapol/czac020
65. Zhang B, Yue J, Duan Z, Zhao Y, Williams S, Huang L, et al. Maternal experience of intermittent kangaroo mother care for late preterm infants: a mixed-methods study in four postnatal wards in China. *BMJ Open*. (2021) 11:e050221. doi: 10.1136/bmjopen-2021-050221
66. Mu PF, Lee MY, Chen YC, Yang HC, Yang SH. Experiences of parents providing kangaroo care to a premature infant: a qualitative systematic review. *Nurs Health Sci*. (2020) 22:149–61. doi: 10.1111/nhs.12631
67. Anderzén-Carlsson A, Lamy ZC, Tingvall M, Eriksson M. Parental experiences of providing skin-to-skin care to their newborn infant—part 2: a qualitative meta-synthesis. *Int J Qual Stud Health Wellbeing*. (2014) 9:24907. doi: 10.3402/qhw.v9.24907
68. Arya S, Chhabra S, Singhal R, Kumari A, Wadhwa N, Anand P, et al. Effect on neonatal sepsis following immediate kangaroo mother care in a newborn intensive care unit: a post-hoc analysis of a multicentre, open-label, randomised controlled trial. *EClinicalMedicine*. (2023) 60:102006. doi: 10.1016/j.eclinm.2023.102006
69. Li XY, Lee S, Yu HF, Ye XY, Warre R, Liu XH, et al. Breaking down barriers: enabling care-by-parent in neonatal intensive care units in China. *World J Pediatr*. (2017) 13:144–51. doi: 10.1007/s12519-016-0072-4
70. Wang Y, Du S. Time to rebuild the doctor-patient relationship in China. *Hepatobiliary Surg Nutr*. (2023) 12:235–8. doi: 10.21037/hbsn-23-104
71. Molina-Mula J, Gallo-Estrada J. Impact of nurse-patient relationship on quality of care and patient autonomy in decision-making. *Int J Environ Res Public Health*. (2020) 17:835. doi: 10.3390/ijerph17030835
72. Almazan JU, Cruz JP, Albougami AS, Alamri MS, Adolfo CS. Maternity-ward nurses' kangaroo mother care attitudes and practices: implications and future challenges. *Scand J Caring Sci*. (2019) 33:848–56. doi: 10.1111/scs.12681
73. Vittner D, Casavant S, McGrath JM, A. Meta-ethnography: skin-to-skin holding from the caregiver's perspective. *Adv Neonatal Care*. (2015) 15:191–200. doi: 10.1097/ANC.0000000000000169
74. Umberger E, Canvasser J, Hall SL. Enhancing NICU parent engagement and empowerment. *Semin Pediatr Surg*. (2018) 27:19–24. doi: 10.1053/j.sempedsurg.2017.11.004
75. Calibo AP, De Leon Mendoza S, Silvestre MA, Murray JCS, Li Z, Mannava P, et al. Scaling up kangaroo mother care in the Philippines using policy, regulatory and systems reform to drive changes in birth practices. *BMJ Glob Health*. (2021) 6:e006492. doi: 10.1136/bmjgh-2021-006492
76. UNICEF. *Facilitators Guide for Training on Kangaroo Mother Care*. New York, NY (2018). p. 1–44.
77. Cattaneo A, Amani A, Charpak N, De Leon-Mendoza S, Moxon S, Nimbalkar S, et al. Report on an international workshop on kangaroo mother care: lessons learned and a vision for the future. *BMC Pregn Childb*. (2018) 18:170. doi: 10.1186/s12884-018-1819-9
78. Hailegebriel TD, Bergh AM, Zaka N, Roh JM, Gohar F, Rizwan S, et al. Improving the implementation of kangaroo mother care. *Bull World Health Organ*. (2021) 99:69–71. doi: 10.2471/BLT.20.252361



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Combination effects of environmental tobacco smoke exposure and nutrients supplement during pregnancy on obesity in Chinese preschool children

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Objective: This study aimed to explore the combination effects of prenatal exposure to environment tobacco smoke (ETS) and nutrients supplement during pregnancy on childhood obesity in preschoolers.

Methods: A cross-sectional study was conducted with 58,814 child-mother dyads from 235 kindergartens in Longhua District of Shenzhen, China in 2021. A self-administered structured questionnaire was completed by mothers to collect socio-demographic characteristics, prenatal ETS exposure, and nutrients supplement in pregnancy, and preschoolers' heights and weights were measured at the same time. After controlling for potential confounding variables, logistic regression models and cross-analyses were used to examine the independent and combination effects of maternal prenatal ETS exposure and nutrients supplementation during pregnancy on obesity in preschool children.

Results: The results of our study showed that prenatal ETS exposure increased the risk of childhood obesity (AOR = 1.22, 95% CI = 1.11–1.34) in preschoolers. In addition, risk of childhood obesity was significantly higher when mothers didn't take supplements of multivitamins (AOR = 1.12, 95% CI = 1.05–1.20), folic acid (AOR = 1.23, 95% CI = 1.10–1.37) and iron (AOR = 1.11, 95% CI = 1.04–1.19) during pregnancy. The cross-over analysis showed that the combination of prenatal ETS exposure with mothers taking no multivitamins (AOR = 1.40, 95% CI = 1.21–1.62), no folic acid (AOR = 1.55, 95% CI = 1.12–2.14) and no iron (AOR = 1.38, 95% CI = 1.19–1.59) during pregnancy also increased the risk of obesity among Chinese preschoolers. We also discovered additive interactive effects between prenatal ETS exposure and no maternal multivitamin, folic acid and iron supplementation in pregnancy on the risk of obesity in preschoolers.

Conclusion: The combination of prenatal exposure to ETS with no supplementation of these nutrients might jointly increase the risk of childhood obesity. Public health interventions are needed to reduce prenatal exposure to ETS and to encourage mothers to take appropriate multivitamin, folic acid and iron supplements during pregnancy.

KEYWORDS

childhood obesity, environmental tobacco smoke (ETS), nutrients supplement, preschool children, combination effects

1 Introduction

Childhood obesity has become a major public health problem worldwide, with the global childhood obesity rate increasing year by year. According to a survey of 128.9 million people from 1975 to 2016 (1), the global obesity rate for the age range of 5–19 years, increased from 0.7% in 1975 to 5.6% in 2016 for girls, and from 0.9% in 1975 to 7.8% in 2016 for boys, with estimates of 50 million girls and 74 million boys being obese worldwide by 2016. In line with the global obesity epidemic, the obesity rate of children in China has also shown an increasing trend. For example, according to the Health and Nutrition Survey (2), the childhood obesity rate in China increased from 5.3% in 1991 to 16.2% in 2015 in children and adolescents aged 6–17 years. These increasing prevalence rates are concerning given that childhood obesity is likely to persist into adulthood (3, 4), and is an important risk factor for the development of chronic diseases in adulthood such as type 2 diabetes, cardiovascular disease, chronic kidney disease and cancer (5, 6), many mental health problems and premature death (7).

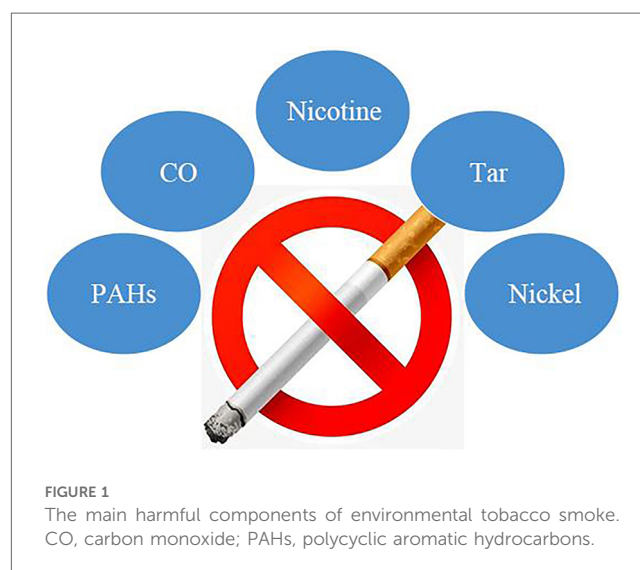
Childhood obesity is considered a multi-factorial metabolic disease (8). From the perspective of Developmental Origins of Health and Disease (DOHaD) hypothesis (9, 10), the occurrence of childhood obesity is influenced by exposure to a range of risk and protective factors during early life (i.e., pre-pregnancy, pregnancy and infancy). Early life may be a critical period for the development of excess weight children due to it being a time of strong body cell division and differentiation, as well as a key period when the formation of tissues and organs are particularly sensitive to external stimuli (11). Exposure to a variety of risk factors during pregnancy may therefore lead to metabolic “programming” that can alter postpartum susceptibility to obesity. This metabolic programming persists into adulthood and plays an important role in the development of chronic diseases in adulthood (12, 13). According to the DOHaD hypothesis, if the fetus is stunted due to intrauterine malnutrition, it will attempt to overcome these limitations by adopting a thrifty energy phenotype (14, 15) which can lead to the occurrence of low birth weight (LBW). When then encountering a nutrient-rich postpartum environment, this mismatch between the state of the postpartum and intrauterine nutritional environments may accelerate the growth of infants and young children and result in the childhood obesity (16).

The most direct cause of intrauterine malnutrition is maternal malnutrition during pregnancy. Our previous research found that inadequate folic acid supplementation during pregnancy was associated with an increased risk of obesity in preschoolers born with SGA, and that this relationship was altered by prenatal multivitamin and iron supplementation (17). However, intrauterine malnutrition is not only related to the mother’s nutrient supplementation, but also to the normal function of the placenta (18). The placenta and umbilical cord are the most important organs connecting the mother and the fetus: being responsible for transporting nutrients and oxygen, and timely discharging the fetal metabolic waste (19). If the placenta is damaged or underdeveloped, it may not be able to deliver

enough nutrients and oxygen from the mother to the fetus, eventually leading to intrauterine growth restriction or LBW (20). Our previous studies have shown that prenatal exposure to cooking oil fumes can impair placental development or alter the structure and function of the placenta (21). Several studies have also shown that prenatal exposure to air pollution can lead to an increase in placental vascular resistance (22, 23). These results suggest that exposure to air pollution may affect the function of the placenta, thereby creating a malnourished environment for the fetus.

Environmental tobacco smoke (ETS) is one of the main sources of indoor air pollution (24). ETS contains more than 7,000 chemicals (25), with the main harmful components including nicotine, tar, carbon monoxide (CO), polycyclic aromatic hydrocarbons (PAHs), nitrogen oxides, nickel, cadmium (26, 27) (see Figure 1). Currently, the rate of maternal exposure to ETS during pregnancy is high in many countries. For example, a retrospective cohort study by Crane et al. found that the rate of prenatal exposure to ETS was 11.1% (28), and two studies from Saudi Arabia and Spain reported that the proportion of women exposed to ETS during pregnancy was 31.7 and 55.5%, respectively (29, 30). In China, a survey of 15 provincial and municipal health care institutions across the country by Wang et al. found that 20.2% of women were exposed to ETS during pregnancy (31).

Our previous research showed that prenatal exposure to mosquito coil smoke (MCS) was associated with an increased risk of childhood obesity (32). Moreover, a meta-analysis reported that children with mothers smoking during pregnancy had a 50% increased risk of being overweight compared to children with non-smoking mothers in pregnancy (33). Similarly, a study by Durmus et al. reported that children whose mothers smoked during pregnancy had an increased risk of obesity at age 4 (34). However, the effect of prenatal ETS exposure on obesity in preschool children has not been studied. In addition, given the emerging evidence that maternal prenatal consumption of nutritional supplements may be protective for LBW, we believe it



is plausible that this may also be protective for obesity in young children. Moreover, the combination effects of prenatal ETS exposure and nutrients supplement on childhood obesity is unclear. This study therefore aimed to explore the relationship between prenatal ETS exposure, and maternal nutritional supplementation with childhood obesity. We hypothesized that (1) maternal prenatal ETS exposure would be a risk factor; (2) maternal prenatal nutritional supplementation would be a protective factor for childhood obesity; and (3) the combination of prenatal ETS exposure and a lack of nutrient supplementation will show an interactive effect upon the risk of childhood obesity.

2 Materials and methods

2.1 Setting and subjects

A population-based survey was conducted from October to December 2021 in 235 kindergartens in the Longhua District of Shenzhen, China, with a total of 67,324 child-mother dyads recruited. Within this sample, 7771 preschool children born post-term (gestational age >42 weeks) or as giant infants (birth weight >4,000 g) were not included in this study. Three child-mother pairs were excluded due to missing information on prenatal exposure to environmental tobacco smoke, and 736 dyads were excluded due to missing data on the weight or height of the

child. This resulted in a total of 58,814 child-mother pairs being included in the final analysis (Figure 2).

The study was approved by the Ethic Committee of the School of Public Health of Sun Yat-sen University. A written informed consent was obtained from the mothers of all the children involved in the study, in accordance with the Declaration of Helsinki.

2.2 Data collection

The following process was utilized to develop the self-administered structured questionnaires used in this study. First, we set up a research group and clarified the purpose and object of this study: that was, the effects of exposure to various environmental factors in early life on the obesity in Chinese preschool children. Second, we read a large number of domestic and foreign literature, and referred to the formative questionnaires used in past studies. In addition, from this literature review we identified various environmental factors that a child may be exposed to at various early stages of life. From these activities, we developed the initial draft of the content and structure of the questionnaire. Third, we liaised with experts from the Women's and Children's Hospital of Longhua District of Shenzhen on how to design the questionnaire's questions and the answers, and arrange them in a logical and chronological order. Fourth, as a result of these discussions, we adjusted the

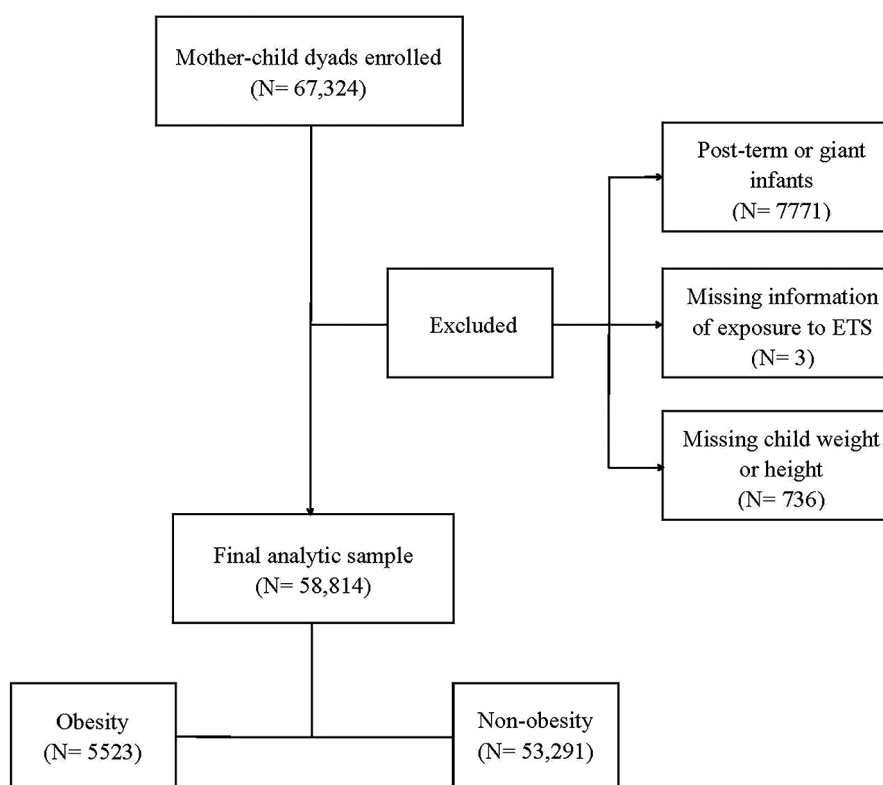


FIGURE 2
Flow chart of the analytic sample selection process.

layout of the draft questionnaire, including the adjustment of the language, the control of the time of filling in the questionnaire, and the arrangement of the cover instructions and the confidentiality explanation. Fifth, before the formal survey, we conducted a pilot survey and reliability and validity tests. We had made timely changes to the problems identified during the pilot survey, including improving the wording of questions that were poorly understood, the unreasonable option settings, and adding more comprehensive wording to improve the readers' understanding of some variables, such as the frequency and amount of exposure. Finally, after repeated discussion and modification by experts in many fields such as epidemiology, child education, child health care and health management, the final questionnaire was determined to be ready for the study.

The enrolled mothers were instructed to complete a self-administered structured questionnaire to collect the following information (1): Social-demographic characteristics of the parents' age at the childbirth, parents' education level, household income and parents' marital status; (2) Child's birth date and gender; (3) Birth-related information including gestational age and birth weight; (4) Maternal pre-pregnancy weight and height, and weight gain during pregnancy; (5) Maternal household air pollution exposure during pregnancy including environmental tobacco smoke, cooking oil fumes, mosquito coil smoke and incense burning smoke.

2.3 Prenatal ETS exposure measurement

The researchers asked the mothers the following question to measure their prenatal ETS exposure throughout pregnancy: "Did anyone in the family living with the mother smoke (including e-cigarettes) during pregnancy?" (Two answer options: "No" or "Yes".) If the answer was "yes," then prenatal ETS exposure during the pregnancy was considered to be present.

The following questions were used to measure the degree of ETS exposure during each trimester of pregnancy: (1) "During your pregnancy in 1–13 weeks (first trimester)/in 14–27 weeks (second trimester)/after 28 weeks (third trimester), how many cigarettes did others smoke per day in your home?" (Five answer options: 1 score for "1–5 cigarettes/per day", 2 score for "6–10 cigarettes/per day", 3 score for "11–15 cigarettes/per day", 4 score for "16–20 cigarettes/per day", and 5 score for ">20 cigarettes/per day".); (2) "During your pregnancy in 1–13 weeks (first trimester)/in 14–27 weeks (second trimester)/after 28 weeks (third trimester), how long were you exposed to ETS per day?" (Seven answer options: 1 score for "1–15 min/per day", 2 score for "16–30 min/per day", 3 score for "31–45 min/per day", 4 score for "46–60 min/per day", 5 score for "61–90 min/per day", 6 score for "91–120 min/per day", and 7 score for ">120 min/per day").

The score of ETS exposure in frequency of cigarettes per day was the sum of each trimester's cigarette score calculated as in question (1) above. This resulted in a possible score ranging from 0 to 15. For example, if a preschool child's mother was exposed to 1–5 cigarettes per day during the 1st trimester, 6–10 cigarettes per day during the 2nd trimester and >20 cigarettes

per day during the 3rd trimester respectively, then the preschool children's score would be "1 + 2 + 5 = 8". Similarly, the score of ETS exposure in average time per day was calculated in the same way based upon the results of question (2) above, producing a possible score ranging from 0 to 21. The ordinal rankings for the score of ETS exposure in number per day were combined to produce 3 ordinal categories (0, 1–4, ≥5) representing never, low, and high frequency of cigarette exposure. Similarly, the ordinal rankings for the score of ETS exposure in time per day were merged to produce 3 ordinal categories (0, 1–5, ≥6) representing never, low, and high average time per day of ETS exposure.

2.4 Maternal nutrients supplement measurement

The following question was asked of mothers to measure the prenatal maternal nutrients supplement exposure throughout their pregnancy (17, 35): (1) "Did you take multivitamin supplements during pregnancy?" (2) "Did you take folic acid supplements during pregnancy?" (3) "Did you take iron supplements during pregnancy?" (Two answer options: "No" or "Yes").

2.5 Obesity assessment

Well-trained nurses from Longhua Maternity & Child Healthcare Hospital took standardized measurements of the height and weight of each preschool children. A portable electronic weight scale (fractional value 0.01 kg) was placed on a level ground, and the children were asked to stand in the center of the scale without a hat, barefoot, and wearing close-fitting lightweight clothing. Once the values were stable, the nurses read and recorded the measurements, accurate to 0.1 kg. Height was measured with a column body altimeter (fractional value = 0.1 cm). The column human altimeter was placed vertically against a wall on a horizontal surface. Preschool children were asked to stand barefoot and bareheaded on a pedal, with their heels close together, feet spaced at an angle of 60°, chest raised, abdomen pulled in and eyes looking straight ahead. The nurses slid the slider to the apex of the measured child's skull and read the measurement at the same eye height as the slider.

Body mass index (BMI) was calculated by dividing weight in kilograms by height in meters squared (kg/m^2). We used BMI reference values based upon data from two national representative cross-sectional surveys: The National Growth Survey of Children under 7 years in the Nine Cities of China in 2005 and The Physical Fitness and Health Surveillance of Chinese School Students in 2005 (36, 37). The LMS method was used to smooth the BMI, with estimates of L, M, and S parameters, values of percentile and Z-score curves which were required were calculated, and then standardized growth charts were generated (38, 39). Adult cut-offs for overweight and obesity at 18 years was used to study the cut-offs for children 2–18 years of age. This study defined obesity as a BMI equal to or greater than the reference values for sex and age (36).

2.6 Confounding variables

According to the relevant literature and previous research (17, 20, 40, 41), potential confounding variables included child's sex, child's age, parents' age at the childbirth, maternal prepregnancy BMI, parents' education level, household income, prenatal exposure to cooking oil fumes, mosquito coil smoke and incense burning smoke during pregnancy, child's ETS exposure during 0–3 years of age, child's nutritional status and physical activity frequency of 0–3 years old.

2.7 Statistical analysis

The means and standard derivations (SD) were calculated to describe the continuous variables, and frequencies with percentages were calculated to describe the dichotomous or categorical variables. Student's *t*-tests or chi-square tests were used for comparing between preschool children with and without obesity.

A cross-over analysis was performed to assess the combination effects on obesity between prenatal ETS exposure and nutritional supplementation. The associations between prenatal ETS exposure and nutritional supplementation with obesity were evaluated using unconditional binary logistic regression models, after adjusting for the confounding variables. Odds ratio (OR) and 95% confidence intervals (95% CIs) were presented to show the strength of association. The multiplicative interaction was estimated by the interaction of odds ratio (IOR) in the logistic regression models. If the 95% CIs of the IOR did not span 1, then the multiplicative interaction was considered significant. Moreover, the relative excess risk due to interaction (RERI) and the attributable proportion due to interaction (AP) were calculated. The 95% CIs of RERI and AP spanned 0; the additive interaction was considered non-significant.

P-values were two-sided with alpha set at <0.05. The statistical analysis was performed with R statistical software (version 4.1.1).

3 Results

3.1 Social-demographic characteristics of participants with and without obesity

Table 1 shows the social-demographic characteristics and birth-related information of the participants. Of the included 58,814 preschool children in our study, 5,523 (9.39%) were obese. The mean age was 4.36 (SD = 0.92) years old for preschool children, 28.58 (SD = 4.39) years old for their mothers, and 30.70 (SD = 5.01) years old for their fathers. Maternal pre-pregnancy BMI was 20.68 (SD = 2.86) kg/m². The rates of preterm birth (PTB) and small for gestational age (SGA) were 8.73 and 10.17%, respectively. More than half of mothers (65.24%) and fathers (66.33%) had a college degree or higher, and 84.87% of the families had the income being ≥10,000 CNY per month.

Significant differences were observed for the following characteristics between obese and non-obese preschool children: the child's age, child's sex, preterm birth, small for gestational age, parents' marital state, parents' education level, maternal pre-pregnancy BMI, household income, being a single child, ETS exposure during 0–1 years of age, prenatal exposure to cooking oil fumes, cooking fuel type, mosquito coil smoke and incense burning smoke, child's nutritional status and physical activity frequency. More details are presented in Table 1.

3.2 Associations between prenatal ETS exposure and obesity in preschoolers

Table 2 presents the associations between prenatal ETS exposure and obesity in preschoolers. After adjusting for the potential confounding variables, compared with no prenatal ETS exposure, prenatal ETS exposure significantly increased the risk of obesity in preschoolers (AOR = 1.22, 95% CI = 1.11–1.34). Further, assessing the associations between the prenatal ETS exposure score in number, time per day and obesity in preschoolers, compared with those without the prenatal ETS exposure, participants with a low score (AOR = 1.15, 95% CI = 1.01–1.32) or a high score (AOR = 1.33, 95% CI = 1.08–1.63) on prenatal ETS exposure in number of cigarettes per day had a high risk of obesity. Similarly, participants with a low score (AOR = 1.16, 95% CI = 1.03–1.32) or a high score (AOR = 1.40, 95% CI = 1.08–1.81) of prenatal ETS exposure in average time per day also had a high risk of obesity.

Table 3 displays the effects of different trimester of prenatal ETS exposure on obesity in preschoolers. Compared to children without ETS exposure in the whole pregnancy, only those exposed to ETS in all three trimesters of pregnancy (AOR = 1.18, 95% CI = 1.04–1.34) experienced a significantly increased the risk of obesity as preschoolers. In contrast, participants who were only exposed to prenatal ETS in the 1st trimester (AOR = 1.28, 95% CI = 0.82–2.01), in the 3rd trimester (AOR = 1.44, 95% CI = 0.76–2.74), in both 1st and 2nd trimester (AOR = 1.47, 95% CI = 0.88–2.48), or in the both 1st and 3rd trimester (AOR = 1.32, 95% CI = 0.72–2.43) had elevated odds ratios that did not exhibit a statistically significant increase in the risk of obesity due to wide confidence limits presumably due to the relatively low frequency of obesity cases.

3.3 Associations between prenatal nutrients supplementation and obesity in preschoolers

After adjusting for the potential confounding variables, the results of logistic regressions showed that no prenatal multivitamin (AOR = 1.12, 95% CI = 1.05–1.20), folic acid (AOR = 1.23, 95% CI = 1.10–1.37) or iron (AOR = 1.11, 95% CI = 1.04–1.19) supplementation significantly increased the risk of obesity in preschoolers (see Table 4).

TABLE 1 Baseline characteristics of the participating children with and without obesity.

Demographic characteristics	Total	Obesity		t/χ^2	p
		Yes	No		
Number of subjects (N,%)	58,814	5,523 (9.39)	53,291 (90.61)		
Child's age [(Mean ± SD) (years)]	4.36 ± 0.92	4.45 ± 0.89	4.35 ± 0.92	−7.46	<0.001
Child's sex, N (%)				207.43	<0.001
Male	30,852	3,406 (61.67)	27,446 (51.50)		
Female	27,962	2,117 (38.33)	25,845 (48.50)		
Preterm birth, N (%)				33.10	<0.001
No	53,680	4,926 (89.19)	48,754 (91.49)		
Yes	5,134	597 (10.81)	4,537 (8.51)		
Small for gestational age (N,%)				33.40	<0.001
No	52,834	5,085 (92.07)	47,749 (89.60)		
Yes	5,980	438 (7.93)	5,542 (10.40)		
Maternal age [((Mean ± SD) (years)]	28.58 ± 4.39	28.50 ± 4.51	28.59 ± 4.38	1.331	0.183
Paternal age [((Mean ± SD) (years)]	30.70 ± 5.01	30.75 ± 5.13	30.70 ± 5.00	−0.699	0.484
Maternal marital state (N,%)				25.78	<0.001
Married	56,995	5,290 (95.78)	51,705 (97.02)		
Others ^a	1,819	233 (4.22)	1,586 (2.98)		
Paternal marital state, N (%)				22.66	<0.001
Married	56,996	5,294 (95.85)	51,702 (97.02)		
Others ^a	1,818	229 (4.15)	1,589 (2.98)		
Maternal education level, N (%)				38.55	<0.001
Junior high school or lower	8,634	938 (16.98)	7,696 (14.44)		
High school	11,810	1,178 (21.33)	10,632 (19.95)		
College or higher	38,370	3,407 (61.69)	34,963 (65.61)		
Paternal education level, N (%)				41.65	<0.001
Junior high school or lower	7,828	868 (15.71)	6,960 (13.06)		
High school	11,973	1,186 (21.47)	10,787 (20.24)		
College or higher	39,013	3,469 (62.82)	35,544 (66.70)		
Household income (CNY/month), N (%)				39.02	<0.001
0–9,999	8,893	978 (17.71)	7,915 (14.85)		
10,000–19,999	20,402	1,936 (35.06)	18,469 (34.60)		
20,000–29,999	12,777	1,139 (20.62)	11,638 (21.84)		
30,000–39,999	6,942	590 (10.68)	6,352 (11.92)		
≥40,000	9,797	880 (15.93)	8,917 (16.79)		
Maternal prepregnancy BMI [((Mean ± SD) (kg/m ²)]	20.68 ± 2.86	21.31 ± 3.10	20.62 ± 2.82	−15.82	<0.001
Single child or not, N (%)				106.64	<0.001
No	18,533	1,401 (25.37)	17,132 (32.15)		
Yes	40,281	4,122 (74.63)	36,159 (67.85)		
Environmental tobacco smoke exposure during 0–1 years of age, N (%)				3.91	0.048
No	43,515	4,026 (72.90)	39,489 (74.10)		
Yes	15,299	1,497 (27.10)	13,802 (25.90)		
Environmental tobacco smoke exposure during 1–3 years of age, N (%)				2.01	0.156
No	44,680	4,152 (75.18)	40,528 (76.05)		
Yes	14,134	1,371 (24.82)	12,763 (23.95)		
Prenatal cooking oil fumes exposure, N (%)				15.24	<0.001
No	12,358	1,273 (23.05)	11,085 (20.80)		
Yes	46,456	4,250 (76.95)	42,206 (79.20)		
Cooking fuel type, N (%)				20.04	<0.001
No	12,358	1,273 (23.05)	11,085 (20.80)		
Gas and natural gas	40,978	3,765 (68.17)	37,213 (69.83)		
Electricity	4,658	399 (7.22)	4,259 (7.99)		
Coal	471	45 (0.81)	426 (0.80)		
Others	349	41 (0.74)	308 (0.58)		
Prenatal mosquito coil smoke exposure, N (%)				25.22	<0.001
No	41,146	3,701 (67.01)	37,445 (70.27)		
Yes	17,668	1,822 (32.99)	15,846 (29.73)		
Prenatal incense burning smoke exposure, N (%)				13.55	<0.001
No	53,267	4,926 (89.19)	48,341 (90.71)		
Yes	5,547	597 (10.81)	4,950 (9.29)		

(Continued)

TABLE 1 Continued

Demographic characteristics	Total	Obesity		t/χ^2	p
		Yes	No		
Nutritional status of 0–1 year old, N (%)				34.42	<0.001
Poor	812	72 (1.31)	740 (1.39)		
General	14,868	1,218 (22.05)	13,650 (25.61)		
Well	43,134	4,233 (76.64)	38,901 (73.00)		
Nutritional status of 1–3 year old, N (%)				133.18	<0.001
Poor	943	65 (1.18)	878 (1.65)		
General	18,935	1,416 (25.64)	17,519 (32.87)		
Well	38,936	4,042 (73.18)	34,894 (65.48)		
Physical activity frequency of 0–1 year old (days/week), N (%)				58.48	<0.001
0	311	53 (0.96)	258 (0.48)		
1	2,876	340 (6.16)	2,536 (4.76)		
2–3	11,389	1,151 (20.84)	10,238 (19.21)		
4–6	15,704	1,455 (26.34)	14,249 (26.74)		
7	28,534	2,524 (45.70)	26,010 (48.81)		
Physical activity frequency of 1–3 year old (days/week), N (%)				102.91	<0.001
0	259	55 (1.00)	204 (0.38)		
1	3,532	432 (7.82)	3,100 (5.82)		
2–3	14,219	1,443 (26.13)	12,776 (23.97)		
4–6	15,474	1,387 (25.11)	14,087 (26.44)		
7	25,330	2,206 (39.94)	23,124 (43.39)		

^aIncluding unmarried, divorced, remarried, and spouse loss.

TABLE 2 The associations between prenatal ETS exposure and obesity among Chinese preschool children.

	Total (N)	Cases (n ,%)	COR (95% CI)	AOR (95% CI) ^a
Prenatal ETS exposure				
No	54,698	5,048 (9.23)	1.00	1.00
Yes	4,116	475 (11.54)	1.28 (1.16–1.42)***	1.22 (1.11–1.34)***
The score of prenatal ETS exposure in number per day				
Never	54,698	5,048 (9.23)	1.00	1.00
Low	3,084	342 (11.09)	1.23 (1.09–1.38)**	1.15 (1.01–1.32)*
High	1,032	133 (12.89)	1.46 (1.21–1.75)***	1.33 (1.08–1.63)**
p -value			<0.001	<0.001
The score of prenatal ETS exposure in time per day				
Never	54,698	5,048 (9.23)	1.00	1.00
Low	3,505	393 (11.21)	1.24 (1.11–1.39)***	1.16 (1.03–1.32)*
High	611	82 (13.42)	1.52 (1.21–1.93)***	1.40 (1.08–1.81)*
p -value			<0.001	<0.001

^aAdjusted for child’s sex, child’s age, parents’ age at the childbirth, maternal pre-pregnancy BMI, parents’ education level, household income, ETS exposure during 0–3 years of age, prenatal exposure to cooking oil fumes, mosquito coil smoke and incense burning smoke, nutritional status and physical activity frequency in models.

* $p < 0.05$.

** $p < 0.01$.

*** $p < 0.001$.

3.4 Combination effects of prenatal ETS and nutrients supplement exposure on obesity

Table 5 shows the results of crossover analysis on combination effects of maternal prenatal exposure to ETS and nutritional supplementation on obesity in preschool children. Compared to preschool children with mothers who took nutritional supplements and had no ETS during pregnancy, participants with prenatal exposure to ETS and had mothers who did not take nutritional supplements during pregnancy had the highest risk of obesity (AOR = 1.40, 95% CI = 1.21–1.62 for ETS exposure

and no multivitamin supplementation; AOR = 1.55, 95% CI = 1.12–2.14 for ETS exposure and no folic acid supplementation; and AOR = 1.38, 95% CI = 1.19–1.59 for ETS exposure and no iron supplementation). This was followed by participants with no prenatal nutritional supplementation only (AOR = 1.17, 95% CI = 1.10–1.25 for multivitamins; AOR = 1.29, 95% CI = 1.16–1.45 for folic acid; AOR = 1.15, 95% CI = 1.08–1.23 for iron), and with prenatal ETS exposure and nutritional supplementation (AOR = 1.21, 95% CI = 1.00–1.45 for ETS exposure and multivitamins supplementation; AOR = 1.19, 95% CI = 1.05–1.35 for ETS exposure and folic acid supplementation;

TABLE 3 The associations between trimester-specific ETS exposure during pregnancy and obesity among Chinese preschool children.

Trimesters of ETS exposure			Total (N)	Cases (n,%)	COR (95% CI)	AOR (95% CI) ^a
1st	2nd	3rd				
NO	NO	NO	54,698	5,048 (9.12)	1.00	1.00
YES	NO	NO	183	25 (11.01)	1.34 (0.88–2.04)	1.28 (0.82–2.01)
NO	YES	NO	33	5 (15.31)	1.49 (0.58–3.82)	0.99 (0.30–3.26)
NO	NO	YES	80	14 (9.23)	1.72 (0.98–3.04)	1.44 (0.76–2.74)
YES	YES	NO	119	19 (9.03)	1.57 (0.97–2.55)	1.47 (0.88–2.48)
YES	NO	YES	93	12 (12.77)	1.27 (0.70–2.32)	1.32 (0.72–2.43)
NO	YES	YES	121	12 (12.84)	0.98 (0.54–1.77)	0.90 (0.48–1.68)
YES	YES	YES	3,012	388 (11.44)	1.27 (1.14–1.41)***	1.18 (1.04–1.34)*

^aAdjusted for child's sex, child's age, parents' age at the childbirth, maternal pre-pregnancy BMI, parents' education level, household income, ETS exposure during 0–3 years of age, prenatal exposure to cooking oil fumes, mosquito coil smoke and incense burning smoke, nutritional status and physical activity frequency in models.

* $p < 0.05$.

*** $p < 0.001$.

TABLE 4 The associations between prenatal nutrients supplementation and obesity among Chinese preschool children.

Nutrients	Total (N)	Cases (n,%)	COR (95% CI)	AOR (95% CI) ^a
Multivitamin				
Yes	24,633	2,064 (8.38)	1.00	1.00
No	34,181	3,459 (10.12)	1.23 (1.16–1.30)***	1.12 (1.05–1.20)***
Folic acid				
Yes	54,728	4,996 (9.13)	1.00	1.00
No	4,086	527 (12.90)	1.47 (1.33–1.61)***	1.23 (1.10–1.37)***
Iron				
Yes	23,992	1,944 (8.10)	1.00	1.00
No	34,822	3,579 (10.28)	1.30 (1.20–1.37)***	1.11 (1.04–1.19)**

^aAdjusted for child's sex, child's age, parents' age at the childbirth, maternal pre-pregnancy BMI, parents' education level, household income, ETS exposure during 0–3 years of age, prenatal exposure to cooking oil fumes, mosquito coil smoke and incense burning smoke, nutritional status and physical activity frequency and other two nutrients in models.

** $p < 0.01$.

*** $p < 0.001$.

TABLE 5 The combination effects of prenatal ETS exposure and nutrients supplement on obesity among Chinese preschool children.

Prenatal ETS exposure	Nutrients supplement	Total (N)	Cases (n,%)	AOR (95% CI) ^a	IOR (95% CI) ^a	RERI (95% CI) ^a	AP (95% CI) ^a
ETS	Multivitamin						
NO	YES	23,089	1,907 (8.26)	1.00			
NO	NO	31,609	3,141 (9.94)	1.17 (1.10–1.25)***			
YES	YES	1,544	157 (10.17)	1.21 (1.00–1.45)			
YES	NO	2,572	318 (12.36)	1.40 (1.21–1.62)***	1.04 (0.87–1.24)	0.08 (0.04–0.12)	0.07 (0.04–0.10)
ETS	Folic acid						
NO	YES	50,976	4,575 (8.97)	1.00			
NO	NO	3,722	473 (12.71)	1.29 (1.16–1.45)***			
YES	YES	3,752	421 (11.22)	1.19 (1.05–1.35)**			
YES	NO	364	54 (14.84)	1.55 (1.12–2.14)**	1.01 (0.76–1.35)	0.06 (0.02–0.10)	0.06 (0.02–0.09)
ETS	Iron						
NO	YES	22,475	1,799 (8.00)	1.00			
NO	NO	32,223	3,249 (10.08)	1.15 (1.08–1.23)***			
YES	YES	1,517	145 (9.56)	1.19 (0.99–1.44)			
YES	NO	2,599	330 (12.70)	1.38 (1.19–1.59)***	1.01 (0.84–1.20)	0.07 (0.03–0.11)	0.07 (0.03–0.10)

^aAdjusted for child's sex, child's age, parents' age at the childbirth, maternal pre-pregnancy BMI, parents' education level, household income, ETS exposure during 0–3 years of age, prenatal exposure to cooking oil fumes, mosquito coil smoke and incense burning smoke, nutritional status and physical activity frequency in models.

** $p < 0.01$.

*** $p < 0.001$.

and AOR = 1.19, 95% CI = 0.99–1.44 for ETS exposure and iron supplementation). Further interaction analysis obtained significantly additive interactions between ETS exposure and the three nutrient supplements, but no multiple interactions between them.

3.5 Sensitivity analysis

We conducted sensitivity analyses after excluding participants with any prenatal exposure to cooking fuel with coal, mosquito coil smoke and incense burning smoke ($n = 19,862$). The results of the sensitivity analyses were similar to the aforementioned findings. More details are presented in [Supplementary Tables S1–S4](#).

4 Discussion

To our best knowledge, this is the first study on the combination effects of maternal prenatal ETS exposure and prenatal nutrients supplementation on obesity in Chinese preschool children. Our study found that prenatal exposure to ETS during pregnancy was significantly associated with the increased risk of obesity in preschoolers. The strength of this association increased with the average time of daily exposure to ETS and the average number of lit cigarettes exposed to each day during pregnancy. We propose that the 1st trimester might be the critical period for prenatal ETS exposure increasing the risk of preschoolers' obesity. In addition, we also found that mothers not taking multivitamin, folic acid and iron supplementation during pregnancy had children with an increased risk of obesity. Furthermore, we discovered additive interactive effects between prenatal ETS exposure and no maternal multivitamin, folic acid and iron supplementation in pregnancy on the risk of obesity in preschoolers.

4.1 Associations between prenatal ETS exposure and obesity in preschoolers

Several previous studies have indicated that maternal exposure to tobacco smoke during pregnancy increases the risk of excess weight in children. For example, the CESAR study in the UK showed a positive association between maternal smoking during pregnancy and their child being overweight, with a pooled odds ratio of 1.26 (95% CI = 1.03–1.55) (42). Similarly, a Canadian study found that children born to active smoking mothers had higher BMIs at ages 2 and 3 than children born to non-smoking mothers (43). In addition, two previous studies suggested that prenatal nicotine exposure had a positive effect on the risk of obesity (33, 44). In line with these findings, our study showed that maternal ETS exposure during the pregnancy was associated with the presence of obesity in preschool children. Interestingly, using a cross-over analysis we found that exposure to ETS during the 1st trimester (the 1st trimester only, both the 1st and 2nd trimester, both the 1st and 3rd trimester marginally significantly and the all three trimesters of pregnancy significantly) increased the risk of preschoolers' obesity (see [Table 3](#)), which suggests

that the 1st trimester might be the critical period for the detrimental effect of prenatal ETS exposure on children's obesity (45). Similarly, several prior studies also found that mothers who smoked in the 1st trimester or throughout pregnancy had a higher risk of obesity in their children (44, 46).

Possible mechanisms for prenatal ETS exposure affecting childhood obesity are as follows. First, prenatal exposure to ETS can alter placenta weight (47), structure (48) and blood vessel function (49). The harmful effects of tobacco smoke are mainly mediated through the release of nicotine and carbon monoxide (CO) (50). Among them, nicotine and CO can all easily cross the placental barrier. Several studies have reported that exposure to nicotine in the mother's body can result in significantly higher levels of nicotine in the fetal blood than in the maternal blood (51, 52). Nicotine can cause uterine blood vessels to constrict and placental blood vessel resistance to increase by inducing the release of catecholamines (53) and reducing the release of vasodilators such as nitric oxide (NO) (54) from the mother. In addition, CO in tobacco smoke can increase the level of carboxyhemoglobin in the umbilical cord arteries, which aggravates fetal hypoxia (54, 55). This can eventually lead to intrauterine growth restriction (IUGR) and low birth weight (LBW), which was called thrifty energy phenotype (15). According to postnatal catch-up growth theory, the mismatch between IUGR and postnatal excess nutrition may lead to rapid weight gain, which in turn leads to the occurrence of overweight and obesity in early childhood (16). Second, epigenetic changes, especially DNA methylation, are also possible mechanisms by which ETS causes childhood obesity. For example, Novakovic et al. (56) found that hypomethylation of the CpG sites of the *AHRR* gene in the umbilical cord blood of the offspring of smokers persisted until 18 months of age even without exposure to tobacco smoke after birth. *AHRR* gene serves not only to regulate fat metabolism involved in mediating xenobiotic metabolism but is also involved in cell growth and differentiation, further influencing fetal birth weight (57). Our previous study (58) also found that *AHRR* DNA methylation of cord and maternal blood might be associated with LBW. In addition, air pollutants can enter and cross the placenta, so they may have an impact on the health of offspring through changes in placental epigenetic patterns (59–61). Indeed, mothers who lived near major roads, an indicator of traffic-related air pollution, have shown decreased levels of placental *LINE1* (62). Of course, due to the large number of chemicals contained in tobacco smoke, the further research is necessary for fully understanding the mechanisms of prenatal ETS exposure leading to offspring's obesity in the later life.

4.2 Associations between prenatal nutrients supplement and obesity in preschoolers

Maternal nutritional supplementation during pregnancy can also affect the risk of childhood obesity. For example, a Chinese study suggested that pregnant women who take multi-micronutrient (MM) during pregnancy, including iron, folic acid

(FA), multivitamin, zinc supplements, and maternal formula, have a lower risk of their offspring being obese at birth and overweight at 3 months of age (63). Similarly, a study in America showed that maternal vitamin B12 (VB₁₂) and B6 (VB₆) concentrations were associated with weight gain in offspring from birth to age 3 (64). In addition, the results of a rat experiment indicated that maternal VB₁₂ deficiency led to high triglyceride and cholesterol levels in offspring (65). Moreover, other studies have found that maternal vitamin D (VD) deficiency can also lead to obesity and other obesity-related diseases in offspring later in life (66, 67). Our previous study found that prenatal FA supplementation (OR = 0.72, 95% CI = 0.55–0.93) was associated with a lower risk of obesity in preschoolers (17). Similarly, we also found that no maternal multivitamin, folic acid and iron supplementation during pregnancy significantly increased the risk of obesity in preschool children.

Regarding the potential mechanism, DNA methylation may play a key role in the effect of prenatal nutrients supplement on childhood obesity. In the one-carbon cycle, FA acts as a carbon carrier and VB₁₂ as a co-factor of methionine synthase. Both FA and VB₁₂ are important regulators of DNA methylation and play an important role in early life development (68). There is growing evidence that FA and VB₁₂ changes the methylation status of genes associated with offspring growth (*IGF2*), metabolism (*RXRA*), and appetite control (*LEP*) through consumption of methyl donors, ultimately affecting offspring health (69, 70). For example, *LEP* produces the hormone leptin, which is involved in regulating energy metabolism, making the children eat less, increasing energy release, and inhibiting fat cell synthesis to lose weight (70). *LEP* gene promoter sequence in the cord blood of obese children showed a hypomethylated state (71). At the same time, iron also plays an important role in FA metabolism and one-carbon cycle. When the mothers took FA and iron together during the pregnancy, iron can affect the transcription of FA transporters (72) and regulate the metabolism of one-carbon (73). The mechanism of VD deficiency leading to childhood obesity includes affecting the process of fat formation in offspring, the secretion of adipocytokines, inflammatory response, oxidative stress, etc. (67, 74). An experimental study on rats (75) had found that maternal VD deficiency during pregnancy would promote the proliferation and differentiation of adipocytes in male offspring, and eventually appear obese phenotypes, including an increase in body weight and fat mass. The emergence of this phenotype was likely related to changes in promoter and CpG island methylation levels of several genes, such as the hypermethylation of *Vldlr* gene and the demethylation of *Hif1a* gene.

4.3 Combination effects of prenatal ETS exposure and maternal nutrients supplement during pregnancy on childhood obesity

In the present study, we explored the combination effects of prenatal ETS exposure and maternal nutritional supplementation

during pregnancy exposure on childhood obesity. We found that maternal nutritional supplementation in pregnancy might reduce the risk of preschoolers' obesity associated with prenatal ETS exposure. In line with our findings, Wang et al. reported that prenatal mercury exposure was associated with a higher risk of childhood obesity, and adequate intake of FA could reduce this risk (76). Moreover, the cross-over analysis in our study discovered the additive interaction between prenatal ETS exposure and no maternal nutrients supplement during pregnancy on the risk of childhood obesity (see Table 5). These findings suggest that prenatal exposure to ETS and nutritional supplements during pregnancy may have a combined effect on childhood obesity.

Maternal exposure to tobacco smoke during pregnancy had been associated with decreased levels of micronutrients (77, 78), particularly those that play a role in the production of methyl donors. A study in the United States (79) found reductions in one-carbon pathway micronutrients with gestational tobacco smoke exposure, including maternal FA, VB₆ and VB₁₂. We propose the possible following mechanism for the combination effects between prenatal ETS exposure and maternal nutritional supplementation in pregnancy on offspring's obesity in childhood. In general, higher air pollution exposure was associated with lower methylation of specific CpG sites in GC (61, 80, 81). However, as mentioned earlier, FA as a methyl donor, co-participates in the one-carbon cycle with the assistance of multivitamin (VB₆ and VB₁₂) and iron, and several prior studies (82, 83) found that higher FA intake was often associated with increased levels of methylation. It has been suggested that several components in tobacco smoke, such as organic nitrite, nitrous oxide, cyanate and isocyanate, increase oxidative stress and interact with FA and VB₁₂, causing the inactivation of these micronutrients (84). FA and VB₁₂ deficiencies also reduce DNA methylation via homocysteine increase, ultimately aggravating the effect of air pollution on DNA methylation (81). This was also verified in a study, which showed that maternal exposure to tobacco smoke during pregnancy was significantly associated with lower FA levels, lower VB₆ and VB₁₂ levels, and increased homocysteine levels (79, 84). Therefore, it may be reasonable to assume that the methylation process, caused by FA supplementation, may counteract the hypomethylation caused by tobacco smoke. In addition, FA could also improve the placental function through anti-inflammatory effects and reduce the risk of IUGR and LBW (85). However, due to the lack of targeted experimental studies, more research is needed to explore the combined mechanisms of ETS and nutrients supplement exposure during pregnancy leading to childhood obesity in the future.

4.4 Limitation

The findings of this study need to be interpreted in consideration of the following limitations. First, all participants were recruited from Longhua District of Shenzhen city, which might cause selection bias and limit the generalizability of our findings due to variations in prenatal ETS exposure and

nutritional supplementation practices across other areas. Second, the data on ETS exposure in the three trimesters of pregnancy was subjectively recalled by the mother, which might result in memory recall bias and social desirability bias. Third, considering the low rate of active smoking among women of reproductive age in China (86), data on active smoking was not collected. Fourth, unfortunately we did not collect any detailed information about the dose and frequency of maternal nutritional supplementation, or information on the specific vitamins that comprised the multivitamin used by the mothers during pregnancy. This might limit our ability to assess the associations between mothers consuming nutritional supplements during pregnancy and obesity in preschoolers. Fifth, although a range of covariates were included, there were still unmeasured potential confounding variables such as paternal obesity, parental and children diet, household ventilation conditions and ETS exposure in public places during pregnancy which might influence the findings. Sixth, cross-sectional studies limit any conclusions on the causal relationship for the combination effects of maternal prenatal ETS exposure and nutritional supplementation on obesity in preschool children, so the prospective birth cohort studies are needed to determine their causal relationship.

5 Conclusions

In conclusion, our study found that maternal prenatal ETS exposure can increase the risk of childhood obesity, while maternal nutritional supplementation during pregnancy can reduce the risk of obesity. Moreover, the combination of prenatal ETS exposure and a lack of maternal nutritional supplementation during pregnancy may jointly affect childhood obesity. These findings support the need for public health interventions to reduce maternal prenatal exposure to ETS and encourage appropriate consumption of multivitamins, folic acid and iron supplements by mothers during pregnancy.

Data availability statement

The datasets presented in this article are not readily available because the datasets generated and/or analyzed during the current study are not publicly available due to privacy protection of the participants, but are available from the corresponding author on reasonable request.

Ethics statement

The studies involving humans were approved by the Institutional Review Board of the School of Public Health, Sun Yat-sen University, Guangzhou, China (protocol code: No.2015-016). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

W-XZ: Writing – original draft, Visualization, Methodology, Formal Analysis, Data curation, Conceptualization. ES: Writing – review & editing, Supervision. W-KY: Writing – review & editing, Supervision, Project administration, Funding acquisition. X-NY: Writing – review & editing, Project administration, Investigation. G-MW: Writing – review & editing, Project administration, Investigation. D-LS: Writing – review & editing, Project administration, Investigation. D-XX: Writing – review & editing, Project administration, Investigation. Y-FZ: Writing – review & editing, Project administration, Investigation. W-QC: Writing – review & editing, Supervision, Resources, Project administration, Methodology, Funding acquisition, Conceptualization.

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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.

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Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fped.2024.1423556/full#supplementary-material>

References

1. NCD Risk Factor Collaboration (NCD-RisC). 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
2. Ma SJ, Zhang YQ, 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. *Zhonghua Yu Fang Yi Xue Za Zhi*. (2020) 54:133–8. doi: 10.3760/cma.j.issn.0253-9624.2020.02.004
3. Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of childhood and adult obesity in the United States, 2011–2012. *J Am Med Assoc*. (2014) 311:806–14. doi: 10.1001/jama.2014.732
4. Simmonds M, Llewellyn A, Owen CG, Woolacott N. Predicting adult obesity from childhood obesity: a systematic review and meta-analysis. *Obes Rev*. (2016) 17:95–107. doi: 10.1111/obr.12334
5. Weihrauch-Blüher S, Wiegand S. Risk factors and implications of childhood obesity. *Curr Obes Rep*. (2018) 7:254–9. doi: 10.1007/s13679-018-0320-0
6. Weihrauch-Blüher S, Schwarz P, Klusmann JH. Childhood obesity: increased risk for cardiometabolic disease and cancer in adulthood. *Metabolism*. (2019) 92:147–52. doi: 10.1016/j.metabol.2018.12.001
7. Smith JD, Fu E, Kobayashi MA. Prevention and management of childhood obesity and its psychological and health comorbidities. *Annu Rev Clin Psychol*. (2020) 16:351–78. doi: 10.1146/annurev-clinpsy-100219-060201
8. Lee EY, Yoon KH. Epidemic obesity in children and adolescents: risk factors and prevention. *Front Med*. (2018) 12:658–66. doi: 10.1007/s11684-018-0640-1
9. Bianco-Miotto T, Craig JM, Gasser YP, van Dijk SJ, Ozanne SE. Epigenetics and DOHaD: from basics to birth and beyond. *J Dev Orig Health Dis*. (2017) 8:513–9. doi: 10.1017/S2040174417000733
10. Hoffman DJ, Powell TL, Barrett ES, Hardy DB. Developmental origins of metabolic diseases. *Physiol Rev*. (2021) 101:739–95. doi: 10.1152/physrev.00002.2020
11. Vrijheid M, Fossati S, Maitre L, Márquez S, Roumeliotaki T, Agier L, et al. Early-life environmental exposures and childhood obesity: an exposome-wide approach. *Environ Health Perspect*. (2020) 128:67009. doi: 10.1289/EHP5975
12. Ben-Shlomo Y, Kuh D. A life course approach to chronic disease epidemiology: conceptual models, empirical challenges and interdisciplinary perspectives. *Int J Epidemiol*. (2002) 31:285–93. doi: 10.1093/ije/31.2.285
13. Hsu CN, Hou CY, Hsu WH, Tain YL. Early-life origins of metabolic syndrome: mechanisms and preventive aspects. *Int J Mol Sci*. (2021) 22:11872. doi: 10.3390/ijms222111872
14. Dulloo AG. Regulation of fat storage via suppressed thermogenesis: a thrifty phenotype that predisposes individuals with catch-up growth to insulin resistance and obesity. *Horm Res*. (2006) 65(Suppl 3):90–7. doi: 10.1159/000091512
15. Spranger L, Weiner J, Bredow J, Zeitl U, Grittnner U, Boschmann M, et al. Thrifty energy phenotype predicts weight regain in postmenopausal women with overweight or obesity and is related to FGFR1 signaling. *Clin Nutr*. (2023) 42:559–67. doi: 10.1016/j.clnu.2023.02.020
16. Gluckman PD, Hanson MA, Low FM. Evolutionary and developmental mismatches are consequences of adaptive developmental plasticity in humans and have implications for later disease risk. *Philos Trans R Soc Lond B Biol Sci*. (2019) 374:1–8. doi: 10.1098/rstb.2018.0109
17. Lu Q, Strodl E, Liang Y, Huang L, Hu B, Chen W. Joint effects of prenatal folic acid supplement with prenatal multivitamin and iron supplement on obesity in preschoolers born SGA: sex specific difference. *Nutrients*. (2023) 15:380. doi: 10.3390/nu15020380
18. Belkacemi L, Nelson DM, Desai M, Ross MG. Maternal undernutrition influences placental-fetal development. *Biol Reprod*. (2010) 83:325–31. doi: 10.1095/biolreprod.110.084517
19. Sun C, Groom KM, Oyston C, Chamley LW, Clark AR, James JL. The placenta in fetal growth restriction: what is going wrong? *Placenta*. (2020) 96:10–8. doi: 10.1016/j.placenta.2020.05.003
20. Hu P, Fan L, Ding P, He Y, Xie C, Niu Z, et al. Association between prenatal exposure to cooking oil fumes and full-term low birth weight is mediated by placental weight. *Environ Res*. (2018) 167:622–31. doi: 10.1016/j.envres.2018.08.014
21. Hu P, Wang C, Ding P, He YH, Xie C, Tian FY, et al. Placental weight mediates association between prenatal exposure to cooking oil fumes and preterm birth. *J Matern Fetal Neonatal Med*. (2022) 35:7248–58. doi: 10.1080/14767058.2021.1946783
22. Carvalho MA, Bernardes LS, Hettfleisch K, Pastro LD, Vieira SE, Saldiva SR, et al. Associations of maternal personal exposure to air pollution on fetal weight and fetoplacental Doppler: a prospective cohort study. *Reprod Toxicol*. (2016) 62:9–17. doi: 10.1016/j.reprotox.2016.04.013
23. Ouidir M, Tekola-Ayele F, Canty T, Grantz KL, Sciscione A, Tong D, et al. Acute ambient air pollution exposure and placental Doppler results in the NICHD fetal growth studies—singleton cohort. *Environ Res*. (2021) 202:111728. doi: 10.1016/j.envres.2021.111728
24. Jackson DB, Testa A. The intersection between adverse childhood experiences and environmental tobacco smoke in U.S. households with children. *Nicotine Tob Res*. (2021) 23:732–40. doi: 10.1093/ntr/ntaa220
25. US CFDC, US NCFC, US OOSA. *How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease: A Report of the Surgeon General*. Atlanta (GA): Centers for Disease Control and Prevention (US) (2010).
26. Moon SY, Kim TW, Kim YJ, Kim Y, Kim SY, Kang D. Public facility utility and third-hand smoking exposure without first and second-hand smoking according to urinary cotinine level. *Int J Environ Res Public Health*. (2019) 16:855. doi: 10.3390/ijerph16050855
27. Matt GE, Quintana P, Zakarian JM, Hoh E, Hovell MF, Mahabee-Gittens M, et al. When smokers quit: exposure to nicotine and carcinogens persists from thirdhand smoke pollution. *Tob Control*. (2016) 26:548–56. doi: 10.1136/tobaccocontrol-2016-053119
28. Crane JM, Keough M, Murphy P, Burrage L, Hutchens D. Effects of environmental tobacco smoke on perinatal outcomes: a retrospective cohort study. *BJOG*. (2011) 118:865–71. doi: 10.1111/j.1471-0528.2011.02941.x
29. Wahabi HA, Alzeidan RA, Fayed AA, Mandil A, Al-Shaikh G, Esmail SA. Effects of secondhand smoke on the birth weight of term infants and the demographic profile of Saudi exposed women. *BMC Public Health*. (2013) 13:341. doi: 10.1186/1471-2458-13-341
30. Aurrekoetxea JJ, Murcia M, Rebagliato M, Fernández-Somoano A, Castilla AM, Guxens M, et al. Factors associated with second-hand smoke exposure in non-smoking pregnant women in Spain: self-reported exposure and urinary cotinine levels. *Sci Total Environ*. (2014) 470–471:1189–96. doi: 10.1016/j.scitotenv.2013.10.110
31. Wang XY, Juan J, Zhou M, Wang X, Zhang XS. Association of maternal age at delivery with pregnancy complications and pregnancy outcomes in 15 urban hospitals. *Chin J Woman Child Health Res*. (2022) 33:24–30. doi: 10.3390/j.issn.1673-5293.2022.11.005
32. Liang Y, Strodl E, Lu Q, Liu X, Hu B, Chen W. Combined effect of prenatal mosquito coil smoke exposure and early postnatal nutritional status on obesity among preschoolers. *Atmosphere*. (2023) 14:1004. doi: 10.3390/atmos14061004
33. Ino T. Maternal smoking during pregnancy and offspring obesity: meta-analysis. *Pediatr Int*. (2010) 52:94–9. doi: 10.1111/j.1442-200X.2009.02883.x
34. Durmus B, Kruithof CJ, Gillman MH, Willemsen SP, Hofman A, Raat H, et al. Parental smoking during pregnancy, early growth, and risk of obesity in preschool children: the generation R study. *Am J Clin Nutr*. (2011) 94:164–71. doi: 10.3945/ajcn.110.009225
35. Xiang C, Luo J, Yang G, Sun M, Liu H, Yang Q, et al. Dietary supplement use during pregnancy: perceptions versus reality. *Int J Environ Res Public Health*. (2022) 19:4063. doi: 10.3390/ijerph19074063
36. Li H, Ji CY, Zong XN, Zhang YQ. Body mass index growth curves for Chinese children and adolescents aged 0 to 18 years. *Zhonghua Er Ke Za Zhi*. (2009) 47:493–8. doi: 10.3760/cma.j.issn.0578-1310.2009.07.004
37. Li H, Zhang X. Reference data of body mass index (BMI) for Chinese children from birth to 7 years. *Chin J Child Health Care*. (2004) 12:8–11.
38. Ghouli H, Ben KW, Ouerghi N, Zouaoui M, Dridi A, Gmada N, et al. Body mass index reference curves for Tunisian children. *Arch Pediatr*. (2018) 25:459–63. doi: 10.1016/j.arcped.2018.09.005
39. Tambalis KD, Panagiotakos DB, Arnaoutis G, Psarra G, Maraki M, Mourtakos S, et al. Establishing cross-sectional curves for height, weight, body mass index and waist circumference for 4- to 18-year-old Greek children, using the lambda mu and sigma (LMS) statistical method. *Hippokratia*. (2015) 19:239–48.
40. Yang J, Strodl E, Wu C, Yin X, Wen G, Sun D, et al. Association between environmental tobacco smoke exposure in early life and autistic-like behaviors in Chinese preschoolers. *J Psychosom Res*. (2022) 152:110680. doi: 10.1016/j.jpsychores.2021.110680
41. Liu X, Strodl E, Wu C, Huang L, Yin X, Wen G, et al. Critical window for the association between prenatal environmental tobacco smoke exposure and preterm birth. *Environ Res*. (2022) 212:113427. doi: 10.1016/j.envres.2022.113427
42. Gorog K, Pattenden S, Antova T, Niciu E, Rudnai P, Scholtens S, et al. Maternal smoking during pregnancy and childhood obesity: results from the CESAR study. *Matern Child Health J*. (2011) 15:985–92. doi: 10.1007/s10995-009-0543-5
43. Braun JM, Daniels JL, Poole C, Olshan AF, Hornung R, Bernert JT, et al. Prenatal environmental tobacco smoke exposure and early childhood body mass index. *Paediatr Perinat Epidemiol*. (2010) 24:524–34. doi: 10.1111/j.1365-3016.2010.01146.x

44. Banderali G, Martelli A, Landi M, Moretti F, Betti F, Radaelli G, et al. Short and long term health effects of parental tobacco smoking during pregnancy and lactation: a descriptive review. *J Transl Med.* (2015) 13:327. doi: 10.1186/s12967-015-0690-y
45. Kuh D, Ben-Shlomo Y, Lynch J, Hallqvist J, Power C. Life course epidemiology. *J Epidemiol Community Health.* (2003) 57:778–83. doi: 10.1136/jech.57.10.778
46. Ko TJ, Tsai LY, Chu LC, Yeh SJ, Leung C, Chen CY, et al. Parental smoking during pregnancy and its association with low birth weight, small for gestational age, and preterm birth offspring: a birth cohort study. *Pediatr Neonatol.* (2014) 55:20–7. doi: 10.1016/j.pedneo.2013.05.005
47. Ghasemi-Tehrani H, Fallah S, Mozafarian N, Miranzadeh S, Sadeghi S, Azidhak A. Effect of exposure to air pollution on placental weight in Isfahan-Iran. *J Family Reprod Health.* (2017) 11:90–6.
48. Soto SF, Melo JO, Marchesi GD, Lopes KL, Veras MM, Oliveira IB, et al. Exposure to fine particulate matter in the air alters placental structure and the renin-angiotensin system. *PLoS One.* (2017) 12:e0183314. doi: 10.1371/journal.pone.0183314
49. Yue H, Ji X, Zhang Y, Li G, Sang N. Gestational exposure to PM(2.5) impairs vascularization of the placenta. *Sci Total Environ.* (2019) 665:153–61. doi: 10.1016/j.scitotenv.2019.02.101
50. Bednarczuk N, Milner A, Greenough A. The role of maternal smoking in sudden fetal and infant death pathogenesis. *Front Neurol.* (2020) 11:586068. doi: 10.3389/fneur.2020.586068
51. Luck W, Nau H, Hansen R, Steldinger R. Extent of nicotine and cotinine transfer to the human fetus, placenta and amniotic fluid of smoking mothers. *Dev Pharmacol Ther.* (1985) 8:384–95. doi: 10.1159/000457063
52. Wickström R. Effects of nicotine during pregnancy: human and experimental evidence. *Curr Neuropharmacol.* (2007) 5:213–22. doi: 10.2174/157015907781695955
53. Monheit AG, VanVunakis H, Key TC, Resnik R. Maternal and fetal cardiovascular effects of nicotine infusion in pregnant sheep. *Am J Obstet Gynecol.* (1983) 145:290–6. doi: 10.1016/0002-9378(83)90713-5
54. Morales-Prieto DM, Fuentes-Zacarias P, Murrieta-Coxa JM, Gutierrez-Samudio RN, Favaro RR, Fitzgerald JS, et al. Smoking for two- effects of tobacco consumption on placenta. *Mol Aspects Med.* (2022) 87:101023. doi: 10.1016/j.mam.2021.101023
55. Bailey LJ, Johnston MC, Billet J. Effects of carbon monoxide and hypoxia on cleft lip in A/J mice. *Cleft Palate Craniofac J.* (1995) 32:14–9. doi: 10.1597/1545-1569_1995_032_0014_eocmah_2.3.co_2
56. Novakovic B, Ryan J, Pereira N, Boughton B, Craig JM, Saffery R. Postnatal stability, tissue, and time specific effects of AHRR methylation change in response to maternal smoking in pregnancy. *Epigenetics.* (2014) 9:377–86. doi: 10.4161/epi.27248
57. Chang R, Zhang Y, Sun J, Xu K, Li C, Zhang J, et al. Maternal pre-pregnancy body mass index and offspring with overweight/obesity at preschool age: the possible role of epigenome-wide DNA methylation changes in cord blood. *Pediatr Obes.* (2023) 18:e12969. doi: 10.1111/njpo.12969
58. Tian FY, Hivert MF, Wen X, Xie C, Niu Z, Fan L, et al. Tissue differences in DNA methylation changes at AHRR in full term low birth weight in maternal blood, placenta and cord blood in Chinese. *Placenta.* (2017) 52:49–57. doi: 10.1016/j.placenta.2017.02.017
59. Ghazi T, Naidoo P, Naidoo RN, Chuturgoon AA. Prenatal air pollution exposure and placental DNA methylation changes: implications on fetal development and future disease susceptibility. *Cells.* (2021) 10:3025. doi: 10.3390/cells10113025
60. Janssen BG, Godderis L, Pieters N, Poels K, Kiciński M, Cuypers A, et al. Placental DNA hypomethylation in association with particulate air pollution in early life. *Part Fibre Toxicol.* (2013) 10:22. doi: 10.1186/1743-8977-10-22
61. Cai J, Zhao Y, Liu P, Xia B, Zhu Q, Wang X, et al. Exposure to particulate air pollution during early pregnancy is associated with placental DNA methylation. *Sci Total Environ.* (2017) 607–608:1103–8. doi: 10.1016/j.scitotenv.2017.07.029
62. Kingsley SL, Eliot MN, Whitsel EA, Huang YT, Kelsey KT, Marsit CJ, et al. Maternal residential proximity to major roadways, birth weight, and placental DNA methylation. *Environ Int.* (2016) 92–93:43–9. doi: 10.1016/j.envint.2016.03.020
63. Cheng G, Sha T, Gao X, Wu X, Tian Q, Yang F, et al. Effects of maternal prenatal multi-micronutrient supplementation on growth and development until 3 years of age. *Int J Environ Res Public Health.* (2019) 16:2744. doi: 10.3390/ijerph16152744
64. McCullough LE, Miller EE, Mendez MA, Murtha AP, Murphy SK, Hoyo C. Maternal B vitamins: effects on offspring weight and DNA methylation at genomically imprinted domains. *Clin Epigenetics.* (2016) 8:8. doi: 10.1186/s13148-016-0174-9
65. Kumar KA, Lalitha A, Pavithra D, Padmavathi IJN, Ganeshan M, Rao KR, et al. Maternal dietary folate and/or vitamin B12 restrictions alter body composition (adiposity) and lipid metabolism in Wistar rat offspring. *J Nutr Biochem.* (2013) 24:25–31. doi: 10.1016/j.jnutbio.2012.01.004
66. Wu Y, Zeng Y, Zhang Q, Xiao X. The role of maternal vitamin D deficiency in offspring obesity: a narrative review. *Nutrients.* (2023) 15:533. doi: 10.3390/nu15030533
67. Li P, Li P, Liu Y, Liu W, Zha L, Chen X, et al. Maternal vitamin D deficiency increases the risk of obesity in male offspring mice by affecting the immune response. *Nutrition.* (2021) 87–88:111191. doi: 10.1016/j.nut.2021.111191
68. Mahajan A, Sapehia D, Thakur S, Mohanraj PS, Bagga R, Kaur J. Effect of imbalance in folate and vitamin B12 in maternal/parental diet on global methylation and regulatory miRNAs. *Sci Rep.* (2019) 9:17602. doi: 10.1038/s41598-019-54070-9
69. McGee M, Bainbridge S, Fontaine-Bisson B. A crucial role for maternal dietary methyl donor intake in epigenetic programming and fetal growth outcomes. *Nutr Rev.* (2018) 76:469–78. doi: 10.1093/nutrit/nuy006
70. Pauwels S, Ghosh M, Duca RC, Bekaert B, Freson K, Huybrechts I, et al. Dietary and supplemental maternal methyl-group donor intake and cord blood DNA methylation. *Epigenetics.* (2017) 12:1–10. doi: 10.1080/15592294.2016.1257450
71. Pauwels S, Ghosh M, Duca RC, Bekaert B, Freson K, Huybrechts I, et al. Maternal intake of methyl-group donors affects DNA methylation of metabolic genes in infants. *Clin Epigenetics.* (2017) 9:16. doi: 10.1186/s13148-017-0321-y
72. Radziejewska A, Suliburska J, Kolodziejski P, Chmurzynska A. Simultaneous supplementation with iron and folic acid can affect SLC11a2 and SLC46a1 transcription and metabolite concentrations in rats. *Br J Nutr.* (2020) 123:264–72. doi: 10.1017/S0007114519002721
73. Oppenheim EW, Adelman C, Liu X, Stover PJ. Heavy chain ferritin enhances serine hydroxymethyltransferase expression and de novo thymidine biosynthesis. *J Biol Chem.* (2001) 276:19855–61. doi: 10.1074/jbc.M100039200
74. Sergeev IN. Vitamin D—cellular Ca²⁺ link to obesity and diabetes. *J Steroid Biochem Mol Biol.* (2016) 164:326–30. doi: 10.1016/j.jsbmb.2015.11.008
75. Wen J, Hong Q, Wang X, Zhu L, Wu T, Xu P, et al. The effect of maternal vitamin D deficiency during pregnancy on body fat and adipogenesis in rat offspring. *Sci Rep.* (2018) 8:365. doi: 10.1038/s41598-017-18770-4
76. Wang G, DiBari J, Bind E, Steffens AM, Mukherjee J, Bartell TR, et al. In utero exposure to mercury and childhood overweight or obesity: counteracting effect of maternal folate status. *BMC Med.* (2019) 17:216. doi: 10.1186/s12916-019-1442-2
77. Lokki AI, Heikkinen-Eloranta J, Ohman H, Heikkinen S, Surcel H, Nielsen HS. Smoking during pregnancy reduces vitamin D levels in a Finnish birth register cohort. *Public Health Nutr.* (2020) 23:1273–7. doi: 10.1017/S1368980018003932
78. Prasodjo A, Pfeiffer CM, Fazili Z, Xu Y, Liddy S, Yoltan K, et al. Serum cotinine and whole blood folate concentrations in pregnancy. *Ann Epidemiol.* (2014) 24:498–503.e1. doi: 10.1016/j.annepidem.2014.04.004
79. Joglekar R, Grenier C, Hoyo C, Hoffman K, Murphy SK. Maternal tobacco smoke exposure is associated with increased DNA methylation at human metastable epialleles in infant cord blood. *Environ Epigenetics.* (2022) 8:dvac005. doi: 10.1093/eepp/dvac005
80. Plusquin M, Guida F, Polidoro S, Vermeulen R, Raaschou-Nielsen O, Campanella G, et al. DNA methylation and exposure to ambient air pollution in two prospective cohorts. *Environ Int.* (2017) 108:127–36. doi: 10.1016/j.envint.2017.08.006
81. Yadav S, Longkumer I, Garg PR, Joshi S, Rajkumari S, Devi NK, et al. Association of air pollution and homocysteine with global DNA methylation: a population-based study from north India. *PLoS One.* (2021) 16:e0260860. doi: 10.1371/journal.pone.0260860
82. Sae-Lee C, Corsi S, Barrow TM, Kuhnle G, Bollati V, Mathers JC, et al. Dietary intervention modifies DNA methylation age assessed by the epigenetic clock. *Mol Nutr Food Res.* (2018) 62:e1800092. doi: 10.1002/mnfr.201800092
83. Gaskins AJ, Hood RB, Ford JB, Hauser R, Knight AK, Smith AK, et al. Traffic-related air pollution and supplemental folic acid intake in relation to DNA methylation in granulosa cells. *Clin Epigenetics.* (2023) 15:84. doi: 10.1186/s13148-023-01503-y
84. Tuentner A, Bautista Nino PK, Vitezova A, Pantavos A, Bramer WM, Franco OH, et al. Folate, vitamin B12, and homocysteine in smoking-exposed pregnant women: a systematic review. *Matern Child Nutr.* (2019) 15:e12675. doi: 10.1111/mcn.12675
85. Zhao M, Chen YH, Dong XT, Zhou J, Chen X, Wang H, et al. Folic acid protects against lipopolysaccharide-induced preterm delivery and intrauterine growth restriction through its anti-inflammatory effect in mice. *PLoS One.* (2013) 8:e82713. doi: 10.1371/journal.pone.0082713
86. Centers for Disease Control and Prevention (CDC). Current tobacco use and secondhand smoke exposure among women of reproductive age—14 countries, 2008–2010. *MMWR Morb Mortal Wkly Rep.* (2012) 61:877–82.



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Air pollutants and ovarian reserve: a systematic review of the evidence

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Background: Growing evidence indicates an association between ambient air pollution and decreased human reproductive potential. This study aims to systematically review the association between air pollutants and female ovarian reserve.

Methods: The literature was searched in six electronic databases through June 2024. Screening the 136 articles retrieved for inclusion criteria resulted in the selection of 15 human observational studies that evaluated the effect of environmental pollutants on ovarian reserve markers. The study protocol was registered on the International Prospective Register of Systematic Reviews (PROSPERO, registration code: CRD42023474218).

Results: The study design of the selected studies was found to be cross-sectional (2 of 15), retrospective cohort (10 of 15), prospective cohort (2 of 15), and case-control (1 of 15). The study population was distributed as follows: Asians (53%, eight studies), Americans (33%, five studies), and Europeans (14%, two studies). The main findings showed a higher body of evidence for the environmental pollutants PM_{2.5}, PM₁₀, and NO₂, while a low body of evidence for PM₁, O₃, SO₂, and a very low body of evidence for benzene, formaldehyde, and benzo(a)pyrene, yet consistently showing significant inverse association data. The overall methodological quality of the selected studies was rated moderated across the 14 domains of the National Institutes of Health (NIH) toolkit.

Conclusion: The data suggest that increased exposure to air pollutants seems to be associated with reduced ovarian reserve, with the most substantial evidence for pollutants such as PM_{2.5}, PM₁₀, and NO₂. However, more evidence is needed to draw conclusions about causality.

KEYWORDS

air pollutants, fine particulate matter, ovarian reserve, fertility, systematic review

Introduction

Public health data on air pollution from the global burden of disease (GBD) estimates 213 million disability-adjusted life years (DALYs)—equal to 0.84% of the global DALY—6.67 million deaths in 2019 (1). Much of the scientific community has supported the association between air pollution and the risk of cardiovascular (2–4), respiratory (5, 6), endocrine (7), reproductive (8), and all-cause mortality to date (9, 10). Until now, there is substantial consistency around biological mechanisms involving inflammation, oxidative stress, endocrine disruption, and epigenetic changes.

Some early studies pointed to air pollution exposure being associated with reduced fertility and a range of adverse pregnancy outcomes, such as miscarriage, preterm delivery, and stillbirth, regardless of having natural pregnancies or undergoing assisted reproductive technologies (2, 11–14). The underlying mechanism of female fertility decline due to air pollutants remains unclear. At the same time, limited evidence speculates that impaired ovarian reserve caused by oxidative stress and inflammatory response caused by air pollution may be a critical path.

The number and quality of the ovarian follicle pool are commonly referred to as ovarian reserve, which indicates a woman's reproductive potential or fertility (15). After puberty, follicle development begins under gonadotropin stimulation (16), and the entire development process mainly includes the development of a small number of primordial follicles to the antral stage and the selection of an antral follicle for growth to the preovulatory stage during each menstrual cycle (16).

In clinical settings, a common practice is to use hormonal and ultrasound markers as proxies of ovarian reserve (17, 18). In this context, ultrasound antral follicle count (AFC), serum levels of follicle-stimulating hormone (FSH), anti-Müllerian hormone (AMH), inhibin B, and E2 have been proposed as potential markers of fertility, among which AMH is considered the most sensitive and specific available marker (19, 20). Indeed, AFC results tend to have operator skill-dependent variability, whereas serum AMH is the best predictor of ovarian reserve for its high representativeness of small AFC (19, 20). Also, previous studies found that AMH levels remain stable during the menstrual cycle and can be detected on any day of the period (21).

Animal studies have documented that exposure to particulate matter 2.5 (PM_{2.5}) is associated with decreased levels of reproductive hormones and the number of antral and primordial ovarian follicles in mice. Gai and colleagues showed that PM_{2.5} reduced AMH levels and increased interleukin 6 (IL-6) and tumor necrosis factor- α (TNF- α) levels in mouse ovarian tissue (22). A significant reduction in the proportion of primordial follicles was observed by Ogliari and colleagues in mice exposed to diesel exhaust with doses equal to the average daily levels of PM_{2.5} (fine particles in ambient air 2.5 μ m or less in size) reported by the World Health Organization (23).

However, till today, the body of evidence on the association between exposure to air pollutants and markers of ovarian reserve in women lacks a synthesis of evidence. Therefore, to fill this gap, this study aimed to systematically investigate the association between major environmental air pollutants and female fertility in childbearing females.

Methods

Search strategy, study selection, and data extraction

A computer search of the literature on databases, namely, MEDLINE and the Cochrane Library, identified no previous systematic reviews on exposure to environmental pollutants and ovarian reserve in women. The present systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, adhering to the PRISMA 27-item checklist (Page et al., 2021). An *a priori* protocol for search strategy and inclusion criteria was established and registered, with no particular changes to the information provided at the time of registration on the International Prospective Register of Systematic Reviews (PROSPERO), an international prospective registry of systematic reviews (CRD42023474218). We performed separate searches in the US National Library of Medicine (PubMed), Medical Literature Analysis and Retrieval System Online (MEDLINE), EMBASE, Scopus, Ovid, and Google Scholar to find human observational studies that evaluated the effect of major environmental pollutants [PM₁, PM_{2.5}, PM₁₀, NO₂, O₃, SO₂, CO, polycyclic aromatic hydrocarbons (PAHs), black carbon, 1,3-butadiene, benzene, diesel PM, formaldehyde, methylene chloride, and tetrachloroethylene] on female fertility expressed by recognized markers such as AMH, poor ovarian reserve (POR), and antral follicle count (AFC). Therefore, the primary objective was to assess the amount, consistency, and direction of the association between any of these pollutants and markers of ovarian reserve. We also considered the gray literature using the vast archive of preprints¹ the study selection phase and the database² to access abstracts of significant conferences and other unreviewed material.

The following criteria were applied to include various studies in the analysis: (1) human observational study; (2) reporting of the effect of environmental pollutants on women's fertility as expressed by recognized ovarian reserve markers; and (3) studies that involved women of childbearing age. Animal studies, conference abstracts, reviews, letters, editorials, nonclinical trial studies, and studies involving children and/or adolescents were excluded.

The search strategy used in PubMed and MEDLINE and adapted to the other four electronic sources included keywords such as antral follicle count, ovarian reserve, PM, black carbon, and air pollutant(s) combined through the use of Boolean indicators such as AND and OR (Table 1). The search strategy used the Boolean indicator NOT to exclude opinion articles, letters, reviews, and meta-analyses. The literature search had no time restrictions, and articles were retrieved until June 2024. Two researchers (RZ and FC) searched the articles—separately and in duplicate—reviewed the titles and abstracts of the retrieved articles, checked the full texts, and selected the articles for inclusion in the study. Interrater reliability (IRR) was used to estimate intercoder agreement and then κ statistic to measure accuracy and precision. According to PRISMA concepts and quality assessment steps, a κ coefficient of at least 0.9 was obtained in all data extraction steps (24).

¹ <https://arxiv.org/in>

² <http://www.opengrey.eu/>

Quality assessment within and across studies and overall quality assessment

The methodological quality of the included studies was independently assessed by two researchers (RZ and FC) using the National Institutes of Health Quality Assessment Toolkits for Observational Cohort and Cross-Sectional Studies (25, 26). According to the criteria given in the toolkit, the ratings—high (good), fair (moderate), or poor—were assigned to the studies. This toolkit contains 14 questions assessing several aspects associated with the risk of bias, types I and II errors, transparency, and confounding factors: study question, population, participation rate, inclusion criteria, sample size justification, time of exposure/outcome measurement, timing, exposure levels, defined exposure, blinded assessors, repeated exposure, defined outcomes, loss to follow-up, and confounding factors. Items 6, 7, and 13 did not refer to cross-sectional studies; the maximum possible scores for cross-sectional and prospective studies were 8 and 14, respectively. Disagreements on the methodological quality of the included studies (e.g., interpretation of toolkit domains, appropriateness, and response type) between the two investigators were resolved through discussion until a consensus was reached with a third investigator (RS). A modified version of the grading system, namely, Grading of Recommendations Assessment, Development, and Evaluation (GRADE) (27) was used to assess the quality of evidence of the studies included in this systematic review. The following factors were considered: strength of association between air pollutants exposure and related female fertility, methodological quality/study design, consistency, bias, precision, size, and (where possible) dose–response gradient of effect estimates in the evidence base. Evidence was graded as very low, low, moderate, and high, as in the GRADE grading system.

Results

The first systematic search of the literature yielded 321 entries. After excluding the duplicates, 136 were classified as potentially relevant and selected for the title and abstract analysis. Then, 99 were excluded for not meeting the characteristics of the approach or the review goal. After reviewing the full text of the remaining records, only 15 met the inclusion criteria and were included in the systematic review (28–42). The PRISMA flowchart illustrating the number of studies at each stage of the review is shown in Figure 1. The final study base included 15 observational studies reporting on the effect of environmental pollutants on markers of ovarian reserve in childbearing females.

The details of the study design, sample size (*N*), country, author(s) and year of publication, exclusion criteria, population age, exposure pollutant(s), outcome(s) of ovarian reserve, significant findings, and covariates considered for adjust models are provided in Table 2.

The study design of selected studies was found to be cross-sectional (2 of 15), retrospective cohort (10 of 15) (28–32, 34, 36, 38, 40–42), prospective cohort (2 of 15) (33, 39), and case–control (1 of 15) (37). The study population was distributed as follows: Asians (53%, eight studies), Americans (33%, five studies), and Europeans (14%, two studies).

TABLE 1 Search strategy used in the US national library of medicine (PubMed) and medical literature analysis and retrieval system online (MEDLINE) and adapted to the other sources, according to selected descriptors.

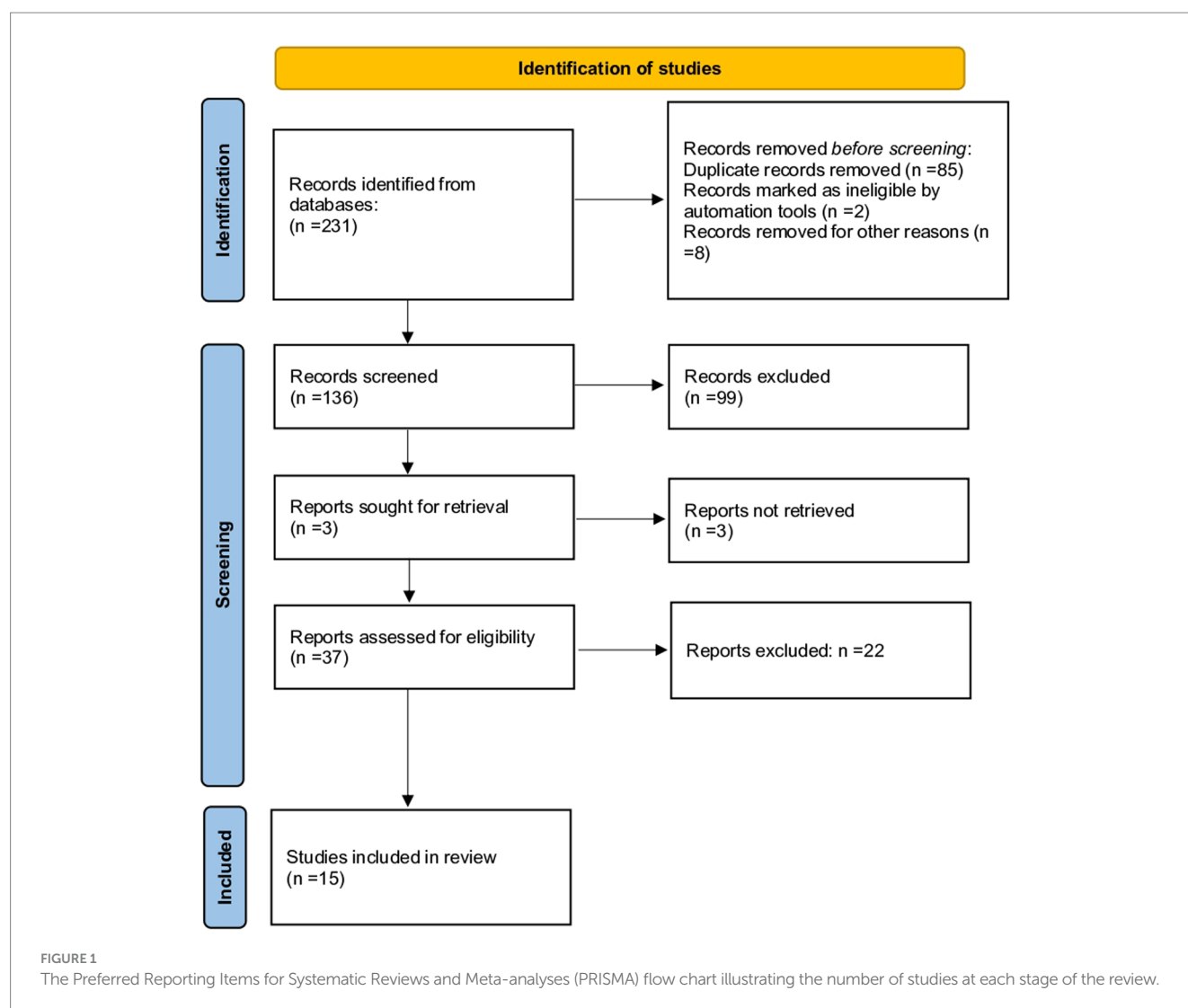
	Strategy	Descriptors used
#1	Population	(Women[tiab]) OR (female*[tiab]) OR (childbearing[tiab]) OR (fertil*[tiab])
#2	Intervention/Exposure	(Particulate matter[tiab]) OR (black carbo[tiab]) OR (air pollut*[tiab]) OR (ambient pollut*[tiab])
#3	Comparator	(Categor*[tiab]) OR (exposure[tiab]) OR (occupational exposure[tiab]) OR (tertile*[tiab]) OR (quartile*[tiab]) OR (quintile*[tiab]) OR (level*[tiab])
#4	Outcomes	(Antral follicle count[tiab]) OR (oocyt*[tiab]) OR (Follicle-stimulating hormone*[tiab]) OR (Ovarian Reserve[tiab])
#5	Exclusion keywords	(Review[tiab]) OR (systematic review[tiab]) OR (narrative review[tiab]) OR (meta-analysis[tiab]) OR (editorial[tiab]) OR (letter[tiab]) OR (commentary[tiab]) OR (perspective[tiab]) OR (book[tiab])
#6	Search strategy	#1 AND #2 AND #3 AND #4 NOT #5
	Filters:	Sort by: Most Recent. Date: 31 June 2024. Time restriction: none.

Data extraction from the selected studies resulted in a total of 14 entries of environmental pollutants (PM, PM2.5, PM10, NO₂, O₃, CO, SO₂, 1,3-butadiene, benzene, diesel PM, formaldehyde, methylene chloride, tetrachloroethylene, and benzo(a)pyrene). A majority of 65% of those resulting air pollutants, that is, PM1, PM2.5, PM10, NO₂, O₃, benzene, formaldehyde, SO₂, and benzo(a)pyrene reported on a meaningful association with marker(s) of ovarian reserve. Indeed, no significant association resulted in CO, 1,3-butadiene, diesel PM, methylene chloride, and tetrachloroethylene about ovarian reserve. For ovarian reserve markers, the majority of the selected studies considered AMH (62%) as an outcome, followed by AFC (31%), and POR (7%).

Table 3 summarizes findings on different environmental pollutants associated with female ovarian reserve items. To focus on the evidence surrounding each environmental pollutant about ovarian reserve, the available retrieved literature will be elucidated as follows.

PM2.5 and ovarian reserve

For the pollutant PM2.5, 10 studies (28, 30, 32, 33, 35, 36, 38, 39, 41, 42) were retrieved, providing moderate strength of evidence. Six of these studies considered AMH as an outcome: Pang and colleagues (28) indicated that for every increase of 10 µg/m³ in ambient PM2.5, AMH changed by −2.1% (95% confidence interval [CI]: from −3.5 to −0.6); Kim and colleagues (32) indicated that an increase in the interquartile range (IQR) in mean PM2.5 at 1 and 12 months was associated with a 3% (95% CI: from −0.07 to 0.00) and 10% (95% CI: from −0.18 to −0.01) (28, 30, 32, 33, 35, 36, 38, 39); Abareshi and colleagues (35) showed that each increase of an IQR of ambient PM2.5 was associated with a decrease in serum AMH level of −1.11 (95% CI: from −1.67 to −0.55); La Marca and colleagues (36) showed AMH levels weakly inversely correlated with PM2.5 ($\rho = -0.062$, $p = 0.021$) in the



adjusted models; Wieczorek and colleagues (42) found a negative association between PM_{2.5} exposure and AMH and AFC levels; and finally, Liu and colleagues (41) demonstrated a significant drop in AMH levels and increased risk of low AMH associated with PM_{2.5} exposure during the secondary and antral phases and 1 year before the measurement, even below the current Chinese air quality standard on PM_{2.5} concentrations (75 µg/m³). The other four studies considered AFC or decreased/poor ovarian reserve (DOR/POR) as an outcome: Wu and colleagues (30) used logistic regression models to assess the association between quartiles of PM_{2.5} exposure and POR risk finding that women in the highest quartile of PM_{2.5} exposure during 6 months (OR: 1.44, 95% CI: 1.06–1.96) and 12 months (OR: 1.54, 95% CI: 1.10–2.14) before oocytes retrieval had a higher risk of POR than those in the lowest quartile; Hood and colleagues (33) demonstrated a 2 µg/m³ increase in mean PM_{2.5} exposure to be associated with an AFC reduction of –6.2% per 2 µg/m³ (1 standard deviation (SD) increase; 95% CI: from –11.8 to –0.3) in multivariable adjusted models; Quraishi and colleagues (38) showed that women with DOR had high levels of PM_{2.5} exposure ($p = 0.003$) compared with those without DOR and with low exposure; finally, Gaskins and

colleagues (39) showed that each 2 µg/m increase in estimated PM_{2.5} exposure was associated with a reduction of –7.2% (95% CI: = from –10.4 to –3.8%) lower AFC count.

PM₁₀ and ovarian reserve

For the pollutant PM₁₀, a total of five studies were retrieved (28, 30, 32, 36, 38), providing moderate strength of evidence. Three of these studies considered AMH as an outcome: Kim and colleagues (32) found an inverse PM₁₀–AMH association by multivariable linear mixed-effects adjusted model. For each 10 µg/m³ increase in PM₁₀, AMH varied by –1.9% significantly (95% CI: from –3.3 to –0.5%); Pang and colleagues (28) developed multivariable models showing an increase in the IQR of mean PM₁₀ at 1 month was associated with a decrease (β -coefficient = –0.06, 95% CI: from –0.11 to 0.00) of AMH ratio; Quraishi and colleagues (38) found AMH levels inversely correlated with PM₁₀ ($\rho = -0.088$, $p = 0.001$), and the findings were significant for women with a reduced ovarian reserve in adjusted models. The other two studies considered POR and DOR as an outcome: La Marca and colleagues (36) used logistic regression models

TABLE 2 Description of selected studies exploring the association between air pollutants and markers of ovarian reserve in childbearing women, $N = 12$.

Author, Year	Design	Country	N	Exclusion criteria	Age (years)	Exposure	Outcome	Main findings	Covariates
Wieczorek K, 2024	Retrospective	Europe	511	Women with three spontaneous miscarriages, more than three <i>in vitro</i> fertilization procedures, chemotherapy or radiotherapy of the pelvis, premature ovarian failure, previous surgical treatment of the ovaries, polycystic ovary syndrome, cyst in the ovaries with endometrium, hyperprolactinemia, hypogonadotropic and hypogonadism were excluded.		PM2.5 SO ₂	AMH AFC	A negative association between exposure to PM2.5 and AMH levels and AFC was found. Additionally, exposure to SO ₂ in the fourth quartile of exposure compared to the first one decreases the AFC.	BMI (kg/m ²), age (years), smoking (no/yes), initial infertility diagnosis (male factor; female factor; unexplained), and the second model for age, BMI, smoking, infertility diagnosis, duration of infertility (1–3 years; 3–5 years; > 5 years); alcohol consumption (none or < 1 drink/week; 1–3 drinks/week; everyday).
Liu S, 2024	Retrospective	Asia	4,544	Diagnosis of polycystic ovary syndrome, chromosomal abnormalities, hyperprolactinemia, and women younger than 20 years or older than 49 years or with missing AMH information.	20–49	O ₃	AMH	Significantly increased risk of decreased ovarian reserve occurred with decreased AMH levels associated with environmental O ₃ exposure in Chinese women of reproductive age, especially during the secondary antral follicle stage and 1 year before measurement.	BMI, ethnicity, education, current working status, lifestyle (current smoking status), reproductive factors (infertility factors, parity, regular menstrual cycle, cycle types, and season of AMH measurement).
Liu S, 2023	Retrospective	Asia	5,189	Participants with polycystic ovary syndrome, chromosomal abnormality, hyperprolactinemia, hypothyroidism, history of ovariectomy, age < 20 or > 49 years, and incomplete residency information.	20–49	PM2.5	AMH	Significant decrease in AMH levels and increased risk of low AMH associated with PM2.5 exposure during the secondary and antral phase and 1 year before the measurement, even below the current Chinese air quality standard on PM2.5 concentrations (75 µg/m ³).	Age, BMI, education, current smoking status, employment status, residence, the duration of infertility, infertility factors, parity, and season at AMH measurement based on previous publications
Pang L, 2023	Retrospective	Asia	18,878	Incomplete medical information and exposure data, abnormal chromosomal karyotype, PCOS, ovaries surgical treatment, chemotherapy or radiotherapy, hyperprolactinemia, hypothyroidism, or immunologic diseases under RPL at least 3 times.	20–50	PM2.5 PM10 NO ₂ O ₃	AMH	Higher exposure to PM1, PM2.5, PM10 and NO ₂ were significantly associated with a substantial decline in AMH.	Age, BMI, city, educational level, pattern of menstrual cycles, parity, duration of infertility, season of AMH, calendar year of AMH measurement, short-term air pollution, short-term temperature, and short-term relative humidity.

(Continued)

TABLE 2 (Continued)

Author, Year	Design	Country	N	Exclusion criteria	Age (years)	Exposure	Outcome	Main findings	Covariates
Li H, 2023	Retrospective	America	2,447		25–42	1,3-Butadiene Benzene Diesel particulate matter Formaldehyde Methylene chloride Tetrachloroethylene	AMH	Single-exposure models showed negative associations of AMH with benzene and formaldehyde.	
Wu S, 2022	Retrospective	Asia	2,186	Women who underwent natural cycle or mild stimulation regimen, >40 years of age, used preimplantation genetic testing, used donor oocyte or sperm, had missing residential address, and had a history of ovarian surgery.	<40	PM2.5 PM10 O ₃ NO ₂ CO SO ₂	POR	There is a positive association between exposure to SO ₂ and the risk of POR, especially for women aged 30 years and unexpected POR. Moreover, women with unexpected POR and poor responders had a lower level of long-term exposure to O ₃ , compared with the matched women with NOR.	Age, BMI, smoking status, infertility cause, COH protocol, starting dose of Gn, AMH, FSH, LH, E2, and residential city.
Gregoire AM, 2021	Cross-sectional	America	883	Breast cancer, a history of PCOS, or missing information on PCOS	35–54	PM2.5 PM10 NO2	AMH	Women in the highest quartile of NO2 exposure, a traffic-related pollutant, had higher estimated AMH concentrations compared with the lowest quartile.	Age, education, BMI, and race/ethnicity.
Kim H, 2021	Retrospective	Asia	2,276	Women previously diagnosed with a chromosomal abnormality, having a history of unilateral or bilateral oophorectomy, and aged <20 or >49 years	36.6 ± 4.2	PM10 M2.5 NO ₂ CO SO ₂ O ₃	AMH	The study shows evidence indicating ambient PM10 concentration within a 1-month period is negatively associated with ovarian reserve in women with infertility; also, this negative association was additionally observed for PM2.5 within 1 month and 12 months in Seoul residents.	Age, BMI, season at the time of testing, previous smoking history.
Hood RB, 2021	Prospective	America	565	Women with incomplete scans, on Lupron (a Gonadotropin-releasing hormone antagonist), with PCOS, or missing air pollution exposure information	18–45	PM2.5	AFC	A higher exposure to PM2.5 was associated with lower AFC.	Age, BMI, smoking status, education, year, and season

(Continued)

TABLE 2 (Continued)

Author, Year	Design	Country	N	Exclusion criteria	Age (years)	Exposure	Outcome	Main findings	Covariates
Feng X, 2021	Retrospective	Asia	600	Women with COS for IVF treatment in this menstrual cycle before ovarian reserve assessment, women who did not reside in a registered residential address affiliated to Shanxi, PCOS, if one or both ovaries were difficult to visualize by using transvaginal ultrasonography scanning, hyperprolactinemia, hypothyroidism or immunologic diseases, Ovaries surgical treatment, chemotherapy, or radiotherapy, and RPL at least 3 times.	21–48	PM2.5 PM10 O ₃ NO ₂ CO SO ₂	AFC	In linear adjusted models, air pollutant SO ₂ is associated with lower AFC. Negative associations were observed between AFC and quartiles of NO ₂ levels compared with Q1.	Age, BMI, parity, and infertility diagnosis factors
Abareshi F, 2020	Cross-sectional	Asia	67	Women who did not have menses for 3 months or more, used infertility treatment, or had a history of polycystic ovarian syndrome, pelvic inflammatory disease, chemotherapy, or pelvic radiation.	32.3 ± 6.8	PM1 PM2.5 PM10	AMH	Inverse association between exposure to PM1, PM2.5, and AMH level. Direct association between exposure to PM1, PM2.5, and FSH but not significant in the fully adjusted models.	age, body mass index (BMI), education, regular menstrual cycle, parity, and smoking (yes/no).
La Marca A, 2020	Retrospective	Europe	1,463	exclusion of patients with severe chronic comorbidities reported in the reason for AMH analysis.	18–53	PM2.5 PM10 NO ₂	AMH	AMH levels were inversely related to environmental pollutants, such as PM10, PM2.5, and NO ₂ . After subdividing the dataset into quartiles for PM10 and PM2.5, the influence of age on AMH serum levels was found to be stronger than that exerted by PM. For NO ₂ quartiles, higher AMH levels were observed in the third quartile compared to the fourth quartile, even after adjustment for age, indicating a more substantial influence of NO ₂ exposure on AMH serum levels.	Age

(Continued)

TABLE 2 (Continued)

Author, Year	Design	Country	N	Exclusion criteria	Age (years)	Exposure	Outcome	Main findings	Covariates
Ye X, 2020	Case-control	Asia		Eligibility criteria for POF cases: under 40 years of age at the first time of diagnosis; amenorrhea for at least 4 months; an increased FSH level > 25 IU/L on two occasions > 4 weeks apart. Having known causes of POF (such as karyotypic abnormalities, ovarian surgery, autoimmune diseases, etc.) were excluded. Eligibility criteria for the controls included healthy women with regular menstrual cycles, without hormonal therapy in the last 6 months, and without endocrine system diseases.	33 ± 6	BaP	AMH	Among PAHs, BaP exhibited the strongest associations with these reproductive hormones in the logistic regression model. After adjustment for age, body mass index, educational levels, and household income, per one-unit increase in the log-transformed BaP (the most carcinogenic PAH congener) concentration was significantly correlated with a 2.191-fold increased risk of POF.	Age, body mass index, educational level, and household income.
Quraishi SM, 2019	Retrospective	America	7,463		34.9 ± 4.6	PM2.5 PM10 NO ₂	AFC	Women with DOR have high levels of exposure to PM2.5, PM10, and NO ₂ compared with those without DOR and who have low exposure.	Age, race, BMI, clinic location, and other infertility factors.
Gaskins AJ, 2019	Prospective	America	632	Incomplete scans, those done while the woman was on Lupron, those done on women with polycystic ovaries, repeated scans, and scans lacking complete exposure data.	18–45	PM2.5	AFC	Every 2 µg/m increase in estimated PM2.5 exposure was associated with a –7.2% lower AFC adjusting for age, body mass index, smoking status, and year and season of the count. The association of PM2.5 with AFC was stronger among women with female factor infertility (–16.3% per 2 µg/m).	Age, BMI, smoking status, and year and season.

AMH, Anti-Müllerian hormone; BMI, Body Mass Index; RPL, Recurrent Pregnancy Losses; PCOS, Polycystic Ovary Syndrome; POR, poor ovarian reserve (< 4 oocytes retrieved); COH, Controlled ovarian hyperstimulation; Gn, Gonadotropins; FSH, Follicle-stimulating hormone; LH, luteinizing hormone; E2, Estradiol; AFC, Antral Follicle Count; DOR, Diminished Ovarian Reserve.

TABLE 3 Summary of findings on different environmental pollutants associated with ovarian reserve markers in childbearing females.

Exposure	Number of evidence based studies	Strength of association	Strength of evidence (GRADE)
PM1	2	PM1–AMH association by adjusted multivariable linear mixed effect model. For every 10 µg/m ³ increment in PM1, the AMH changed by –8.8% (95% CI: from –12.1 to –5.3%), significant.	⊕ low
		In fully adjusted regression models, each one-IQR increase in PM1 was associated with –0.89 (95% confidence interval (CI): from –1.43 to –0.35, $p \leq 0.01$) decrease in serum level of AMH.	
PM2.5	10	PM2.5–AMH association by adjusted multivariable linear mixed effect model. For every 10 µg/m ³ increment in PM2.5, the AMH changed by –2.1% (95% CI: from –3.5 to –0.6%), significant.	⊕⊕ moderate
		Logistic regression models were employed to assess the association between quartiles of exposure to PM2.5 and the risk of POR. Women in the highest quartile of PM2.5 exposure during 6 months (OR: 1.44, 95% CI: 1.06–1.96) and 12 months (OR: 1.54, 95% CI: 1.10–2.14) before oocytes retrieval had a higher risk of POR than those in the lowest quartile, significant.	
		In multivariable models, an interquartile range (IQR) increase in 1- and 12-month average PM2.5 was associated with 3% (95% CI: from –0.07 to 0.00) and 10% (95% CI: from –0.18, to –0.01) lower AMH ratio, respectively.	
		In adjusted multivariable models, a 2 µg/m ³ increase in average PM2.5 exposure was associated with a 6.2% (95% CI: from –11.8 to –0.3) lower AFC.	
		In fully adjusted models, each one-IQR increase in PM2.5 was associated with a –1.11 (95% CI: from –1.67 to –0.55, $p \leq 0.01$) decrease in serum level of AMH.	
		In adjusted models, AMH levels were inversely related to PM2.5 ($\rho = -0.062$, $p = 0.021$).	
		Women with DOR had high levels of exposure to PM2.5 ($p = 0.003$) compared with those without DOR and who had low exposure.	
		Every 2-µg/m increase in estimated PM2.5 exposure was associated with a –7.2% (95% CI: from –10.4 to –3.8%) lower antral follicle count.	
		In the adjusted multivariate model, a significant association between ovarian reserve parameters and air pollution was observed in the fourth quartile of PM2.5 exposure for AFC ($p = 0.044$) and AMH ($p = 0.032$) compared with the first quartile when exposure was treated as a categorical variable.	
		When PM2.5 exposure levels were equal to the 50th percentile (32.6–42.3 µg/m ³) or more, monotonically decreased AMH levels and increased risks of low AMH were seen with increasing PM2.5 concentrations during W1 and W4 ($p < 0.05$).	
PM10	5	PM10–AMH association by adjusted multivariable linear mixed effect model. For every 10 µg/m ³ increment in PM10, the AMH changed by –1.9% (95% CI: from –3.3 to –0.5%), significant.	⊕⊕ moderate
		Logistic regression models were employed to assess the association between quartiles of exposure to PM10 and the risk of POR. Women in the third quartile of PM10 exposure for 3 months (OR: 0.82, CI: 95%: 0.70–0.97) and 6 months (OR: 0.78, 95% CI: 0.66–0.91) before oocytes retrieval had a higher risk of POR compared with those in the lowest quartile, significant.	
		In multivariable models, an IQR increase in 1-month average PM10 was associated with a decrease (β -coefficient = –0.06, 95% CI: from –0.11 to 0.00, Table 2) in the AMH ratio.	
		In adjusted models, AMH levels were inversely related to PM10 ($\rho = -0.088$, $p = 0.001$), significant.	
		Women with DOR had high levels of exposure to PM10 ($p = 0.01$) compared with those without DOR and who had low exposure.	

(Continued)

TABLE 3 (Continued)

Exposure	Number of evidence based studies	Strength of association	Strength of evidence (GRADE)
Benzene	1	Benzene-AMH association by adjusted linear models. A negative association of AMH with benzene (percentage reduction in AMH per IQR increase = 5.5, 95% CI: 1.0–9.8), significant.	⊕ very low
Formaldehyde	1	Formaldehyde-AMH association by adjusted linear models. A negative association of AMH with formaldehyde (percentage reduction in AMH per IQR increase = 6.1, 95% CI: 1.6–10), significant.	⊕ very low
O ₃	3	O ₃ -AMH association by adjusted multivariable linear mixed effect model. For every 10 µg/m ³ increment in O ₃ , the AMH changed by −4.5 (95% CI: from −7.1 to −1.9), significant	⊕ low
		Women in the third quartile of O ₃ exposure for 3 months (OR: 1.19, 95% CI: 1.00–1.42) and 12 months (OR: 1.28, 95% CI: 1.08–53) before oocytes retrieval had a higher risk of POR than those in the lowest quartile, significant.	
		In linear adjusted models, each 10 µg/m ³ increase in ozone was associated with 2.34% (0.68, 3.97%), 2.08% (0.10, 4.01%), 4.20% (1.67, 6.67%), and 8.91% (5.79, 11.93%) decreased AMH levels during W1–W4.	
SO ₂	3	Logistic regression models were employed to assess the association between quartiles of exposure to SO ₂ and the risk of POR. Women in the third quartile of SO ₂ exposure for 6 months (OR: 2.10, 95% CI: 1.67–2.64) and 12 months (OR: 2.53, 95% CI: 2.01–3.19) before oocytes retrieval had a higher risk of POR than those in the lowest quartile, significant.	⊕ low
		In linear adjusted models, every 10 µg/m ³ increase in SO ₂ concentration level during the entire development stage of antral follicle was associated with a −0.01 change in AFC (95% CI: from −0.016 to −0.002), significant.	
		In adjusted multivariate model, SO ₂ concentrations significantly decrease AFC ($p = 0.038$).	
NO ₂	5	NO ₂ -AMH association by adjusted multivariable linear mixed effect model. For every 10 µg/m ³ increment in NO ₂ , the AMH changed by −4.5 (95% CI: from −7.1 to −1.9), significant.	⊕⊕ moderate
		Multivariable-adjusted linear regression to estimate the percent change in AMH in relation to ambient residential NO ₂ (quartile exposure). Women in the highest quartile of NO ₂ exposure had higher estimated AMH concentrations (Q4 vs. Q1, 42.9%; 95% CI: from −3.4 to 111.4) compared with the lowest quartile, not significant.	
		In linear adjusted models, negative associations were observed between AFC and quartiles of NO ₂ levels: Q2 (−0.138 change, 95% CI: from −0.198 to −0.078), Q3 (−0.058 change, 95% CI: from −0.170 to 0) and Q4 (−0.068 change, 95% CI: from −0.127 to −0.009) compared with Q1, significant.	
		In adjusted models, AMH levels were inversely related to NO ₂ ($\rho = -0.111$, $p < 0.001$), significant.	
		Women with DOR had high levels of exposure to NO ₂ ($p < 0.001$) compared with those without DOR and who had low exposure.	
BaP	1	In adjusted logistic regression models, per one-unit increase in the log-transformed BaP concentration was significantly correlated with a 2.191-fold increased risk of POF (OR: 2.191, 95% CI: 1.6–2.9, $p < 0.05$).	⊕ very low

to assess the association between PM10 exposure quartiles and the risk of POR. Women in the third quartile of PM10 exposure for 3 months (OR: 0.82, 95% CI: 0.70–0.97) and 6 months (OR: 0.78, 95% CI: 0.66–0.91) before oocytes retrieval had a higher risk of POR than those in the lowest quartile; Wu and colleagues (30) showed that women with decreased ovarian reserve (DOR) had high levels of PM10 exposure ($p = 0.01$) compared with those without DOR and with low exposure.

NO₂ and ovarian reserve

For the pollutant NO₂, a total of five studies were retrieved (28, 31, 34, 36, 38), providing moderate strength of evidence. Three of these studies considered AMH as an outcome: Feng and colleagues (34) reported a significant inverse NO₂-AMH association by a multivariable linear mixed-effect adjusted model. Here, for each

10 $\mu\text{g}/\text{m}^3$ increase in NO_2 , AMH changed by -4.5% (95% CI: from -7.1 to -1.9) significantly; Gregoire and colleagues (31) performed a multivariable-adjusted linear regression to estimate the percent change in AMH in relation to residential ambient NO_2 (exposure quartile) and found that women in the highest quartile of NO_2 exposure had higher estimated AMH concentrations (Q4 vs. Q1, 42.9%; 95% CI: from -3.4 to 111.4) than the lowest quartile; however, the data lacked statistical significance; Pang and colleagues (28) demonstrated that in the adjusted models, AMH levels were inversely, statistically related to NO_2 ($\rho = -0.111$, $p < 0.001$). The other two studies considered AFC and DOR as an outcome: La Marca and colleagues (36) performed adjusted linear models observing negative, statistically significant associations between AFC and quartiles of NO_2 levels: Q2 (-0.138 change, 95% CI: from -0.198 to -0.078), Q3 (-0.058 change, 95% CI: from -0.170 to 0) and Q4 (-0.068 change, 95% CI: from -0.127 to -0.009) compared with Q1; Quraishi and colleagues (38) showed that women with DOR had high levels of NO_2 exposure ($p < 0.001$) compared with those without DOR and with low exposure, and the difference was statistically significant.

PM1 and ovarian reserve

For the pollutant PM1, only two studies were retrieved (28, 35), providing an overall low strength of evidence. Abareshi and colleagues (35) studied the PM1–AMH association by multivariable linear mixed-effects adjusted model, finding that for each 10 $\mu\text{g}/\text{m}^3$ increase in PM1, AMH varied significantly by -8.8% (95% CI: from -12.1 to -5.3%). Pang and colleagues (28) implemented fully adjusted regression models, finding that each IQR increase in ambient PM1 was associated with a -0.89 (95% CI: from -1.43 to -0.35 , $p \leq 0.01$) decrease in serum AMH level.

SO_2 and ovarian reserve

For the pollutant SO_2 , only three studies were retrieved (30, 34), providing an overall low strength of evidence. Feng and colleagues (34) employed logistic regression models to assess the association between quartiles of SO_2 exposure and the risk of POR, finding that women in the third quartile of SO_2 exposure during 6 months (OR: 2.10, 95% CI: 1.67–2.64) and 12 months (OR: 2.53, 95% CI: from 2.01 to 3.19) before oocytes retrieval had a higher risk of POR than those in the lowest quartile. Wiecek and colleagues (42), in adjusted multivariate models, found SO_2 concentrations significantly decreased AFC ($p = 0.038$). Wu and colleagues (2) employed adjusted linear models showing a 10 $\mu\text{g}/\text{m}^3$ increase in SO_2 concentration level during the entire antral follicle development phase to be statistically associated with a -0.01 change in AFC (95% CI: from -0.016 to -0.002).

O_3 and ovarian reserve

For the pollutant O_3 , only three studies were retrieved (28, 30), providing an overall low strength of evidence. Pang and colleagues (28) studied the O_3 –AMH association by multivariable linear mixed-effect adjusted model, finding that for each 10 $\mu\text{g}/\text{m}^3$ increase in O_3 , AMH varied significantly by -4.5% (95% CI, from -7.1 to -1.9). In adjusted linear models, Liu and colleagues (40) showed that each 10 $\mu\text{g}/\text{m}^3$

increase in ozone was associated with a decrease in AMH levels of 2.34% (0.68, 3.97%), 2.08% (0.10, 4.01%), 4.20% (1.67, 6.67%), and 8.91% (5.79, 11.93%) during W1–W4. Wu and colleagues (2) showed that women in the third quartile of O_3 exposure during 3 months (OR: 1.19, 95% CI: 1.00–1.42) and 12 months (OR: 1.28, 95% CI: 1.08–1.53) before oocytes retrieval had a higher risk of POR than those in the lowest quartile.

Benzene and ovarian reserve

For the pollutant benzene, only one report was retrieved (29), providing an overall very low strength of evidence. Li and colleagues studied the benzene–AMH association using adjusted linear models, finding a negative, significant association of AMH with benzene [percent reduction in AMH per increase in interquartile range (IQR) = 5.5, 95% CI: 1.0–9.8].

Formaldehyde and ovarian reserve

For the pollutant formaldehyde, only one report was retrieved (29), providing an overall very low strength of evidence. Li and colleagues studied the formaldehyde–AMH association using adjusted linear models and found a negative and statistically significant association of AMH with formaldehyde (percent reduction in AMH per increase in the IQR = 6.1, 95% CI = 1.6–10).

Benzo(a)pyrene and ovarian reserve

For the pollutant benzo(a)pyrene (BaP), only one report was retrieved (37), providing an overall very low strength of evidence. Ye and colleagues ran adjusted logistic regression models, finding each one-unit increase in log-transformed BaP concentration to be significantly related to a 2.191-fold increased risk of premature ovarian failure (POF; OR: 2.191, 95% CI: 1.6–2.9, $p < 0.05$).

Quality assessment and risk of bias

The methodological quality of the included studies was independently assessed by two researchers (RZ and FC) using the National Institutes of Health Quality Assessment Toolkits for Observational Cohort and Cross-Sectional Studies (25, 26) (Figures 2, 3). The overall methodological quality of the selected studies was rated moderate across the 14 toolkit domains. In particular, the risk was rated low for domains such as study question, population, exposure measures, outcome measures, sample size, and confounding factors across studies. Some concerns arose in some studies for domains such as inclusion criteria, participation rate, and multiple exposure. In contrast, a medium to high risk of bias was found for the domain participation rate, blinding of the outcome, and loss to follow-up across selected studies.

Discussion

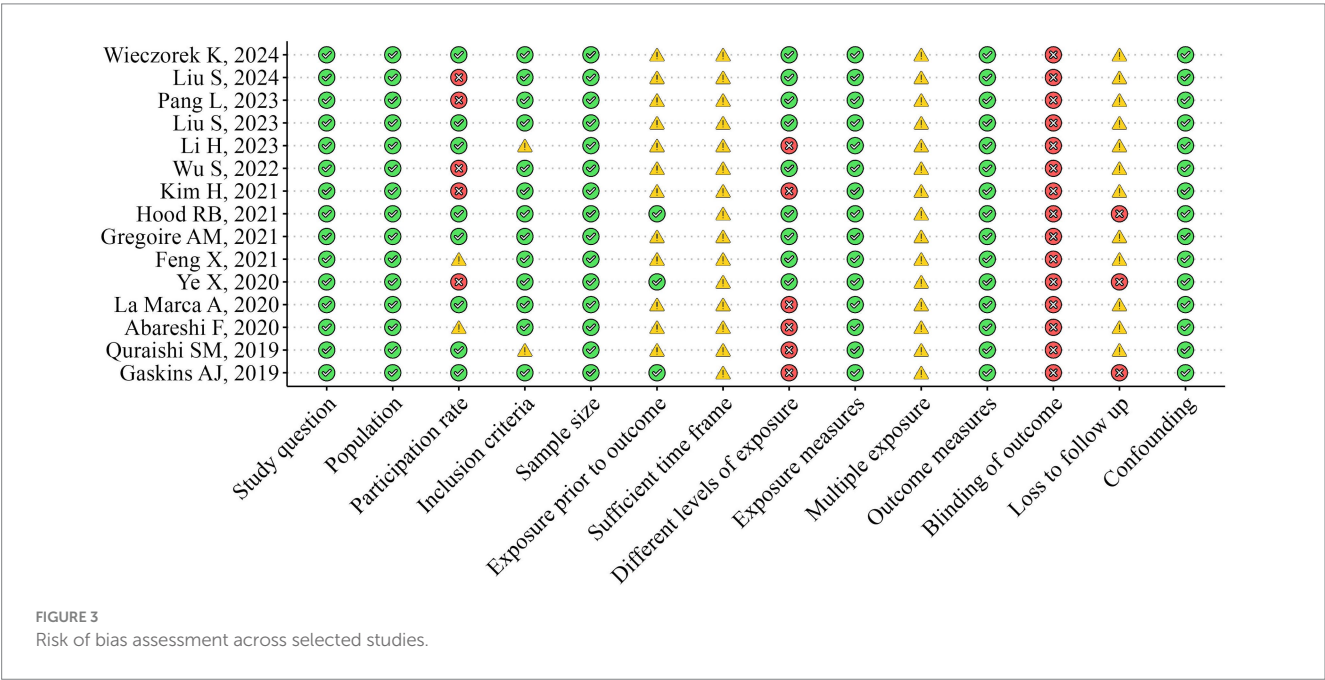
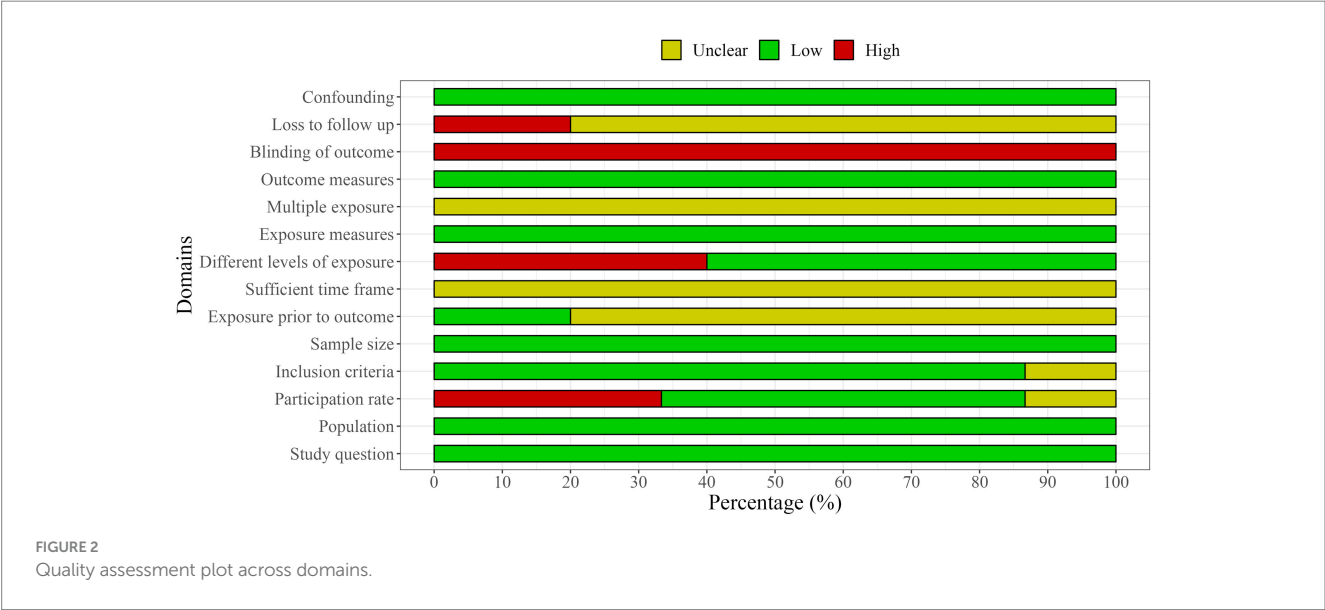
This review aimed to systematically explore the association between major environmental pollutants and markers of ovarian reserve as proxies of female fertility. After retrieving 15 original

reports from the literature screening process, we found a cluster of exposure items reporting on PM1, PM2.5, PM10, NO₂, O₃, SO₂, CO, PAHs, 1,3-butadiene, benzene, diesel PM, formaldehyde, methylene chloride, and tetrachloroethylene as environmental pollutants in relation to ovarian reserve markers as AMH, AFC, and indices of poor or reduced ovarian reserve. The main findings showed a higher body of evidence for the environmental pollutants PM2.5, PM10, and NO₂, while a low body of evidence for PM1, O₃, SO₂, and a very low body of evidence for benzene, formaldehyde, and benzo(a)pyrene, yet consistently showing significant inverse association data.

Although the mechanisms underlying the adverse health effects of exposure to air pollution have not yet been established,

inflammation and oxidative stress have been suggested to be the key pathways. Indeed, folliculogenesis has been described to be impaired by increased oxidative stress and cell apoptosis induced by ambient polluted air (43).

For the inflammatory pathway, it has been reported that PM2.5 exposure can support the enhancement of inflammatory fluid markers, as indicated by changes in IL-6 and TNF-levels (44), as well as morphological changes in ovarian tissue, such as mitochondrial structural changes, vascular congestion, and hemorrhage, triggered by the inflammation itself (39). Therefore, this response might result in ovarian damage and reduced fertility. Along these lines, findings on animal models showed that IL-6 and TNF- α concentrations and the number of apoptotic



cells were increased in ovarian tissue and histological structures of the ovary showing signs of hemorrhage and vascular congestion in mice exposed to PM_{2.5} compared with the control group (22).

For oxidative stress, reactive oxygen species (ROS) and mitochondrial DNA (mtDNA) have been shown to impact cellular aging in the human body, including in the female reproductive tract (45). Some studies have suggested that an excess of ROS May hurt ovarian aging. ROS are highly reactive oxygen-containing compounds, such as superoxide anions, hydrogen peroxide, and hydroxyl radicals. ROS are formed endogenously by oxygen metabolism during cellular processes. Usually, cells can eliminate excess ROS; however, when produced in excess, these compounds cause oxidative stress and cellular damage. High concentrations of ROS in cells lead to mitochondrial and nuclear DNA damage and apoptosis. These types of damage have been shown to affect ovarian follicle development and ovulation negatively.

Further explaining the findings, three other paths have been described by the scientific community so far, which include vitamin D3 metabolism, vitamin A metabolism, and bile acid biosynthesis. Indeed, vitamins D and A have long been implicated in human reproduction. Vitamin D signaling is directly involved in the expression of AMH, which is produced by ovarian granulosa cells and is known for its role in regulating follicular recruitment and selection. Therefore, vitamin D deficiency in females May contribute to impaired ovarian physiology through altered AMH signaling (46). Given that enzymes known to be involved in retinoid synthesis are found in the ovary, it is plausible that vitamin A deficiency May lead to deterioration in oocyte quality. Emerging evidence also suggests that air pollution May directly (through reduced ultraviolet B [UVB] exposure) and indirectly (through reduced time spent outdoors) decrease skin production of vitamin D3 (47) and reduce levels of the vitamin A precursor, β -carotene (a potent antioxidant), in the body (48).

Last, as little evidence has linked exposure to PAHs to ovarian reserve, it is useful to point out that PAHs are ubiquitous environmental pollutants worldwide and generated mainly during incomplete combustion of organic materials, including anthropogenic combustion sources (vehicle emissions, cigarette smoke, waste incineration, and so on) and natural combustion sources (volcanic activities, forest fires, etc.) (49, 50). Inhalation, ingestion, and skin contact are the main routes of exposure to PAHs. BaP, as the most carcinogenic PAH congener, has been described to retard follicular development in the ovary and decrease follicle viability, probably through activation of Aryl hydrocarbon Receptor (AhR) signaling (51). Here, reports on animal models also found that exposure to traffic-related air pollution correlated with a reduction in the number of antral follicles (23, 52, 53), yet further human research is needed to fill the gap.

Limitations

First, the ascertainment of exposure was heterogeneous among the studies. Most studies assessed air quality using a specific air monitoring station, while others estimated exposure based on

proximity to the potential source. In addition, the reference levels of each pollutant could vary between studies. These factors, together with the small number of articles found, make a quantitative approach to this problem difficult.

Conclusion

Increased exposure to air pollutants might be associated with reduced female ovarian reserve, and while the evidence is more substantial for pollutants such as PM_{2.5}, PM₁₀, and NO₂, more evidence is needed to allow conclusions about causality to be drawn. In light of these findings, global action is required for all significant modern pollutants. Global efforts May act synergistically with other international environmental policy programs to avoid any of the risks associated with this topic, such as birth rate cuts or the use of assisted reproductive technologies. A rapid and large-scale transition from all fossil fuels to clean, renewable energy is a win-win strategy to prevent pollution while mitigating climate change, thereby achieving a double benefit for the planet's health.

Data availability statement

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

Author contributions

RZ: Conceptualization, Writing – original draft, Writing – review & editing. FC: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Supervision, Writing – review & editing. TN: Project administration, Supervision, Validation, Visualization, Writing – review & editing. LL: Investigation, Writing – review & editing. IB: Project administration, Supervision, Validation, Writing – review & editing. FM: Supervision, Validation, Visualization, Writing – review & editing. GC: Supervision, Validation, Visualization, Writing – review & editing. AG: Software, Supervision, Validation, Writing – review & editing. OG: Data curation, Formal analysis, Project administration, Writing – original draft, Writing – review & editing. RS: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – review & editing.

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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.

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Supplementary material

The Supplementary material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fpubh.2024.1425876/full#supplementary-material>

References

- 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.
- Wu S, Zhang Y, Wu X, Hao G, Ren H, Qiu J, et al. Association between exposure to ambient air pollutants and the outcomes of in vitro fertilization treatment: a multicenter retrospective study. *Environ Int*. (2021) 153:106544. doi: 10.1016/j.envint.2021.106544
- de Bont J, Jaganathan S, Dahlquist M, Persson Å, Stafoggia M, Ljungman P. Ambient air pollution and cardiovascular diseases: An umbrella review of systematic reviews and meta-analyses. *J Intern Med*. (2022) 291:779–800. doi: 10.1111/joim.13467
- Murro I, Lisco G, Di Noia C, Lampignano L, Zupo R, Giagulli VA, et al. Endocrine disruptors and obesity: An overview. *Endocr Metab Immune Disord Drug Targets*. (2022) 22:798–806. doi: 10.2174/1871530322666220328122300
- Guan W-J, Zheng X-Y, Chung KF, Zhong N-S. Impact of air pollution on the burden of chronic respiratory diseases in China: time for urgent action. *Lancet*. (2016) 388:1939–51. doi: 10.1016/S0140-6736(16)31597-5
- Gordon SB, Bruce NG, Grigg J, Hibberd PL, Kurmi OP, Lam K-BH, et al. Respiratory risks from household air pollution in low and middle income countries. *Lancet Respir Med*. (2014) 2:823–60. doi: 10.1016/S2213-2600(14)70168-7
- Mousavi SE, Delgado-Saborit JM, Adivi A, Pauwels S, Godderis L. Air pollution and endocrine disruptors induce human microbiome imbalances: a systematic review of recent evidence and possible biological mechanisms. *Sci Total Environ*. (2022) 816:151654. doi: 10.1016/j.scitotenv.2021.151654
- Veras MM, Caldini EG, Dolnikoff M, Saldiva PHN. Air pollution and effects on reproductive-system functions globally with particular emphasis on the Brazilian population. *J Toxicol Environ Health B Crit Rev*. (2010) 13:1–15. doi: 10.1080/10937401003673800
- Li T, Zhang Y, Wang J, Xu D, Yin Z, Chen H, et al. All-cause mortality risk associated with long-term exposure to ambient PM in China: a cohort study. *Lancet Public Health*. (2018) 3:e470–7. doi: 10.1016/S2468-2667(18)30144-0
- Chen J, Hoek G. Long-term exposure to PM and all-cause and cause-specific mortality: a systematic review and meta-analysis. *Environ Int*. (2020) 143:105974. doi: 10.1016/j.envint.2020.105974
- Chu C, Zhu Y, Liu C, Chen R, Yan Y, Ren Y, et al. Ambient fine particulate matter air pollution and the risk of preterm birth: a multicenter birth cohort study in China. *Environ Pollut*. (2021) 287:117629. doi: 10.1016/j.envpol.2021.117629
- Li Q, Zheng D, Wang Y, Li R, Wu H, Xu S, et al. Association between exposure to airborne particulate matter less than 2.5 µm and human fecundity in China. *Environ Int*. (2021) 146:106231
- Xue T, Zhu T, Geng G, Zhang Q. Association between pregnancy loss and ambient PM using survey data in Africa: a longitudinal case–control study, 1998–2016. *Lancet Planet Health*. (2019) 3:e219–ee225. doi: 10.1016/S2542-5196(19)30047-6
- Zhang Y, Wang J, Chen L, Yang H, Zhang B, Wang Q, et al. Ambient PM and clinically recognized early pregnancy loss: a case–control study with spatiotemporal exposure predictions. *Environ Int*. (2019) 126:422–9. doi: 10.1016/j.envint.2019.02.062
- Donnez J, Dolmans M-M. Fertility preservation in women. *N Engl J Med*. (2017) 377:1657–65. doi: 10.1056/NEJMr1614676
- McGee EA, Hsueh AJ. Initial and cyclic recruitment of ovarian follicles. *Endocr Rev*. (2000) 21:200–14. doi: 10.1210/edrv.21.2.0394
- Broekmans FJ, Kwee J, Hendriks DJ, Mol BW, Lambalk CB. A systematic review of tests predicting ovarian reserve and IVF outcome. *Hum Reprod Update*. (2006) 12:685–718. doi: 10.1093/humupd/dml034
- Sharara FI, Scott RT Jr, Seifer DB. The detection of diminished ovarian reserve in infertile women. *Am J Obstet Gynecol*. (1998) 179:804–12. doi: 10.1016/S0002-9378(98)70087-0
- Fanchin R, Schonauer LM, Righini C, Guibourdenche J, Frydman R, Taieb J. Serum anti-Müllerian hormone is more strongly related to ovarian follicular status than serum inhibin B, estradiol, FSH and LH on day 3. *Hum Reprod*. (2003) 18:323–7. doi: 10.1093/humrep/deg042
- Kaya C, Pabuccu R, Satrioglu H. Serum anti-Müllerian hormone concentrations on day 3 of the in vitro fertilization stimulation cycle are predictive of the fertilization, implantation, and pregnancy in polycystic ovary syndrome patients undergoing assisted reproduction. *Fertil Steril*. (2010) 94:2202–7. doi: 10.1016/j.fertnstert.2009.12.002
- Tsepelidis S, Devreker F, Demeestere I, Flahaut A, Gervy C, Englert Y. Stable serum levels of anti-Müllerian hormone during the menstrual cycle: a prospective study in normo-ovulatory women. *Hum Reprod*. (2007) 22:1837–40. doi: 10.1093/humrep/dem101
- Gai H-F, An J-X, Qian X-Y, Wei Y-J, Williams JP, Gao G-L. Ovarian damages produced by aerosolized fine particulate matter (PM) pollution in mice: possible protective medications and mechanisms. *Chin Med J*. (2017) 130:1400–10. doi: 10.4103/0366-6999.207472
- Ogliari KS, Lichtenfels AJ, MRR DM, Ferreira AT, Dolnikoff M, PHN S. Intrauterine exposure to diesel exhaust diminishes adult ovarian reserve. *Fertil Steril*. (2013) 99:1681–1688.e2. doi: 10.1016/j.fertnstert.2013.01.103
- Belur J, Tompson L, Thornton A, Simon M. Interrater reliability in systematic review methodology: exploring variation in coder decision-making. *Sociol Methods Res*. (2021) 50:837–65. doi: 10.1177/0049124118799372
- Koren-Hakim T, Gumieiro DN, Drevet S. Quality of the selected observational study was assessed using the National Institutes of Health (NIH) quality assessment tool for observational cohort and cross-sectional studies. Criteria 1. Was the research question or objective in this paper clearly stated? Criteria 2. Was the study population clearly specified and defined? Criteria 3. Was the participation rate of eligible persons at least 50%? Criteria 4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion. Available at: <https://pdfs.semanticscholar.org/dd03/e83e07f3ac68d55542dcd5cfc6c84a02ea0.pdf> (Accessed June 25, 2024).
- Schwingshackl L, Schünemann HJ, Meerpohl JJ. Improving the trustworthiness of findings from nutrition evidence syntheses: assessing risk of bias and rating the certainty of evidence. *Eur J Nutr*. (2020) 60:2893–903. doi: 10.1007/s00394-020-02464-1
- Piggott T, Morgan RL, Cuello-Garcia CA, Santesso N, Mustafa RA, Meerpohl JJ, et al. Grading of recommendations assessment, development, and evaluations (GRADE) notes: extremely serious, GRADE's terminology for rating down by three levels. *J Clin Epidemiol*. (2020) 120:116–20. doi: 10.1016/j.jclinepi.2019.11.019
- Pang L, Yu W, Lv J, Dou Y, Zhao H, Li S, et al. Air pollution exposure and ovarian reserve impairment in Shandong province, China: the effects of particulate matter size and exposure window. *Environ Res*. (2023) 218:115056. doi: 10.1016/j.envres.2022.115056
- Li H, Hart JE, Mahalingaiah S, Nethery RC, James P, Bertone-Johnson E, et al. Environmental exposures and anti-Müllerian hormone: a mixture analysis in the nurses' health study II. *Epidemiology*. (2023) 34:150–61. doi: 10.1097/EDE.0000000000001547
- Wu S, Hao G, Zhang Y, Chen X, Ren H, Fan Y, et al. Poor ovarian response is associated with air pollutants: a multicentre study in China. *EBioMedicine*. (2022) 81:104084. doi: 10.1016/j.ebiom.2022.104084
- Gregoire AM, Upson K, Niehoff NM, Chin HB, Kaufman JD, Weinberg CR, et al. Outdoor air pollution and anti-Müllerian hormone concentrations in the sister study. *Environ Epidemiol*. (2021) 5:e163. doi: 10.1097/EE9.0000000000000163
- Kim H, Choe S-A, Kim O-J, Kim S-Y, Kim S, Im C, et al. Outdoor air pollution and diminished ovarian reserve among infertile Korean women. *Environ Health Prev Med*. (2021) 26:20. doi: 10.1186/s12199-021-00942-4
- Hood RB, James P, Fong KC, Mínguez-Alarcón L, Coull BA, Schwartz J, et al. The influence of fine particulate matter on the association between residential greenness and ovarian reserve. *Environ Res*. (2021) 197:11162. doi: 10.1016/j.envres.2021.111162
- Feng X, Luo J, Wang X, Xie W, Jiao J, Wu X, et al. Association of exposure to ambient air pollution with ovarian reserve among women in Shanxi province of North China. *Environ Pollut*. (2021) 278:116868. doi: 10.1016/j.envpol.2021.116868

35. Abareshi F, Sharifi Z, Hekmatshoar R, Fallahi M, Lari Najafi M, Ahmadi Asour A, et al. Association of exposure to air pollution and green space with ovarian reserve hormones levels. *Environ Res.* (2020) 184:109342. doi: 10.1016/j.envres.2020.109342
36. La Marca A, Spaggiari G, Domenici D, Grassi R, Casonati A, Baraldi E, et al. Elevated levels of nitrous dioxide are associated with lower AMH levels: a real-world analysis. *Hum Reprod.* (2020) 35:2589–97. doi: 10.1093/humrep/deaa214
37. Ye X, Pan W, Li C, Ma X, Yin S, Zhou J, et al. Exposure to polycyclic aromatic hydrocarbons and risk for premature ovarian failure and reproductive hormones imbalance. *J Environ Sci.* (2020) 91:1–9. doi: 10.1016/j.jes.2019.12.015
38. Quraishi SM, Lin PC, Richter KS, Hinckley MD, Yee B, Neal-Perry G, et al. Ambient air pollution exposure and fecundability in women undergoing in vitro fertilization. *Environ Epidemiol.* (2019) 3:e036. doi: 10.1097/EE9.0000000000000036
39. Gaskins AJ, Mínguez-Alarcón L, Fong KC, Abdelmessih S, Coull BA, Chavarro JE, et al. Exposure to fine particulate matter and ovarian reserve among women from a fertility clinic. *Epidemiology.* (2019) 30:486–91. doi: 10.1097/EDE.0000000000001029
40. Liu S, Liu L, Ye X, Fu M, Wang W, Zi Y, et al. Ambient ozone and ovarian reserve in Chinese women of reproductive age: identifying susceptible exposure windows. *J Hazard Mater.* (2024) 461:132579. doi: 10.1016/j.jhazmat.2023.132579
41. Liu S, Zhao J, Ye X, Fu M, Zhang K, Wang H, et al. Fine particulate matter and its constituent on ovarian reserve: identifying susceptible windows of exposure. *Sci Total Environ.* (2023) 904:166744. doi: 10.1016/j.scitotenv.2023.166744
42. Wiecek K, Szczęśna D, Radwan M, Radwan P, Polańska K, Kilanowicz A, et al. Exposure to air pollution and ovarian reserve parameters. *Sci Rep.* (2024) 14:461. doi: 10.1038/s41598-023-50753-6
43. Dechanet C, Anahory T, Mathieu Daude JC, Quantin X, Reyftmann L, Hamamah S, et al. Effects of cigarette smoking on reproduction. *Hum Reprod Update.* (2011) 17:76–95. doi: 10.1093/humupd/dmq033
44. Hajat A, Allison M, Diez-Roux AV, Jenny NS, Jorgensen NW, Szpiro AA, et al. Long-term exposure to air pollution and markers of inflammation, coagulation, and endothelial activation: a repeat-measures analysis in the multi-ethnic study of atherosclerosis (MESA). *Epidemiology.* (2015) 26:310–20. doi: 10.1097/EDE.0000000000000267
45. Rizzo A, Roscino MT, Binetti F, Sciorsci RL. Roles of reactive oxygen species in female reproduction. *Reprod Domest Anim.* (2012) 47:344–52. doi: 10.1111/j.1439-0531.2011.01891.x
46. Luk J, Torrealday S, Neal Perry G, Pal L. Relevance of vitamin D in reproduction. *Hum Reprod.* (2012) 27:3015–27. doi: 10.1093/humrep/des248
47. Mousavi SE, Amini H, Heydarpour P, Amini Chermahini F, Godderis L. Air pollution, environmental chemicals, and smoking may trigger vitamin D deficiency: evidence and potential mechanisms. *Environ Int.* (2019) 122:67–90. doi: 10.1016/j.envint.2018.11.052
48. Bernard N, Saintot M, Astre C, Gerber M. Personal exposure to nitrogen dioxide pollution and effect on plasma antioxidants. *Arch Environ Health.* (1998) 53:122–8. doi: 10.1080/00039896.1998.10545973
49. Shen G, Wang W, Yang Y, Ding J, Xue M, Min Y, et al. Emissions of PAHs from indoor crop residue burning in a typical rural stove: emission factors, size distributions, and gas-particle partitioning. *Environ Sci Technol.* (2011) 45:1206–12. doi: 10.1021/es102151w
50. Wolska L, Mechlińska A, Rogowska J, Namieśnik J. Sources and fate of PAHs and PCBs in the marine environment. *Crit Rev Environ Sci Technol.* (2012) 42:1172–89. doi: 10.1080/10643389.2011.556546
51. Sadeu JC, Foster WG. Effect of in vitro exposure to benzo[a]pyrene, a component of cigarette smoke, on folliculogenesis, steroidogenesis and oocyte nuclear maturation. *Reprod Toxicol.* (2011) 31:402–8. doi: 10.1016/j.reprotox.2010.12.006
52. Carré J, Gatimel N, Moreau J, Parinaud J, Léandri R. Does air pollution play a role in infertility?: a systematic review. *Environ Health.* (2017) 16:82. doi: 10.1186/s12940-017-0291-8
53. Veras MM, Damasceno-Rodrigues NR, Guimarães Silva RM, Scoriza JN, Saldiva PHN, Caldini EG, et al. Chronic exposure to fine particulate matter emitted by traffic affects reproductive and fetal outcomes in mice. *Environ Res.* (2009) 109:536–43. doi: 10.1016/j.envres.2009.03.006



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Knowledge, attitudes, and support needs of obstetric and gynecological nurses and midwives toward perinatal mental health disorders screening in Central China: a multicenter cross-sectional survey

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Background: The perinatal period is a time of increased vulnerability regarding maternal mental health status. Although guidelines and policies have been published for perinatal mental health disorders (PMHDs) screening in China, the knowledge, attitudes, and support needs of nurses and midwives toward implementing mental health screening programs during pregnancy remain unclear. Thus, this study aimed to investigate the knowledge of PMHDs, attitudes and support needs related to implementing mental health screening during pregnancy among obstetrics and gynecology (OB/GYN) nurses and midwives in the central region of China while identifying the related influencing factors.

Methods: A cross-sectional survey was conducted in 14 cities in Hubei, China, using convenience sampling from July to October 2023. The Chinese version of the Perinatal Mental Health Knowledge Questionnaire, the Chinese version of the Perinatal Mental Health Attitudes Scale, and the Health Care Facilities Support Needs Scale were used to investigate the PMHDs knowledge, attitudes, and support needs of OB/GYN nurses and midwives, respectively. Data were analyzed using SPSS version 27.0. Descriptive and inferential statistics were performed, with a *p*-value of <0.05 considered statistically significant.

Results: The average scores for knowledge, attitudes, and support needs were 6.09 ± 1.99 (total score: 13), 47.67 ± 8.80 (total score: 80), and 29.35 ± 4.66 (total score: 35), respectively. After adjusting for years of nursing experience and years of obstetrics and gynecology nursing experience, the multivariate logistic regression analysis indicated that having mental health-related education or work experience [adjusted OR (aOR) = 1.43, *p* = 0.01], being midwives (aOR = 1.78, *p* < 0.001), and working in specialist maternity hospitals (aOR = 1.55, *p* < 0.001) were significantly associated with higher knowledge scores; having mental health related education or work experience (aOR = 1.59, *p* = 0.014) and working in specialist maternity hospitals (aOR = 1.42, *p* < 0.01) were significantly associated with higher support needs scores.

Conclusion: OB/GYN nurses and midwives demonstrated insufficient knowledge and moderate attitudes toward PMHDs screening, and have great support need

for PMHDs screening. To address these issues, medical organizations and relevant government sectors should enhance training for nurses and midwives on PMHDs and provide professional support to promote routine maternal mental health screening programs and improve perinatal mental health outcomes.

KEYWORDS

pregnant women, perinatal mental health disorders, knowledge, attitudes, support needs, medical staff

Introduction

Maternal mental health is a key aspect of women's overall well-being. The WHO defines maternal mental health as "a state of wellbeing where a mother can cope with life" stresses, work productively, and contribute to her community (1). Life-altering moments such as pregnancy, childbirth, and early parenthood can be stressful for women (2, 3). The perinatal period, encompassing pregnancy and the first year postpartum, particularly heightens maternal mental health vulnerability due to increased external attention, hormonal fluctuations, and changes in body image (4). Globally, almost 1 in 5 women will experience a mental health condition during pregnancy or in the year after birth (5–8). Recent meta-analyses found the prevalence of perinatal depression in mainland China to be 16.3%, with 19.7% for antenatal and 14.8% for postnatal depression (9). A survey in Wuhan, Hubei Province, found depression prevalence among pregnant women to be 30.77% at 3 months, 30.91% at 6 months, and 28.88% at 12 months postpartum (10), which was high.

Among women with perinatal mental health conditions, 20% will experience suicidal thoughts or engage in self-harm, about 20% of women may have suicidal thoughts or self-harm (11). Neglecting women's mental health affects both their well-being and infants' development (2). The adverse effects of poor perinatal mental health disorders (PMHDs) on the fetus may continue into childhood, increasing the risk of cognitive, motor, and emotional problems (12). Early identification and intervention of PMHDs can mitigate the risks to both mothers and babies (13).

The UK's National Institute for Health and Clinical Excellence and the American Psychiatry Association recommend screening all women for anxiety and depression during pregnancy (14, 15). PMHDs screening has implemented in developed countries like the UK, US, and Australia (16–18). However, data showed that under 20% of women are assessed for mental health concerns during this period. Of less than 20% who screened positive for depression, only half received follow-up care, which reflects that healthcare providers may not be engaged in the important task of formally screening their pregnant and postpartum patients for mental health risks or providing referrals for mental health treatment (16).

Currently, there is no unified standard for who should conduct psychological screening for pregnant women. In Western public health systems, midwives play a key role in maternal mental health, leading to relevant studies (19). For example, Hauck et al. (20) and Noonan et al.

(21) surveyed midwives' knowledge, attitudes, and needs regarding PMHDs in Australia and Ireland, respectively. In China, obstetrics and gynecology (OB/GYN) nurses and midwives typically assume different but complementary roles in PMHDs management (22). Nurses need to assess the mental health of pregnant and postpartum women, provide support, educate about PMHDs, and assist in treatment while midwives focus primarily on women's physiological health and childbirth management while monitor their emotional changes and guide them to seek professional mental health help when needed. Failing to understand their knowledge and needs may lead to delayed PMHD identification and treatment. The knowledge, attitudes, and practice model suggest that knowledge and attitudes influence behavior (23). In practice, knowledge and attitudes affect OB/GYN nurses' and midwives' involvement in perinatal mental health screening. Therefore, Understanding OB/GYN nurses' and midwives' knowledge, attitudes, and needs is crucial for effective intervention and screening programs.

In 2020, China's National Health Commission recommended integrating depression screening into routine pregnancy and postnatal visits (24). However, implementation of these guidelines at the grassroots level remains limited. Currently, only Xiao et al. conducted a cross-sectional survey and qualitative interviews among obstetric medical staff in Shenzhen in 2018 (25) and 2019 (26), with 465 and 13 participants, respectively. Notably, Shenzhen is located in southern China and had a population of 17.63 million at the end of 2021 (27). Therefore, the findings are likely to be representative of obstetric medical staff in the region. Hubei Province, located in the central region of China, holds a core position in the strategy of central region development (28) with a population of 5,775,257 residents in 2022. In 2021, the annual birth population of Hubei Province was 404,000, with a birth rate of 6.98‰ (29). It is necessary to explore the current status of knowledge, attitudes, and support needs of OB/GYN medical staff in Hubei Province regarding PMHD screening projects.

Exploring influencing factors is crucial for understanding and improving healthcare professionals' behavior. While some studies have examined the knowledge, attitudes, and support needs related to perinatal mental health screening, research on the influencing factors remains limited. Only Xiao et al.'s study (25) compared the scores of obstetric healthcare professionals with different characteristics regarding PMHDs, revealing that age, education level, years of experience, professional background, and mental health-related education or work experience significantly impacted their knowledge, attitudes, and support needs. Further investigation is needed into the influencing factors affecting the knowledge, attitudes, and support needs of OB/GYN nurses and midwives in PMHDs.

Thus, this study aimed to investigate the knowledge of PMHDs, attitudes, and support needs related to implementing mental health

Abbreviations: PMHDs, perinatal mental health disorders; OB/GYN, obstetrics and gynecology.

screening during pregnancy among OB/GYN nurses and midwives in the central region of China while identifying the related influencing factors.

Materials and methods

Study design, setting, and participants

This study was a cross-sectional survey. Using a convenient sampling method, nurses and midwives in OB/GYN from public hospitals in 14 cities in Hubei Province were invited to participate in the study from July to October 2023.

The inclusion criteria were as follows: (a) nurses and midwives employed in the OB/GYN ward or outpatient clinic of a public hospital in one of the 14 cities of Hubei Province; (b) had at least 1 year of experience working in the OB/GYN ward or outpatient clinic; and (c) were willing to participate in the study. The exclusion criteria were (a) nurses or midwives who were on leave (e.g., maternity leave, sick leave) or absent for other reasons (e.g., external training) during the survey period; (b) nurses or midwives who were undergoing rotation or advanced training in the OB/GYN ward or outpatient clinic during the survey period; and (c) nursing interns or students.

This study obtained ethical approval from the ethics board of the Ethics Committee of the Department of Medicine, Wuhan University (Whu-LFMD-IRB2023055).

Sample size

Memon et al. (30) suggested that 15 to 20 observations per independent variable are strongly recommended in the multiple regression model. A total of 41 items were included in this study, which resulted in a sample size of 615~820. Considering a 20% attrition rate, 738~984 samples were needed. Additionally, Andrade (31) noted that the sample size may need to be larger in multicenter studies because of statistical noise due to variations in patient characteristics, nonspecific treatment characteristics, rating practices, environments, etc. between study centers. Therefore, our study ultimately included 1,271 participants.

Data collection

An online self-administered questionnaire was used for data collection. The first page of the questionnaire provided a brief introduction on the background, objective, voluntary nature of participation, declarations of anonymity and confidentiality, and notes for completing questionnaire. Informed consent was obtained from each participant online by placing a question about their agreement to participate in the study at the beginning of the survey. After informed consent was obtained, the participant could continue to complete the questionnaire.

A pilot study was conducted with 30 nurses to verify the readability and wording of the questionnaire. Modifications were made on the basis of participants' comments, which did not contradict the questionnaire's design. The final questionnaire was then designed via the most extensive online survey platform in China, Wen Juan

Xing (Changsha Ranxing Information Technology Co., Ltd., Hunan, China). Before the main study began, the online survey system was tested by the authors to check the performance of the online survey system in multiple browsers (including Chrome, internet Explorer, Microsoft edge, and Safari) and on different types of devices (including mobile phones, computers, and tablets).

The formal online questionnaire¹ was distributed in the form of QR codes or web pages to WeChat (a popular social application in China) Workgroups between December 1, 2022, and February 20, 2023. To ensure the quality of the responses, duplicate questionnaires submitted by participants with the same IP address ($n=3$) and respondents who took <100 s to complete the questionnaire ($n=26$) were excluded. Finally, a total of 1,300 questionnaires were submitted, and 1,271 without missing values were included in the present work.

Measurements

The online questionnaire designed for the study comprised four sections: demographic information, participants' knowledge of PMHDs, participants' attitudes toward PMHD, and participants' support needs for PMHDs screening programs.

The demographic information questionnaire was self-designed by the researchers according to the research purpose and included age, years of working experience in OB/GYN, nature of the hospital (general hospitals or specialist maternity hospitals), hospital grade, title, category of personnel (nurse or midwife), and whether the respondent had mental health-related study or working experience (yes/no).

The Chinese version of the Perinatal Mental Health Knowledge Questionnaire was used to measure participants' knowledge about PMHDs. The scale was first developed by Australian academics Hauck et al. (20) to measure midwives' knowledge related to women's perinatal psychology with 13 items. In 2017, Xiao et al. (25) translated the questionnaire into Chinese and conducted psychometric property tests. The Chinese version of the questionnaire is a reliable and valid instrument for assessing the PMHDs knowledge of medical staff, with a Cronbach's α of 0.72. The final questionnaire consisted of 3 dimensions and 12 items. The six items related to the risks associated with mental illness included personal and family history, abuse and trauma, attachment, infant weight, hormonal protection and maternal age. Two items specifically addressed the Edinburgh Postnatal Depression Scale (EPDS). Four items related to the signs, symptoms and clinical management of mental illness were also included. Correct answers were scored as 1 point, and incorrect or unclear answers were scored as 0 points, for a total score of 12 points, with higher scores indicating greater knowledge of mental health during pregnancy. The overall evaluation was based on the percentage of correct answers, which was calculated as follows: total mean score/full score $\times$ 100%.

The Chinese version of the Perinatal Mental Health Attitudes Questionnaire was utilized to gauge participants' attitudes toward PMHDs. Initially, developed by the Australian scholars McCall et al. (32). In 2002, this questionnaire was aimed at assessing general practitioners' attitudes toward patients with depression and anxiety

¹ <http://www.wjx.cn>

disorders. In 2012, Australian researchers Jones et al. (33) revised the questionnaire for use in measuring midwives' attitudes toward psychological issues in pregnant women and new mothers. In 2017, Xiao et al. (25) translated and revised it into Chinese to evaluate healthcare professionals' attitudes toward psychological health issues among pregnant women. The Chinese version of the questionnaire includes 15 items across two dimensions, namely, professional competence and comfort, and systemic issues. Examples of items include "My workload limits my ability to focus on depression or anxiety in pregnant women" and "The midwife/nurse/obstetrician should play the first role in dealing with anxiety and depression disorders in pregnant women." A Likert scale ranging from "strongly disagree" to "strongly agree" was used for each item, with scores ranging from 1 to 5. The total score ranges from 15 to 75, with higher scores indicating a more positive attitude of healthcare professionals toward psychological issues among pregnant women.

The Health Care Facilities Support Needs Scale is designed to assess the support needs of healthcare professionals regarding the implementation of mental health screenings for pregnant women. The scale was developed by Xiao et al. in 2018 (25) on the basis of Bandura's social cognitive theory with reference to the relevant literature and expert consultation. This scale consists of 7 items, all of which are related to the need for healthcare professionals to support the implementation of PMHDs screening, e.g., "I think there is a need for hospitals to have specialists in mental health." Each item was rated on a 5-point Likert scale ranging from "strongly disagree" to "strongly agree," with 1–5 points assigned. The total score ranges from 7 to 35, with a higher score indicating greater need from health care facilities. The Cronbach's α of the scale was 0.93 (25).

Statistical analysis

All the statistical analyses were done with SPSS 27.0. Categorical variables were presented as n (%), while continuous data following a normal distribution were described using means and standard deviations (SD). Data that deviated from a normal distribution were represented using median and interquartile range.

For normally distributed data, t -tests or ANOVA were used for intergroup comparisons, while non-normally distributed data were analyzed using the Mann–Whitney or Kruskal–Wallis H test. The mean knowledge, attitudes and support needs scores were used as the cut-off points. Variables with p values less than 0.05 in the univariate analyses were included in the multivariate logistic regression model. The results are reported as odds ratios (ORs) and 95% confidence intervals (CIs). A two-sided p value less than 0.05 was considered statistically significant.

Results

Demographic and baseline characteristics of the participants

In this study, a total of 1,271 questionnaires were collected, with 959 (75.06%) being nurses and 312 (24.55%) being midwives, 664 (52.24%) participants falling within the age bracket of 30–39 years, 1,129 (88.82%) attaining education up to the level of a bachelor's

degree, and 371 (29.10%) working in specialist maternity hospitals. Of the total participants, only 300 (23.60%) had mental health-related education or work experience. Other information is detailed in Table 1.

Nurses' and midwives' knowledge of PMHDs

The average PMHDs knowledge score was 6.09 ± 1.99 , with an average accuracy of 48.5%. The first dimension, related to risk factors, had the highest score. The dimensions of signs, symptoms and clinical management of mental illness had the lowest scores.

Specifically, the item "Women with postnatal depression often feel sad and cry (false)" had the lowest accuracy (3.38%). Additionally, the accuracy of the items "Postnatal depression will go away on its own but occasionally requires treatment (false)" and "Women must not breastfeed if taking medication for mental illness (false)" was also very low, at 9.76 and 17.62%, respectively (Table 2 and Supplementary Figure S1).

Nurses' and midwives' attitudes toward PMHDs

Nurses' and midwives' attitudes toward PMHDs ranged from 16 to 80 scores, with an average of 47.67 ± 8.80 scores. The item "I do not think I can tell the difference between a normal woman and a pregnant woman with psychological problems" had the lowest score (2.23 ± 0.96). The item "Pregnant women with symptoms of depression or anxiety should seek help from a psychologist or psychiatric specialist" had the highest score (4.10 ± 0.91). Additionally, the item "the midwife/nurse/obstetrician should play the first role in dealing with anxiety and depression disorders in pregnant women" also scored high (3.73 ± 0.98) (Table 3).

The support needs of nurses and midwives for the implementation of mental health screening for women during pregnancy

The support needs scores of the nurses and midwives ranged from 7 to 35, with an average of 29.35 ± 4.66 (Table 4). All the items had scores greater than 4 scores, among which the item "I think there is a need for hospitals to have specialists in mental health" had the highest score (4.26 ± 0.71).

Factors associated with knowledge, attitudes, and support needs

The results of the univariate analyses (Table 1) revealed that years of nursing experience, years of OB/GYN nursing experience, mental health-related education or work experience, mode of employment, category of personnel, title, and nature of hospital were the variables influencing the knowledge score ($p < 0.05$). Years of nursing experience, years of OB/GYN nursing experience, mental health-related education or work experience, category of personnel, title, and

TABLE 1 Demographic and baseline characteristics and differences in the knowledge, attitudes, and support needs of the participants (n = 1,271).

Variables	N (%)	Knowledge			Attitude			Support needs		
		Scores (Mean ± SD)	t/F	P	Scores (Mean ± SD)	t/F	P	Scores (Mean ± SD)	t/F	P
Age (years)										
18–29	364(28.64)	5.58 ± 1.84	2.021	0.133	47.22 ± 8.98	0.685	0.504	33.01 ± 5.60	3.426	0.053
30–39	664(52.24)	5.73 ± 1.88			47.88 ± 9.04			33.43 ± 5.44		
≥40	243(19.12)	5.89 ± 1.86			47.75 ± 7.83			33.37 ± 4.34		
Educational background										
College	142(11.17)	5.76 ± 1.88	0.58	0.63	47.07 ± 9.58	0.46	0.71	33.33 ± 5.48	0.53	0.66
Undergraduate	1,117(87.88)	5.71 ± 1.87			47.74 ± 8.70			33.46 ± 5.37		
Master	12(0.94)	5.50 ± 1.45			48.33 ± 9.26			33.67 ± 3.73		
Years of nursing experience										
1–5	212(16.68)	5.00(4.00,7.00)	10.41 ^a	0.02	46.87 ± 9.30	0.89 ^b	0.45	32.86 ± 5.78	3.15 ^b	0.02
6–10	434(34.15)	6.00(4.00,7.00)			47.64 ± 9.15			33.13 ± 5.68		
11–20	449(35.33)	6.00(4.00,7.00)			48.07 ± 8.58			33.71 ± 5.03		
>20	176(13.85)	6.00(5.00,7.00)			47.68 ± 7.77			34.28 ± 4.78		
Years of obstetrics and gynecology nursing experience										
1–5	318(25.02)	5.00(4.00,7.00)	11.92 ^a	<0.01	47.75 ± 9.34	0.50 ^b	0.69	32.71 ± 5.69	4.50 ^b	<0.01
6–10	436(34.30)	6.00(4.00,7.00)			47.34 ± 8.88			33.28 ± 5.65		
11–20	386(30.37)	6.00(4.00,7.00)			48.05 ± 9.01			33.96 ± 4.79		
>20	131(10.31)	6.00(5.00,7.00)			47.40 ± 6.19			34.32 ± 4.98		
Mental health related education or work experience										
No	971(76.40)	5.62 ± 1.88	−3.13	<0.01	47.81 ± 8.96	1.04	0.30	33.19 ± 5.46	−3.13	<0.01
Yes	300(23.60)	6.01 ± 1.80			47.21 ± 8.24			34.30 ± 4.97		
Mode of employment										
Labor dispatch	24(1.89)	5.79 ± 1.25	3.59	0.03	47.25 ± 5.38	0.05	0.96	32.25 ± 6.95	1.40	0.25
Contractual	1,036(81.51)	5.65 ± 1.90			47.70 ± 9.09			33.39 ± 5.43		
Official establishment	211(16.60)	6.02 ± 1.72			47.57 ± 7.60			33.90 ± 4.83		
Categories of personnel										
Nurse	959(75.06)	5.60 ± 1.87	8.68	<0.001	47.78 ± 9.18	2.06	0.13	33.29 ± 5.51	6.69	<0.01
Midwife	312(24.55)	6.08 ± 1.77			47.46 ± 7.38			34.04 ± 4.63		
Tittle										
Nurse	122(9.60)	5.67 ± 1.66	4.04	<0.01	47.61 ± 9.52	0.29	0.84	32.60 ± 5.76	4.19	<0.01
Nurse practitioner	489(38.47)	5.51 ± 1.98			47.47 ± 8.68			33.11 ± 5.41		
Nurse-in-charge	599(47.13)	5.84 ± 1.81			47.89 ± 8.98			33.73 ± 5.31		
Deputy director or chief nurse	61(4.80)	6.15 ± 1.64			47.16 ± 6.19			35.11 ± 4.15		
Nature of hospital										
General hospitals	900(70.81)	5.64 ± 1.86	2.33	0.02	47.59 ± 8.71	0.47	0.64	33.78 ± 5.43	−3.46	<0.001
Specialist maternity hospitals	371(29.1)	5.90 ± 1.87			47.85 ± 9.03			32.66 ± 5.12		

^aH-value.
^bF-value.
Bold values indicate $p < 0.05$, representing statistically significant results.

nature of the hospital were the influencing factors of support needs ($p < 0.05$). We found no significant associations between attitudes and any demographic or baseline characteristics ($p > 0.05$).

In the multivariate logistic regression analysis, variables with p -values less than 0.05 from the univariate analysis were included. Both the knowledge and support needs models were adjusted for years

TABLE 2 Accuracy of PMHDs knowledge for nurses and midwives.

Items	Accuracy
• Related risk factors	
Past personal history of mental illness is a risk for mental illness during childbearing(true)	93.31%
A history of abuse and trauma can increase the risk of mental illness in women(true)	91.90%
Women with mental illness may have attachment problems with their baby(true)	83.24%
Past family history of mental illness is not a risk for mental illness during childbearing(false)	57.12%
Hormones released during pregnancy protect against mental illness(false)	54.13%
Younger mothers are at greater risk of postnatal depression(false)	41.31%
• Edinburgh Postnatal Depression Scale	
The EPDS is a useful screening tool for depression and anxiety(true)	49.05%
The cut off score for EPDS suggesting further assessment is 9(true)	43.27%
• Signs, symptoms and clinical management of mental illness	
Women should not take psychiatric medication during pregnancy (false)	37.37%
Women must not breastfeed if taking medication for mental illness (false)	17.62%
Postnatal depression will go away on its own but occasionally requires treatment (false)	9.76%
Women with postnatal depression often feel sad and cry (false)	3.38%

of nursing experience and years of obstetrics and gynecology nursing experience. The results revealed that having mental health related education or work experience (adjusted OR (aOR)=1.43, 95% CI: [1.08~1.88], $p=0.01$), being midwives (aOR=1.78, 95% CI: [1.33~2.37], $p<0.001$), and working in specialist maternity hospitals (aOR=1.55, 95%CI: [1.20~2.02], $p<0.001$) were significantly associated with higher knowledge scores (Table 5). Additionally, having mental health related education or work experience (aOR=1.59, 95% CI: [1.09~2.31], $p=0.014$) and working in specialist maternity hospitals (aOR=1.42, 95%CI: [1.12~2.12], $p<0.01$) were significantly associated with higher support needs scores (Table 6).

Discussion

This is the first study to assess OB/GYN nurses' and midwives' knowledge, attitudes, and support needs regarding PMHDs in Central China. Results show that they had insufficient knowledge, moderate attitudes towards PMHDs screening, and great support needs for implementing mental health screening during pregnancy.

This study revealed that OB/GYN nurses' and midwives' knowledge about PMHDs was 6.09 ± 1.99 , which was relatively low, close to that reported in Xiao et al.'s study (25) but lower than the mean score reported in Hauck's survey of Australian midwives (8.27 ± 2.67) (20). This may be because perinatal mental health

screening has been implemented in Australia for some time, whereas China is still in the early stages of this effort (24). Additionally, in our study, the item "Women with postnatal depression often feel sad and cry (false)" (only 3.38%) had the lowest accuracy, which is significantly lower than the accuracy rate reported in Australia (68.1%) (20). This discrepancy may be attributed to cultural differences. In China, pregnancy is traditionally viewed as a joyful event, leading to the suppression, underestimation, and unrecognition of negative emotions like sadness. Another contributing factor could be linked to a lack of relevant education, training, and work experience among nurses and midwives. Several studies indicate that both nurses and midwives often feel inadequately equipped in terms of their knowledge and skills concerning PMHDs due to insufficient training in this domain (34, 35). Limited access to continuous professional development opportunities can negatively impact individuals' levels of knowledge related to PMHDs (35, 36). Therefore, there is a need to strengthen the training and education of nurses and midwives about PMHDs. Targeted training has been implemented in Australia (37), which showed that it can significantly enhance the knowledge, skills, and confidence of midwives. However, such training programs are not yet available in China. Thus, there is an urgent need for targeted educational interventions among Chinese healthcare providers.

In this study, nurses and midwives demonstrated moderate attitudes toward the mental health of perinatal women, recognizing that it is within their role to address anxiety and depression disorders in pregnant women. This aligns with Hauck's study in Australia (20), where the majority of midwives (87.7%) agreed that assessing the mental health status of women in their care is part of their role. However, in contrast with Hauck's study, in which less than half (42.7%) of participants believed that mental health issues during pregnancy should always be referred to a specialist, our study revealed that most participants felt that pregnant women experiencing symptoms of depression or anxiety should seek help from a psychologist or psychiatric specialist. Additionally, the average score for the item "I do not think I can tell the difference between a normal woman and a pregnant woman with psychological problems" was 2.23 ± 0.96 , indicating that many participants lacked confidence in their ability to differentiate between normal and problematic psychological conditions. These findings suggest that while there is a willingness among OB/GYN nurses and midwives to engage in maternal mental health screening and care, there is also a significant gap in their professional knowledge, skills, and confidence. This is consistent with earlier results showing that they scored lowest in terms of knowledge about PMHDs signs, symptoms, and clinical management. Another possible explanation for this discrepancy could be the overall shortage of health resources in many Chinese hospitals, leading to overworked nurses and midwives who lack the time and energy to thoroughly assess the mental health status of pregnant women (26). Thus, it is essential to implement training programs focused on the signs, symptoms, and clinical management of PMHDs to enhance the knowledge and skills of OB/GYN nurses and midwives, thereby boosting their professional confidence. Studies in UK (38) and Ireland (39) have demonstrated that such training significantly improves the knowledge, skills, and confidence of midwives, including students. Additionally, improving human resource allocation is necessary to further support these healthcare professionals.

This study revealed that nurses and midwives expressed great support needs for PMHDs screening, aligning with findings from

TABLE 3 Scores and responses of PMHDs attitudes for nurses and midwives.

Items, n(%)	Mean $\pm$ SD	Strongly agree	Agree	Neutral	Disagree	Strongly disagree
Professional competence and comfort						
My workload limits my ability to focus on depression or anxiety in pregnant women	2.72 $\pm$ 1.09	64(5.04)	254(19.98)	391(30.76)	384(30.21)	178(14.00)
I find psychological issues too complex and time-consuming to deal with	2.70 $\pm$ 1.13	60(4.72)	301(23.68)	297(23.37)	422(33.20)	191(15.03)
Pregnant women find it an invasion of privacy for medical staff to routinely ask them about their psychological condition	2.60 $\pm$ 1.08	50(3.93)	239(18.80)	322(25.33)	468(36.82)	192(15.11)
I work so tight a schedule that I cannot routinely assess the mental health of pregnant women	2.50 $\pm$ 1.06	47(3.70)	209(16.44)	278(21.87)	530(41.70)	207(16.29)
The hospital procedures (systems) I worked in prevented the medical staff from knowing enough about the psychological condition of pregnant women and giving adequate psychological care	2.40 $\pm$ 1.04	46(3.62)	158(12.43)	287(22.58)	547(43.34)	233(18.33)
I do not think I can tell the difference between a normal woman and a pregnant woman with psychological problems	2.23 $\pm$ 0.96	32(2.52)	120(9.44)	213(16.76)	651(51.22)	255(20.06)
Systemic issues						
Pregnant women with symptoms of depression or anxiety should seek help from a psychologist or psychiatric specialist	4.10 $\pm$ 0.91	446(35.09)	619(48.70)	135(10.62)	32(2.52)	39(3.07)
The midwife/nurse/obstetrician should play the first role in dealing with anxiety and depression disorders in pregnant women	3.73 $\pm$ 0.98	232(18.25)	657(51.69)	237(18.65)	92(7.24)	53(4.17)
I know very well when a pregnant woman has a psychological problem that needs to be referred to a medical professional	3.58 $\pm$ 0.97	212(16.68)	517(40.68)	372(29.27)	137(10.78)	33(2.60)
I think I'd be in a good position to counsel depressed pregnant women	3.34 $\pm$ 0.95	125(9.83)	441(34.70)	484(38.08)	177(13.93)	44(3.46)
I find it easier to deal with physical problems than mental ones	3.28 $\pm$ 1.06	103(8.10)	541(42.56)	314(24.70)	228(17.94)	85(6.69)
I'm comfortable with interventions for perinatal depression or anxiety	2.91 $\pm$ 0.95	71(5.59)	252(19.38)	498(39.18)	395(31.08)	55(4.33)
The priorities of the medical establishment now encourage me to focus on the problems that pregnant women present rather than identify the underlying problems	2.88 $\pm$ 1.15	89(7.00)	355(27.93)	298(23.45)	378(29.74)	151(11.88)
I feel uncomfortable asking pregnant women about mental disorders	2.58 $\pm$ 1.09	70(5.51)	206(16.21)	302(23.76)	505(39.73)	188(14.79)
I get frustrated when pregnant women with mental health problems consult me	2.49 $\pm$ 1.09	62(4.88)	188(14.79)	282(22.19)	523(41.15)	216(16.99)

TABLE 4 Scores and responses of PMHDs screening support needs for nurses.

Items, n(%)	Mean ± SD	Strongly agree	Agree	Neutral	Disagree	Strongly disagree
I think there is a need for hospitals to have specialists in mental health	4.26 ± 0.71	486(38.24)	664(52.24)	105(8.26)	2(0.16)	14(1.10)
I think maternal mental health should be assessed routinely	4.23 ± 0.71	455(35.80)	686(53.97)	108(8.50)	10(0.79)	12(0.94)
If the hospital offered training in mental health, I'd be happy to attend	4.22 ± 0.73	461(36.27)	663(52.16)	128(10.07)	5(0.39)	14(1.10)
Antenatal care providers should be equipped with skills to recognize maternal mental health	4.22 ± 0.72	445(35.01)	687(54.05)	121(9.52)	4(0.31)	14(1.10)
Health-care workers involved in antenatal care should be trained in the identification and management of maternal psychological problems	4.22 ± 0.70	441(34.70)	698(54.92)	117(9.21)	2(0.16)	13(1.02)
Antenatal care providers should be equipped with skills to treat maternal mental problems	4.13 ± 0.77	406(31.94)	669(52.64)	162(12.75)	19(1.49)	15(1.18)
Health-care workers should have access to information on dealing with perinatal maternal psychosocial problems	4.17 ± 0.73	413(32.49)	691(54.37)	144(11.33)	10(0.79)	13(1.02)

TABLE 5 Multivariate regression analysis (knowledge dimension).

Cut-off value: ≥6/<6	*Adjusted OR (95%CI)	p
Mental health related education or work experience		
No	Ref	
Yes	1.43(1.08 ~ 1.88)	0.01
Mode of employment		
Labor dispatch	Ref	
Contractual	1.14(0.49 ~ 2.61)	0.76
Official establishment	1.42(0.57 ~ 3.23)	0.45
Categories of personnel		
Nurse	Ref	
Midwife	1.78(1.33 ~ 2.37)	<0.001
Tittle		
Nurse	Ref	
Nurse practitioner	0.77(0.49 ~ 1.23)	0.28
Nurse-in-charge	0.91(0.54 ~ 1.54)	0.73
Deputy director or chief nurse	1.44(0.61 ~ 3.42)	0.41
Nature of hospital		
General hospitals	Ref	
Specialist maternity hospitals	1.55(1.20 ~ 2.02)	<0.001

* Adjusted for years of nursing experience, years of obstetrics and gynecology nursing experience.
Bold values indicate $p < 0.05$, representing statistically significant results.

Xiao et al.'s studies (25, 26), which indicated that nurses and midwives require targeted training on PMHDs to enhance their competency in this area. Additionally, Xiao et al.'s study (26) highlighted other support needs among obstetric healthcare professionals, including the implementation of relevant policies to support perinatal mental health disorder screening, the establishment of multidisciplinary teams for mental health management, and the enhancement of public awareness of perinatal mental health disorders to reduce stigma and promote early

TABLE 6 Multivariate regression analysis (support needs dimension).

Cut-off value: ≥29/<29	*Adjusted OR (95%CI)	p
Mental health related education or work experience		
No	Ref	
Yes	1.59(1.09 ~ 2.31)	0.014
Categories of personnel		
Nurse	Ref	
Midwife	1.28(0.88 ~ 1.84)	0.19
Tittle		
Nurse	Ref	
Nurse practitioner	1.03(0.59 ~ 1.81)	0.91
Nurse-in-charge	1.17(0.62 ~ 2.20)	0.64
Deputy director or chief nurse	1.56(0.76 ~ 2.14)	0.08
Nature of hospital		
General hospitals	Ref	
Specialist maternity hospitals	1.42(1.12 ~ 2.12)	<0.01

* Adjusted for years of nursing experience, years of obstetrics and gynecology nursing experience.
Bold values indicate $p < 0.05$, representing statistically significant results.

detection and intervention. In our study, OB/GYN nurses and midwives also emphasized the necessity for hospitals to have specialists in mental health, likely due to the time-consuming nature of addressing psychological problems in pregnant women, given their busy schedules (26, 40). Moreover, considering their limited training in mental health, they prefer having psychologists in hospitals handle such issues, which aligns with the findings mentioned above. Given these findings, we recommend that China develop specific policies to address the identified support needs, such as implementing mandatory PMHDs training programs for OB/GYN nurses and midwives, increasing the integration of mental health specialists into obstetric care teams, and launching public awareness campaigns to facilitate the early identification and intervention of perinatal mental health issues. These steps are

crucial for building a more supportive healthcare environment for both professionals and patients.

This study found that mental health-related education or work experience, personnel categories, and the nature of the hospital are important factors influencing the knowledge scores of OB/GYN nurses and midwives regarding PMHDs. Specifically, those with relevant education or work experience, midwives, and staff in specialist maternity hospitals demonstrated higher knowledge scores. This finding is consistent with Xiao's study (25). Notably, our study revealed that midwives scored higher in knowledge than OB/GYN nurses, even though in traditional Chinese medical practice, ward nurses are generally more focused on the psychological care of pregnant women, while midwives primarily handle delivery-related care (22). This finding may suggest that midwives have increasingly emphasized perinatal mental health in their training and roles in recent years, or that they are more frequently exposed to related mental health issues in their work. Moreover, our study also showed that mental health-related education or work experience and the nature of the hospital were significantly associated with support needs scores. Specifically, nurses and midwives in specialist maternity hospitals had higher scores in both perinatal mental health knowledge and support needs compared to those in general hospitals. This may reflect the greater emphasis and higher standards placed on perinatal mental health training and evaluation in specialist hospitals. Our study further pointed out that those with mental health-related education or work experience not only had higher knowledge scores but also exhibited greater support needs. This result suggests that as knowledge levels increase, healthcare professionals become more aware of their limitations in perinatal mental health care, leading to a stronger desire for learning and support, thereby creating a positive feedback loop.

Limitations

This study provides a snapshot of the prevailing knowledge, attitudes, and support needs among Chinese nurses and midwives. Thus, generalizability to other contexts may be limited. The data were collected solely in Hubei Province, China, and the sample may not be fully representative of the entire country, potentially introducing selection bias. Furthermore, the study relies on quantitative data without the supplementation of qualitative data beyond responses to open questions. Integrating qualitative insights could have offered a more comprehensive understanding of various perspectives. Importantly, relying solely on self-reported practices through survey methods may not fully capture the actual clinical practices and competency of midwives and nurses. Therefore, caution is warranted in interpreting the findings solely on the basis of this survey methodology. Finally, it is worth noting that there may be interactions between knowledge of, attitudes toward, and support needs for PMHDs. Unfortunately, this study did not identify a two-by-two correlation between these three factors. Therefore, further research is needed in the future.

Conclusion

Currently, nurses and midwives specializing in OB/GYN in China exhibit insufficient knowledge about PMHD, with those

having relevant education or work experience, being midwives, and staff in specialist maternity hospitals demonstrated higher knowledge scores. Furthermore, nurses and midwives display moderate attitudes toward PMHDs screening. There is a great need for support from government agencies regarding the implementation of PMHDs screening programs, with those having mental health-related education or work experience and in specialist maternity hospitals had higher scores.

Considering the potential role of nurses and midwives in PMHDs screening programs and the influencing factors mentioned above, it is essential to provide tailored training for nurses and midwives regarding PMHDs-related knowledge and skills. Moreover, providing professional support is crucial for facilitating the promotion of routine maternal mental health screening services in the future.

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 the Ethics Committee of the Department of Medicine, Wuhan University (Whu-LFMD-IRB2023055). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

LZ: Visualization, Writing – original draft, Writing – review & editing. XP: Data curation, Formal analysis, Software, Visualization, Writing – original draft. CC: Data curation, Writing – original draft. JC: Conceptualization, Data curation, Investigation, Writing – review & editing. YP: Formal analysis, Validation, Writing – review & editing. XC: Conceptualization, Funding acquisition, Project administration, Supervision, Writing – review & editing. ZZ: Conceptualization, Project administration, Supervision, Writing – review & editing. CL: Project administration, Resources, Supervision, Writing – review & editing.

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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.

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Supplementary material

The Supplementary material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fpubh.2024.1424075/full#supplementary-material>

References

- WHO. Promoting mental health: concepts, emerging evidence, practice. (2005). Available at: <https://www.who.int/publications/i/item/9241562943> (Accessed March 15, 2024).
- Dowse E, Chan S, Ebert L, Wynne O, Thomas S, Jones D, et al. Impact of perinatal depression and anxiety on birth outcomes: a retrospective data analysis. *Matern Child Health J.* (2020) 24:718–26. doi: 10.1007/s10995-020-02906-6
- Jahan N, Went TR, Sultan W, Sapkota A, Khurshid H, Qureshi IA, et al. Untreated depression during pregnancy and its effect on pregnancy outcomes: a systematic review. *Cureus.* (2021) 13:e17251. doi: 10.7759/cureus.17251
- Cheng C, Chou Y, Chang C, Liou S. Trends of perinatal stress, anxiety, and depression and their prediction on postpartum depression. *Int J Environ Res Public Health.* (2021) 18:9307. doi: 10.3390/ijerph18179307
- Camoni L, Gigantesco A, Guzzini G, Pellegrini E, Mirabella F. Epidemiology of perinatal depression in Italy: systematic review and meta-analysis. *Ann Dell'istituto Sup Sanita.* (2023) 59:139–48. doi: 10.4415/ANN_23_02_07
- Roddy Mitchell A, Gordon H, Atkinson J, Lindquist A, Walker SP, Middleton A, et al. Prevalence of perinatal anxiety and related disorders in low-and middle-income countries: a systematic review and meta-analysis. *JAMA Netw Open.* (2023) 6:e2343711. doi: 10.1001/jamanetworkopen.2023.43711
- Roddy Mitchell A, Gordon H, Lindquist A, Walker SP, Homer CSE, Middleton A, et al. Prevalence of perinatal depression in low-and middle-income countries: a systematic review and meta-analysis. *JAMA Psychiatry.* (2023) 80:425–31. doi: 10.1001/jamapsychiatry.2023.0069
- Yang L, Sun J, Nan Y, Waqas A, Nisar A, Wang D, et al. Prevalence of perinatal anxiety and its determinants in mainland China: a systematic review and meta-analysis. *J Affect Disord.* (2023) 323:193–203. doi: 10.1016/j.jad.2022.11.075
- Nisar A, Yin J, Waqas A, Bai X, Wang D, Rahman A, et al. Prevalence of perinatal depression and its determinants in mainland China: a systematic review and meta-analysis. *J Affect Disord.* (2020) 277:1022–37. doi: 10.1016/j.jad.2020.07.046
- Zhu Y, Sun N, Yin XX, Fang PQ, Gong YH. A follow-up study on the bi-directional relationship between postpartum depressive symptoms and parenting self-efficacy among women in China in the context of fertility policy adjustment: an empirical investigation based on Hubei Province. *Popul Dev.* (2023) 29:27–39.
- O'Connor EA, Perdue LA, Coppola EL, Henninger ML, Thomas RG, Gaynes BN. Depression and suicide risk screening: updated evidence report and systematic review for the us preventive services task force. *JAMA.* (2023) 329:2068–85. doi: 10.1001/jama.2023.7787
- Burger M, Hoosain M, Einspieler C, Unger M, Niehaus D. Maternal perinatal mental health and infant and toddler neurodevelopment - evidence from low and middle-income countries: a systematic review. *J Affect Disord.* (2020) 268:158–72. doi: 10.1016/j.jad.2020.03.023
- Byatt N, Yonkers KA. Addressing maternal mental health: progress, challenges, and potential solutions. *Psychiatr News.* (2021) 56. doi: 10.1176/appi.pn.2021.4.7
- National Institute for Health and Care Excellence (NICE). Antenatal and postnatal mental health: clinical management and service guidance. London, UK: National Collaborating Centre for Mental Health (2014).
- Opinion NAC. Screening for perinatal depression. *Obstet Gynecol.* (2018) 125:1268–71. doi: 10.1097/01.AOG.0000465192.34779.dc
- Diamond R. Perinatal mental health: 2022 year in review. (2022). Available at: <https://www.psychologytoday.com/us/blog/preparing-parenthood/202212/perinatal-mental-health-2022-year-in-review> (Accessed March 15, 2024).
- Moss KM, Reilly N, Dobson AJ, Loxton D, Tooth L, Mishra GD. How rates of perinatal mental health screening in Australia have changed over time and which women are missing out. *Aust N Z J Public Health.* (2020) 44:301–6. doi: 10.1111/1753-6405.12999
- Sidebottom A, Vacquier M, LaRusso E, Erickson D, Hardeman R. Perinatal depression screening practices in a large health system: identifying current state and assessing opportunities to provide more equitable care. *Arch Womens Ment Health.* (2021) 24:133–44. doi: 10.1007/s00737-020-01035-x
- Cibralic S, Pickup W, Diaz AM, Kohlhoff J, Karlov L, Stylianakis A, et al. The impact of midwifery continuity of care on maternal mental health: a narrative systematic review. *Midwifery.* (2023) 116:103546. doi: 10.1016/j.midw.2022.103546
- Hauck YL, Kelly G, Dragovic M, Butt J, Whittaker P, Badcock JC. Australian midwives' knowledge, attitude and perceived learning needs around perinatal mental health. *Midwifery.* (2015) 31:247–55. doi: 10.1016/j.midw.2014.09.002
- Noonan M, Jomeen J, Galvin R, Doody O. Survey of midwives' perinatal mental health knowledge, confidence, attitudes and learning needs. *Women Birth.* (2018) 31:e358–66. doi: 10.1016/j.wombi.2018.02.002
- Li L, Ding Y, Mao LP. Progress of research on midwifery service models and human resource allocation at home and abroad. *J Nurs.* (2016) 31:15–7. doi: 10.3870/j.issn.1001-4152.2016.20.015
- Li Y, Hu T, Xia X, Ge L. Knowledge, attitude, and practice toward photoaging in the Chinese population: a cross-sectional study. *Sci Rep.* (2024) 14:5196. doi: 10.1038/s41598-024-55691-5
- China Bureau of Disease Control and Prevention. Notice on exploring specialized services for the prevention and treatment of depression and Alzheimer's disease. General Office of the National Health and Health Commission (2020). Available at: <http://www.nhc.gov.cn/jkj/s7914/202009/a63d8f82eb53451f97217bef0962b98f.shtml> (Accessed March 15, 2024).
- Xiao X, Lv CM, Di L, Liu H, Bai J, Zhu SN. Analysis of the level of knowledge attitude and support needs of 465 obstetric healthcare professionals regarding mental health screening for women during pregnancy. *J Nurs.* (2018) 25:59–63. doi: 10.16460/j.issn1008-9969.2018.18.059
- Xiao X, Ma H, Zhu S, Li Q, Chen Y. The perceptions and attitudes of obstetric staff and midwives towards perinatal mental health disorders screening: a qualitative exploratory study in Shenzhen, China. *BMC Nurs.* (2023) 22:313. doi: 10.1186/s12912-023-01475-7
- National Bureau of Statistics Shenzhen Survey Team. Shenzhen national economic and social development statistics bulletin 2021. Shenzhen Bureau of Statistics. (2022). Available at: http://tj.sz.gov.cn/gkmlpt/content/9/9763/post_9763042.html?eqid=cbeed34a000638a900000036462f94d#4222 (Accessed March 12, 2024).
- Miao YN, Yang DY. Analysis of S&T Resource Allocation Efficiency in central region based on comprehensive evaluation method. *China Soft Sci.* (2020) 3:134–49. doi: 10.3969/j.issn.1002-9753.2020.03.013
- National Bureau of Statistics Hubei General Investigation Team Hubei Province 2022 national economic and social development statistics bulletin Hubei Provincial Bureau of Statistics (2023). Available at: https://tj.hubei.gov.cn/tjsj/tjgb/ndtjgb/qstjgb/202303/t20230316_4587528.shtml (Accessed March 15, 2024).
- Memon M, Ting H, Hwa C, Ramayah T, Chuah F, Cham T. Sample size for survey research: review and recommendations. *J Appl Struct Equ Model.* (2020) 4:i-xx. doi: 10.47263/JASEM.4(2)01
- Andrade C. Sample size and its importance in research. *Indian J Psychol Med.* (2020) 42:102–3. doi: 10.4103/IJPSYM.IJPSYM_504_19
- McCall L, Clarke DM, Rowley G. A questionnaire to measure general practitioners' attitudes to their role in the management of patients with depression and anxiety. *Aust Fam Physician.* (2002) 31:299–303.
- Jones CJ, Creedy DK, Gamble JA. Australian midwives' awareness and management of antenatal and postpartum depression. *Women Birth.* (2012) 25:23–8. doi: 10.1016/j.wombi.2011.03.001
- Arefadib N, Cooklin A, Nicholson J, Shafiei T. Postnatal depression and anxiety screening and management by maternal and child health nurses in community settings: a scoping review. *Midwifery.* (2021) 100:103039. doi: 10.1016/j.midw.2021.103039
- Johnson J, Hope L, Jones L, Bradley E. A mixed methods study to understand perinatal mental healthcare referral decisions among midwives and health visitors in the UK. *Front Psych.* (2023) 14:1056987. doi: 10.3389/fpsy.2023.1056987
- Silverwood V, Nash A, Chew-Graham CA, Walsh-House J, Sumathipala A, Bartlam B, et al. Healthcare professionals' perspectives on identifying and managing perinatal anxiety: a qualitative study. *Br J Gen Pract.* (2019) 69:e768–76. doi: 10.3399/bjgp19X706025

37. McLachlan HL, Forster DA, Collins R, Gunn J, Hegarty K. Identifying and supporting women with psychosocial issues during the postnatal period: evaluating an educational intervention for midwives using a before-and-after survey. *Midwifery*. (2011) 27:723–30. doi: 10.1016/j.midw.2010.01.008
38. Davies L, Page N, Glover H, Sudbury H. Developing a perinatal mental health module: an integrated care approach. *The Br J Midwifery*. (2016) 24:118–21. doi: 10.12968/bjom.2016.24.2.118
39. Higgins A, Carroll M, Sharek D. Impact of perinatal mental health education on student midwives' knowledge, skills and attitudes: a pre/post evaluation of a module of study. *Nurse Educ Today*. (2016) 36:364–9. doi: 10.1016/j.nedt.2015.09.007
40. Li YL, Liu XM, Meng YJ, Li S. Survey and analysis of non-psychiatric healthcare workers' perception of mental health services in general hospitals. *Nurs Res*. (2018) 32:2968–71. doi: 10.12102/j.issn.1009-6493.2018.18.043



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Risk factors and prediction model for low-birth-weight infants born to women with gestational diabetes mellitus

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Aim: To explore the risk factors for low-birth-weight infants born to pregnant women with GDM to develop a prediction model and to construct a prediction nomogram for the risk of low birth weight infants born to pregnant women with GDM.

Methods: The clinical data of singleton infants diagnosed with gestational diabetes mellitus in Southeast China in 2019 were retrospectively reviewed. Gestational conditions and neonatal weight were assessed.

Results: A total of 386 diabetic mothers and infants were enrolled, including 193 in the low birth weight group and 193 in the normal birth weight group. The statistically significant factors were age over 36 years (OR = 1.916, 95% CI 1.048–3.505), junior high school education (OR = 4.454, 95% CI 1.882–10.543), history of fetal distress (OR = 0.120, 95% CI 0.016–0.925), gestational hypertension (OR = 3.681, 95% CI 1.357–9.986), preeclampsia (OR = 24.652, 95% CI 5.956–102.036), threatened preterm birth (OR = 18.393, 95% CI 8.457–39.999), triglycerides (OR = 0.642, 95% CI 0.485–0.850), and inadequate gestational weight gain (OR = 1.997, 95% CI 1.162–3.432). The area under the receiver operating characteristic curve (AUC) was 0.834 (95% CI: 0.794–0.874, $p < 0.001$), and the sensitivity and specificity were 82.38 and 87.56%, respectively. The goodness-of-fit test likelihood ratio 2 was 2.089 ($p = 0.978$). The comprehensive nomogram model showed that the discrimination and mean absolute error were 0.834 and 0.015, respectively. The calibration curves showed acceptable agreement between the predictions of the column line plots and the observations. The DCA curves showed good positive net yields in the prediction model.

Discussion: This study established a prediction model and risk score for low birth weight in pregnant women with GDM. It helps pregnancy clinics to identify the risk of low birth weight in newborns promptly, in addition to glycemic control and weight management for pregnant women with GDM, and should improve the appropriate treatment plan for pregnant women with higher risk, to provide personalized and precise treatment for pregnant women with GDM and improve infant outcomes.

KEYWORDS

gestational diabetes mellitus, low birth weight infant, nomogram, prediction model, risk factor

Introduction

Gestational diabetes mellitus (GDM) is the first diagnosis of any degree of abnormal glucose metabolism during pregnancy (1) and is usually detected during the second trimester (24–28 weeks) or the third trimester (28 weeks and beyond). GDM is a major public health problem for women worldwide (2). However, the adverse consequences of GDM can be actively prevented and reversed. Through clinical experience, early diagnosis, and treatment of GDM, opportunities arise for clinical intervention and the mitigation of adverse perinatal outcomes (3).

Fetuses receive increased amounts of glucose from mothers with GDM during pregnancy, which promotes insulin secretion and increases fetal growth. Newborn birthweight (NBW) refers to newborn birthweight within 1 h after delivery (4) and is one of the most direct indicators of newborn health. Low birth weight included small for gestational age (SGA) and low birth weight (LBW). Low birth weight increases perinatal morbidity and mortality, including neonatal asphyxia, hypothermia, and abnormal nervous system development, and even increases the risk of future preeclampsia, pregnancy-induced hypertension, and SGA, as well as significantly increases the incidence of mental diseases in women with LBW (5). At the same time, the treatment of poor birth weight and its complications not only causes a large economic burden in the long and short term for the country and society but also increases additional nursing costs (6). Newborn birth weight has become the focus of global public health. Early identification of abnormal fetal weight and timely nursing and health education are highly important for ensuring maternal and offspring health.

Epidemiological studies have shown that infants born to mothers with GDM have a greater rate of adverse perinatal outcomes (e.g., asphyxia, hypoglycemia, and birth defects) than infants born to mothers without GDM (7). Current studies on the birth weight of infants born to diabetic mothers mostly focus on macrosomia. Researchers such as Naha (8), Tomlinson (9), and others have constructed prediction models for macrosomia and large for gestational-age infants born to pregnant women with GDM. Previous studies have shown that pregnant women with GDM are more likely to have large gestational age infants and macrosomia than pregnant women without GDM (10), and some studies have shown that mild GDM is also considered to be related to a reduction in neonatal birth weight after treatment (11). A cross-sectional study conducted in 2021 at Jamhouria Hospital/Neonatal Ward found that gestational diabetic and pre-pregnant diabetic mothers delivered 16.7% of newborns with LBW and 13.3% with macrosomia (12). Prior research has demonstrated that there is no statistically significant variance in the occurrence of LBW and small for SGA between women afflicted with GDM and those who are not (13). The incidence rates display a tendency to rise with time (14). Consequently, GDM does not mitigate the probability of pregnant women delivering infants with LBW. Clinically, a uniform approach to nutritional management, blood sugar control, and health education for pregnant women with gestational diabetes is aimed at reducing the occurrence of adverse pregnancy outcomes. Quite the contrary, when expectant mothers with GDM undergo rigorous dietary, physical activity, or insulin interventions, it may exacerbate the severity of LBW (8). Therefore, building a risk prediction model can help clinicians identify high-risk

GDM pregnant women for delivering LBW babies in the early or mid-pregnancy. This helps to take early intervention measures, such as adjusting dietary structure, to improve pregnancy outcomes and reduce the incidence of LBW babies. However, thus far, few scholars have developed a risk prediction model solely targeting the LBW of GDM newborns as an outcome indicator.

The nomogram model serves as a computational graphical device that substitutes intricate mathematical formulations, effectively portraying the outcomes of regression analyses in an intuitive and visually comprehensible manner. This approach has garnered widespread adoption across diverse medical disciplines. The nomogram inherently accommodates the nuanced impact of each influencing factor on the clinical outcome, assigning distinct scores to each, where the cumulative score serves as a proxy for the risk of a particular clinical event. In clinical practice, physicians can expeditiously evaluate a patient's risk level by leveraging the information encoded within the nomogram, thereby facilitating informed clinical decision-making. Consequently, the development of a nomogram-based risk prediction model in this study presents itself as a streamlined tool, empowering healthcare providers to swiftly assess the risk of delivering LBW infants among GDM pregnant women and tailor personalized treatment strategies accordingly.

Therefore, accurate identification of pregnant women with GDM who may have poor birth weight and individualized intervention and management is very important to improve the occurrence of maternal and child complications and ensure the safety of the mother and child. To date, there is no relevant study on LBW infants born to mothers with GDM in China. In this study, we sought to investigate the demographic and clinical characteristics and risk factors for LBW infants born to mothers with GDM in China to provide a basis for timely identification of risk factors for neonatal underweight during pregnancy, implementation of intervention treatment for pregnant women with GDM, and improvement of neonatal prognosis.

Research design

This was a retrospective case–control study.

Research objects and methods

Research site

A tertiary hospital in southeast China.

Research subjects

Pregnant women with GDM and their newborns who gave birth during regular antenatal check-ups at the research hospital from January 1, 2019, to December 31, 2019, were included. Relevant data during pregnancy and the neonatal period were collected. LBW was included in the case group, and normal birth weight was included in the control group. The sample size of the control group and the case group was 1:1. The gestational age of the control group was matched by the tendency scoring method, and the matching tolerance was set at 0.1.

Diagnostic criteria

The diagnostic criteria for GDM were as follows: according to the 2014 Chinese Guidelines for the Diagnosis and Treatment of Gestational Diabetes Mellitus, a 75 g OGTT (one-step method) was performed at 24–28 weeks of gestation, and the blood glucose value met any one or more of the following criteria: fasting blood glucose at least 5.1 mmol/L; OGTT 1 h blood glucose at least 10.0 mmol/L; and OGTT 2 h blood glucose at least 8.5 mmol/L (15).

Weight measurement

The weight and height of the participants were measured using standard procedures in units of 0.1 kg on a digital scale and 0.1 cm on a stadiometer, respectively, while participants wore light clothes and were barefoot. Prepregnancy weight was self-reported at the first prenatal visit and measured at the second and third-trimester prenatal visits.

Inclusion and exclusion criteria

The inclusion criteria were as follows: ① aged ≥ 18 years; ② pregnant woman diagnosed with gestational diabetes at 24–28 weeks; ③ pregnant woman who underwent prenatal examination and gave birth at the study hospital; and ④ single live birth.

The exclusion criteria were as follows: ① prepregnancy diabetes mellitus; ② incomplete electronic medical record information; ③ newborn suffering from congenital defects and other perinatal diseases that seriously affect growth and development; ④ polycystic ovarian syndrome before pregnancy; ⑤ pregnant women who had received medical treatment for chronic conditions, such as oral glucocorticoids, thiazide diuretics, beta-blockers, ACE inhibitors, or antiretroviral drugs; and ⑥ late abortion or induced labor due to fetal abnormalities.

Sample size

The sample size was calculated using PASS 15.0. According to the preliminary survey, the proportion of patients with inadequate GWG in the LBW group was 55%, and the percentage of patients with exposure to risk factors in the normal weight group was 37%. The level of significance was set at 5%, and the statistical power was set at $1-\beta=0.90$. The sample size of each group was 156, and the minimum sample size was 312. The number of samples was increased by 10% to account for incomplete data, and a minimum sample size of 347 participants was needed.

Variable definition

Pregpregnancy BMI was defined as prepregnancy weight (kilograms) divided by prepregnancy height squared (meters). Prepregnancy BMI status was categorized into 4 levels for the Chinese population as follows: underweight, $< 18.5 \text{ kg/m}^2$; normal weight,

$18.5\text{--}22.9 \text{ kg/m}^2$; overweight, $23\text{--}24.9 \text{ kg/m}^2$; and obese, $\geq 25 \text{ kg/m}^2$ (16).

According to American Institute of Medicine standards, prepregnancy underweight ($\text{BMI} < 18.5 \text{ kg/m}^2$) pregnancy weight gain is appropriate for $12.5\text{--}18.0 \text{ kg}$; prepregnancy weight normal ($18.5 \text{ kg/m}^2 \leq \text{BMI} < 25.0 \text{ kg/m}^2$) pregnancy weight gain is suitable for $11.5\text{--}16.0 \text{ kg}$; prepregnancy overweight ($25.0 \text{ kg/m}^2 \leq \text{BMI} < 30.0 \text{ kg/m}^2$) pregnancy weight gain is $7.0\text{--}11.5 \text{ kg}$; and prepregnancy obesity ($\text{BMI} \geq 30.0 \text{ kg/m}^2$) is suitable for pregnancy weight gain of $5.0\text{--}9.0 \text{ kg}$ (17). If the weight gain during pregnancy is less than or greater than the appropriate amount, there is insufficient weight gain during pregnancy and excessive weight gain during pregnancy, respectively.

LBW was defined as $< 2,500 \text{ g}$ at birth. Preterm birth was defined as a gestational age < 37 weeks at birth.

Research tools/observation indicators

General and basic information, drug use, and physiological indicators were obtained from the hospital's electronic medical records system.

The indicators included in the study included: age, ethnic groups, place of residence, degree of education, occupation, marital status, medical insurance, parity, order of birth, family history, history of miscarriage, history of macrosomia, history of GDM, history of fetal distress, history of premature rupture of membranes. Artificially assisted reproduction, intrahepatic cholestasis of pregnancy, hypertensive disorders of pregnancy, and hyperthyroidism. Hypothyroidism, anemia, threatened preterm labor, polyhydramnios, oligohydramnios, insulin, prepregnancy BMI, pregnancy weight gain, urinary ketone in early pregnancy, urinary ketone in the second trimester, OGTT-0h, OGTT-1h, OGTT-2h, triglycerides in early pregnancy, fasting blood glucose in the first trimester, 2 h postprandial blood glucose in early pregnancy, triglycerides in the second trimester, fasting blood glucose in the second trimester, 2 h postprandial blood glucose in the second trimester, glycated hemoglobin in the second trimester, average weekly abdominal circumference growth rate, the average weekly growth rate of uterine height.

Data analysis

IBM SPSS 27.0 software was used for data analysis. Continuous variables were defined using the mean and standard deviation (SD) after assessing the symmetry of distributions through the observation of histograms. In instances where medians and percentiles P_{25} and P_{75} were presented, this was due to the absence of symmetry. To evaluate the normal distribution of continuous variables, we examined histograms, symmetry, and kurtosis, taking into account the size of our sample. Categorical variables were defined by their total number and frequency (%). Age was modified as a dichotomous variable using advanced pregnancy as the cut-off point. For the variable inferential analysis, normally distributed measurement data were analyzed by two independent sample *t*-tests or analysis of variance for comparisons between groups. Continuous non-normally distributed variables and categorical variables were analyzed by nonparametric Kruskal–Wallis, and Mann–Whitney *U* tests. For categorical variables, we used the χ^2 test or Fisher's exact test (dichotomic variables and $\geq 20\%$ cells with

expected count <5). To assess associations, we used binomial and multinomial logistic regression to obtain crude and adjusted odds ratios (ORs) with 95% confidence intervals (CIs). The nomogram was constructed and drawn using R software version 4.1.2. The C-statistics between the nomograms and each of the independent predictor variables were compared using the DeLong test. Calibration curves were used to analyze the agreement between the predictions of the column line plots and the actual observations. Decision curve analyses (DCA) were performed to assess the clinical utility of the predicted column-line plots by estimating the net benefit under the threshold probabilities of LBW types.

All tests with statistical significance were bilateral, and a p -value <0.05 was considered to indicate statistical significance.

Results

A total of 4,837 pregnant women with GDM were identified in the electronic database, and 2,869 pregnant women with GDM met the inclusion and exclusion criteria after excluding 146 women with multiple births, 14 cases of stillbirth, 207 cases of pregestational diabetes, and 1,601 cases with missing data. A total of 193 cases of neonatal LBW were found, and the incidence of LBW was 6.73%. A total of 193 normal-weight infants born to pregnant women with normal GDM in the same period after PSM1:1 were selected as the control group and the corresponding technical roadmap is shown in Figure 1.

Univariate analysis revealed that age, education level, history of preterm birth, history of fetal distress, hypertensive disorders complicating pregnancy, threatened preterm birth, average weekly abdominal circumference growth rate and weight gain during pregnancy were significantly different ($p < 0.05$), as shown in Table 1.

Considering the importance of triglycerides during pregnancy on birth weight (12), triglycerides were included in the regression analysis

as a potential independent variable. Collinearity diagnosis was performed on latent variables and variables with significant univariate analysis results ($p < 0.05$), and the results showed that all variables did not have collinearity and could be included in multivariate logistic regression analysis. With neonatal LBW as the dependent variable (1 = LBW, 0 = normal birth weight), backward regression was used to screen variables, and $p = 0.15$ was the exclusion criterion. The results showed that age ≥ 36 years, middle school and below education, threatened preterm labor, gestational hypertension, and excessive weight gain during pregnancy were risk factors for LBW born to GDM women. Compared with that of women 18–35 years old, the risk of LBW delivery was 1.795 times greater in GDM women ≥ 36 years old. Compared with women with a college education or above, the risk of LBW delivery was 4.424 times greater for GDM women with a junior high school education or below. Compared with those without preterm birth, the risk of LBW delivery was 18.073 times greater in those with preterm birth. The risk of LBW delivery was 7.829 times greater in those with pregnancy-induced hypertension than in those without pregnancy-induced hypertension. Compared with those who gained a normal weight during pregnancy, the risk of LBW delivery was 2.031 times greater in those who gained less weight during pregnancy. Triglycerides during pregnancy and a history of fetal distress were protective factors. For every 1 mmol/L increase in triglycerides in early pregnancy, the risk of LBW delivery in GDM women decreased 1.538 times. The risk of LBW delivery was 8.065 times greater for GDM women with no previous history of fetal distress than for those with a history of fetal distress, as shown in Table 2.

Evaluation of discrimination

The ROC curve (Figure 2) was constructed by using the predicted probability of logistic regression as the state variable and LBW as the

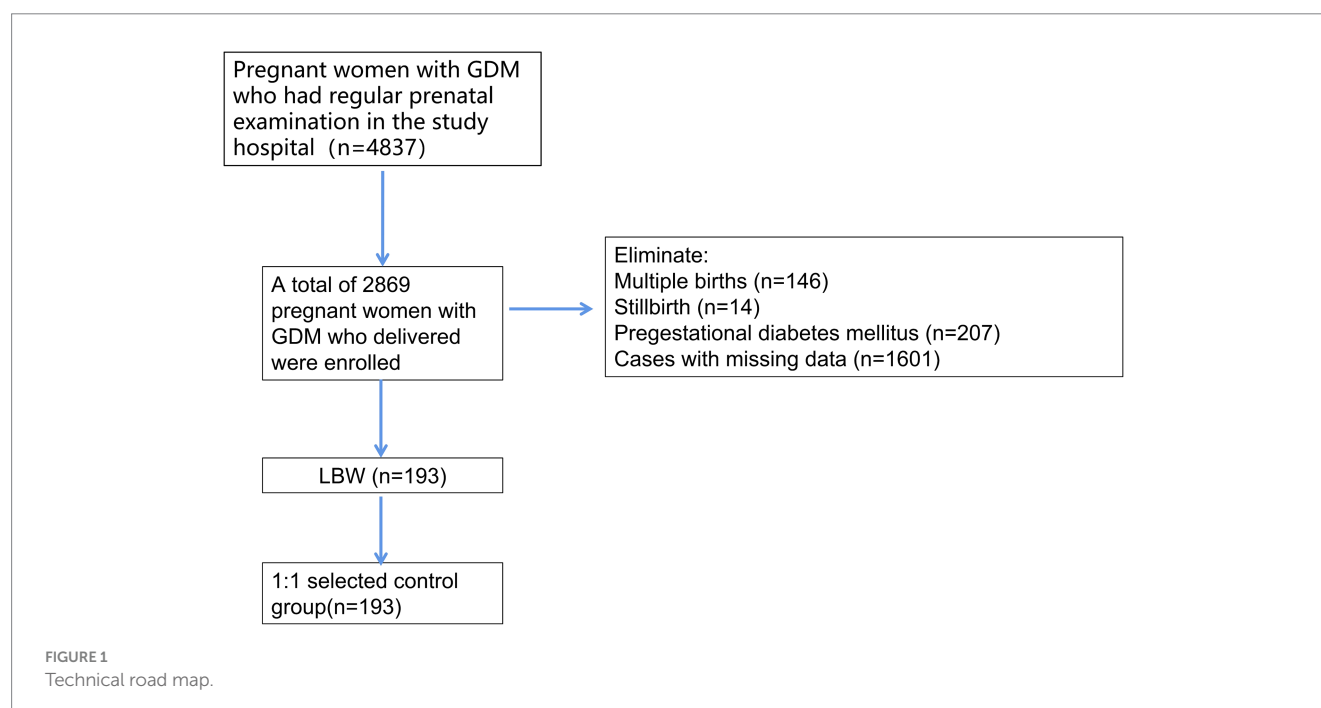


TABLE 1 Factors associated with LBW for pregnant women with GDM [N(%)/X ± SD/M(P₂₅, P₇₅)].

	LBW (n = 193)	Normal weight (n = 193)	$\chi^2/t/Z$	P
Age				
18 ~ 35	140(72.5)	159(82.4)	5.357	0.021
≥36	53(27.5)	34(17.6)		
Degree of education				
Junior high school and below	35(18.1)	10(5.2)		<0.001
High school	61(31.6)	79(40.9)	16.447	
University and above	97(50.3)	104(52.9)		
History of fetal distress				
No	191(99.0)	184(95.3)	4.585	0.032
Yes	2(1.0)	9(4.7)		
Hypertensive disorders of pregnancy				
No	152(78.8)	181(93.8)	18.393	<0.001
Hypertension in Pregnancy	41(21.2)	12(6.2)		
Threatened preterm labor				
No	115(59.6)	182(94.3)	65.553	<0.001
Yes	78(40.4)	11(5.7)		
Pregnancy weight gain				
Underweight gain	127 (65.80)	88 (45.60)	-----	<0.001
Normal weight gain	16(8.29)	22(11.40)		
Hyper weight gain	50(25.91)	83(43.01)		
Average weekly abdominal circumference growth rate	0.69(0.52–0.91)	0.75(0.63–0.93)	–2.412	0.016

TABLE 2 Multiple regression analysis for the factors associated with LBW among pregnant women with GDM.

Determinant	β	S.E	Wals χ^2	P	OR	95%CI	
≥36 years old	0.585	0.305	3.677	0.055	1.795	0.987	3.263
Junior high school and below ^a	1.487	0.438	11.525	0.001	4.424	1.875	10.439
High school ^a	–0.174	0.269	0.416	0.519	0.841	0.496	1.425
A history of fetal distress	–2.084	1.035	4.055	0.044	0.124	0.016	0.946
Gestational hypertension ^b	2.058	0.423	23.661	<0.001	7.829	3.417	17.940
Threatened preterm labor	2.894	0.392	54.428	<0.001	18.073	8.377	38.992
Triglycerides in early pregnancy	–0.430	0.141	9.263	0.002	0.650	0.493	0.858
Insufficient weight gain during pregnancy ^c	0.709	0.275	6.625	0.010	2.031	1.184	3.484

^aUniversity education or above as reference; ^bNo hypertensive diseases during pregnancy as reference; ^cappropriate weight gain during pregnancy as reference.

test variable, and the AUC value was 0.829 (95% CI: 0.789–0.870, $p < 0.001$), indicating that the diagnostic value was good. When the optimal cutoff value of the model was 0.464, the sensitivity and specificity were 70.46 and 82.90%, respectively.

Evaluation of calibration

The Hosmer–Lemeshow goodness of fit test was used to evaluate the calibration ability of the prediction model. The likelihood ratio 2 was 0.353, and the p value was 0.553, indicating that there was no significant difference between the predicted value and the observed value, and the calibration degree of the model had a good degree of fit.

Nomogram

Based on the results of the multivariable analyses, a nomogram for the risk of LBW resulting from GDM was constructed, as shown in Figure 3. Each value of these variables yields a score on the score axis. Each score can easily be added up to create a total score, and by extrapolating the total score to the entire score scale, the likelihood of LBW can be calculated. Pregnancy-induced hypertension was found to have the greatest impact on the prediction of LBW.

The calibration curves overlap the ideal line, indicating that the actual probabilities are in good agreement with the LBW probabilities predicted by the column plot. The discrimination of the nomogram yielded a c-index of 0.834. The mean absolute error of the calibration

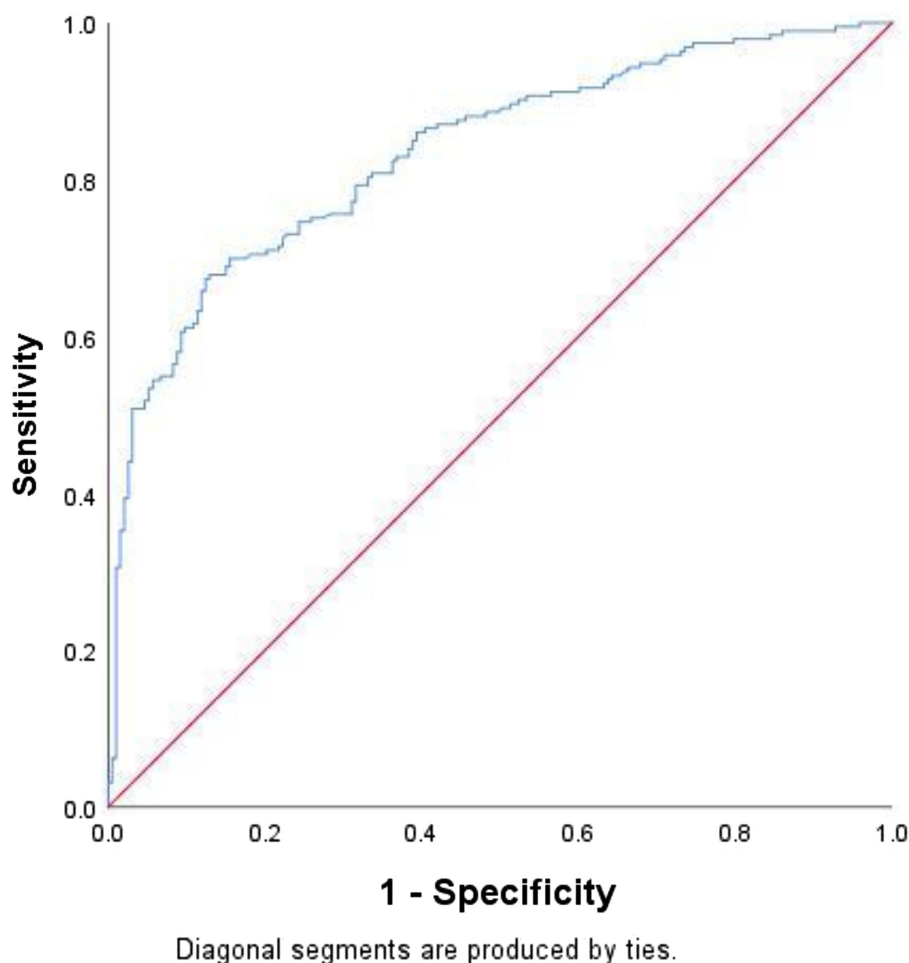


FIGURE 2
ROC curve plots. The sensitivity is the abscissa, and the (1-specificity) is the ordinate.

curve of the nomogram was 0.015 (Figure 3). The DCA plot showed good positive net benefits in the predictive nomogram model for majority threshold probabilities (Figure 4).

Discussion

Principal findings

This is a study of a prediction model and risk score for LBW infants who were born to pregnant women with GDM in Southeast China. The risk score includes several factors during pregnancy.

With the exposure to long- and short-term harm caused by the poor birth weight of neonates born to pregnant women with GDM, related research on the influencing factors of LBW has become a focus. The results of this study showed that the LBW of pregnant women with GDM was mainly related to basic conditions during pregnancy, adverse pregnancy history, insufficient weight gain during pregnancy, and hypertensive disorders during pregnancy.

Clinical implications

Demographic data

We found that the risk of LBW was greater in pregnant women with GDM who had a junior high school education or less than in those with a college education or above. The educational level can be used as an indicator of individual socioeconomic status to a certain extent and is usually an important determinant of diet, living status, and health care during pregnancy (18). Studies have shown that those with lower education levels have fewer prenatal visits (19), poor awareness of health care during pregnancy, and a greater likelihood of delivering LBW.

Age is an important influencing factor of LBW in pregnant women with GDM. Under the influence of various social factors, such as the mature application of reproductive technology, the gradual increase in women's education level, and occupational demand, the number of women of advanced maternal age is gradually increasing, but this population faces greater pregnancy risk. Therefore, the role of health education cannot be ignored. It is necessary to disseminate knowledge about the increased incidence of adverse maternal and infant outcomes in older adult women. At the

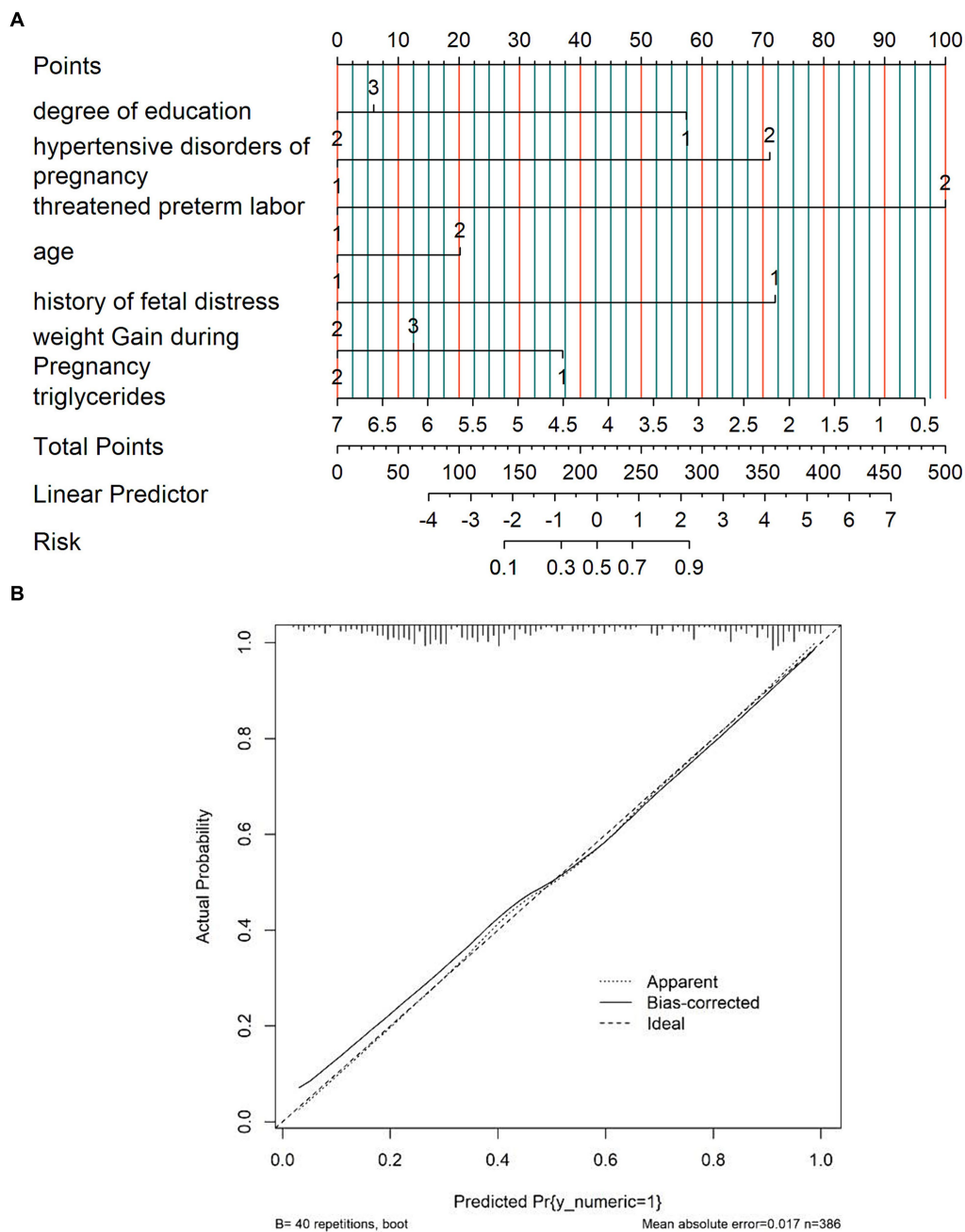


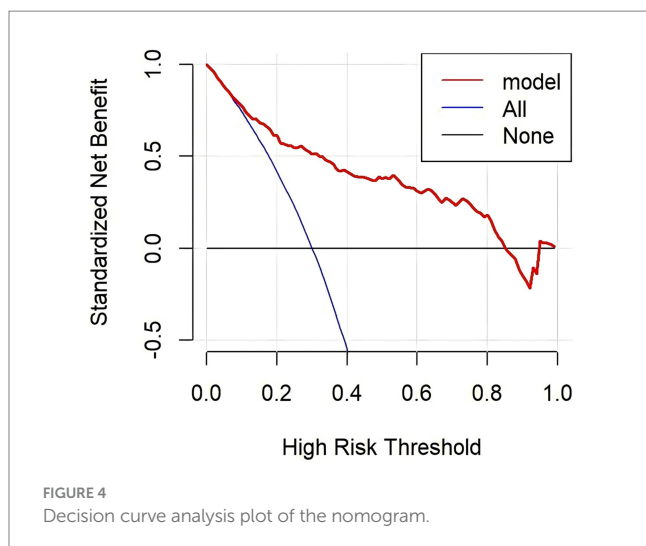
FIGURE 3
Nomogram and calibration curve for the incidence risk of low-birth-weight infants born to women with gestational diabetes mellitus in China:
(A) nomogram and (B) calibration plot.

same time, it is necessary to further improve the prenatal examination system so that all pregnant women can receive standardized and systematic prenatal screening in early pregnancy to ensure the health of mothers and children.

Hypertensive disorders of pregnancy

The presence of hypertensive disorders complicating pregnancy is an important factor for predicting LBW in women with GDM. At present, a large number of international conclusions support that

gestational hypertension and preeclampsia are risk factors for LBW (20), which is consistent with our results. The reason should be that GDM in pregnant women complicated with hypertensive disorders during pregnancy may affect the activity of glycogen glycolysis enzymes in the placenta but make it difficult for the fetus to obtain oxygen and nutrition, thus affecting the growth and development of the fetus (21) and eventually causing pregnant women with GDM to experience LBW. Especially for pregnant women with GDM and preeclampsia, glucose control is more difficult, resulting in poor glucose control. At the same time, placental small vessel spasm significantly reduces placental blood perfusion, causes placental



function decline, and eventually increases the incidence of LBW. Therefore, in addition to close monitoring of blood pressure during pregnancy, health education during pregnancy should be increased. Yue et al. showed that there is an interaction effect between health education during pregnancy and gestational hypertension. Health education for pregnant women with hypertension can reduce the incidence of LBW, improve the awareness rate of knowledge related to gestational hypertension, increase the awareness of pregnancy health care for pregnant women with GDM (22), promote self-monitoring of blood pressure, and promote maternal and child health. Urinary protein should also be routinely monitored in pregnant women with GDM in the prenatal clinic.

Weight gain during pregnancy

As the obesity epidemic continues, many physicians are interested in minimizing gestational weight gain for all women. High rates of gestational weight gain, especially in the first trimester, are associated with an increased risk of gestational diabetes mellitus (23). Studies on the relationship between GDM and neonatal weight have focused more on macrosomia (24). This study revealed that inadequate GWG was a risk factor for LBW infants, but no association was found between excessive GWG and LBW infants. A recent retrospective study in China showed that women with inadequate weight gain were 2.48 times (10) more likely to deliver low LBW than those with adequate weight gain, and the same retrospective study in Portugal was 1.36 times more likely (25). Our study has similar results. In this study, the proportion of pregnant women who experienced insufficient weight gain during pregnancy was 55.70%, which was similar to the results of a Korean study (26). Pregnant women diagnosed with GDM pay more attention to weight control, including diet and physical activity, during the remainder of their pregnancy (27), but they should be aware that an overcontrolled diet can lead to LBW.

Therefore, it is necessary to formulate gestational weight control guidelines for pregnant women with GDM based on prepregnancy BMI, carry out a “gestational diabetes specialist clinic,” guide the diet and exercise intervention of pregnant women with GDM, strengthen blood glucose monitoring, and control pregnancy weight within a reasonable range.

Triglycerides in early pregnancy

Maternal triglycerides (TGs) are important for intrauterine development (28). TGs mainly play a role in saving energy providing energy to the human body and participating in energy metabolism (29). Lipogenesis and fat accumulation are enhanced in early pregnancy to prepare for rapid neonatal growth during later gestational stages. Fatty acids derived from maternal plasma TG can promote the placental expression of insulin-like growth factors to promote intrauterine fetal growth (30). Free fatty acid levels increase during the first and second trimesters of normal pregnancy and return to normal during the third trimester. High TG levels can promote the transport and decomposition of lipids by the placenta, accelerate the synthesis of amino acids and proteins, promote the deposition of fat in the fetus, and lead to macrosomia. It was found that maternal lipid levels in early gestation correlated with neonatal birth weight (31). Previous studies have also shown that high maternal TG levels are associated with increased birth weight in European and Chinese populations (32). Another study in China showed that the birth weight of newborns in the GDM group was correlated with TG, and the correlation coefficient ($r = 0.604$; $p < 0.05$) was not significant in the non-GDM group. It is speculated that TG can be used to monitor advanced GDM (33). This study revealed that elevated TG levels in the first trimester of pregnancy in women with GDM were a protective factor against LBW in neonates. It is suggested that pregnant women diagnosed with GDM need to develop a refined diet control plan according to the TG level in the first trimester to control triglycerides at a reasonable level.

Threatened preterm birth

This study revealed that threatened preterm birth was a risk factor for LBW in pregnant women with GDM, which is consistent with the results of previous studies (34). Therefore, when pregnant women have irregular contractions, vaginal water, and other symptoms of threatened preterm birth, we should be alert to the possibility of preterm birth and delivery of LBW infants and provide timely corresponding medical interventions to improve the fetal protection rate to improve pregnancy outcomes.

History of fetal distress

This study also revealed that GDM with a history of fetal distress in the previous pregnancy was a protective factor for LBW, which may be due to the experience of a previous adverse pregnancy, leading to increased awareness of pregnancy health care in the next

pregnancy, thereby reducing the incidence of LBW. This topic remains to be further analyzed in the future.

Nomogram

The nomogram is an easy, convenient, and quick tool that can be used to predict the likelihood of delivering LBW after a pregnant woman has been diagnosed with GDM. Nomograms can individually estimate the probability of LBW by integrating various risk predictors, which meet our desire for visual tools and fulfill our drive toward personalized prevention. Through a user-friendly digital interface, improved accuracy, and easier-to-understand risk predictions compared to traditional mathematical formulas, rapid computational nomograms can seamlessly integrate risk assessment into clinical decision-making (35). In recent years, nomograms have been gradually applied to obstetrics and gynecology and maternal and child health care in China, for example, Chuangchuang Xu et al. (36) developed a prediction model for early postpartum stress urinary incontinence in women who had vaginal deliveries, and Mei Kan et al. (37) developed a model for identifying GDM in early pregnancy.

With the help of these simple, rapid, inexpensive, and noninvasive tools, we expect to be able to effectively identify individuals with a potentially increased risk of LBW delivery among pregnant women with GDM. For pregnant women with GDM who are at risk of delivering infants with LBW, medical staff need to be more cautious in medical intervention, pay attention to the intrauterine growth and development of their newborns, and provide targeted prenatal care.

Research implications

In conclusion, women with GDM are likely to birth LBW infants. This study confirms the necessity and feasibility of assessing LBW at delivery in all pregnant women with GDM. Using the nomogram, physicians in the obstetrics clinic can quickly and directly identify pregnant women with GDM who are at risk for LBW. Based on this, personalized health interventions are initiated, which can help improve neonatal outcomes.

Strengths and limitations of the study

Overall, our findings provide potential predictive factors for the LBW of infants born to GDM mothers, and the developed risk prediction model facilitates the visual representation of these risks, which is beneficial for clinical application and dissemination. This model also offers useful guidance and practical value for the early identification of high-risk GDM mothers with LBW infants.

The findings of this study should be considered in the context of the following limitations. First, we collected data from only one hospital, and the results are not nationally representative and may not apply to all women in China or elsewhere. Second, the nomogram must be tested for its validation due to its first development. Third, this study was based on a retrospective case–control study to construct a risk prediction model. Some potential confounding factors were not

collected, such as smoking, baseline diet, exercise, and psychological indicators in pregnant women.

Conclusion

This study developed a prediction model and risk score for LBW infants who were born to pregnant women with GDM in Southeast China.

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 The Human Subjects Ethics Committee of Fujian Maternity and Child Health Hospital. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

YP: Writing – original draft, Validation, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. XH: Writing – original draft, Validation, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. XJ: Writing – review & editing, Validation, Project administration, Investigation, Conceptualization.

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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.

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References

- Metzger Boyd E, Lowe Lynn P, Dyer Alan R, Coustan Donald R, Hadden David R, McCance David R, et al. Hyperglycemia and adverse pregnancy outcomes. *N Engl J Med*. (2008) 358:1991–2002. doi: 10.1056/NEJMoa0707943
- Lee KW, Ching SM, Ramachandran V, Yee A, Hoo FK, Chia YC, et al. Prevalence and risk factors for gestational diabetes mellitus in Asia: a systematic review and meta-analysis. *BMC Pregnancy Childbirth*. (2018) 18:494. doi: 10.1186/s12884-018-2131-4
- Mithal A, Bansal B, Kalra S. Gestational diabetes in India: science and society. *Indian J Endocrinol Metab*. (2015) 19:701–4. doi: 10.4103/2230-8210.164031
- Xe XF, Kong BH, Duan T. Obstetrics and gynecology. 9th edn. Beijing: People's Medical Publishing House (2018).
- Xu YN, Xiao SJ, Liu W. Risk prediction of macrosomia in gestational diabetes mellitus. *Chin J Clinical Research*. (2020) 33:371–3.
- Xin P, Jiang GH, Zheng WL. Effect of birth weight on the risk of chronic diseases and blood uric acid in adulthood. *Chin J Epidemiology*. (2021) 42:1213–7.
- Chen J, Xiao H, Yang Y, Tang Y, Yang X, Zhang Z, et al. Demographic and clinical features of small-for-gestational-age infants born to mothers with gestational diabetes mellitus. *Front Pediatr*. (2021) 9:741793. doi: 10.3389/fped.2021.741793
- Xiang AH, Black MH, Li BH, Martinez MP, Sacks DA, Lawrence JM, et al. Racial and ethnic disparities in extremes of fetal growth after gestational diabetes mellitus. *Diabetologia*. (2015) 58:272–81. doi: 10.1007/s00125-014-3420-8
- Naha K, Pandit VR, Seshadri S, Naha K. A simple score to predict fetal outcomes in gestational diabetes mellitus. *Biom J*. (2015) 38:131–5. doi: 10.4103/2319-4170.131399
- Su WJ, Chen YL, Huang PY, Shi XL, Yan FF, Chen Z, et al. Effects of Prepregnancy body mass index, weight gain, and gestational diabetes mellitus on pregnancy outcomes: a population-based study in Xiamen, China, 2011–2018. *Ann Nutr Metab*. (2019) 75:31–8. doi: 10.1159/000501710
- Disse E, Graepi-Dulac J, Joncour-Mills G, Dupuis O, Thivolet C. Heterogeneity of pregnancy outcomes and risk of LGA neonates in Caucasian females according to IADPSG criteria for gestational diabetes mellitus. *Diabetes Metab*. (2013) 39:132–8. doi: 10.1016/j.diabet.2012.09.006
- Radwan MA, El Mansori NA, Elfergani MA, Halies FR, Lawgali MA. Neonatal morbidity pattern among infants born to diabetic mothers at Jamhouria hospital, Benghazi-Libya. *AJPR*. (2021) 38–55
- Ye W, Luo C, Huang J, Li C, Liu Z, Liu F. Gestational diabetes mellitus and adverse pregnancy outcomes: systematic review and meta-analysis. *BMJ*. (2022) 377:e067946. doi: 10.1136/bmj-2021-067946
- Hildén K, Magnuson A, Hanson U, Simmons D, Fadl H. Trends in pregnancy outcomes for women with gestational diabetes mellitus in Sweden 1998–2012: a nationwide cohort study. *Diabet Med*. (2020) 37:2050–7. doi: 10.1111/dme.14266
- Yang HX, Xu XM, Wang ZL. Guidelines for the diagnosis and treatment of gestational diabetes mellitus (2014). *Chin J Perinatol*. (2014) 17:537–45.
- Huang X, Tan H, Cai M, Shi T, Mi C, Lei J. Gestational weight gain in Chinese women – results from a retrospective cohort in Chang-sha, China. *BMC Pregnancy Childbirth*. (2018) 18:185. doi: 10.1186/s12884-018-1833-y
- Institute of Medicine and National Research Council Committee to reexamine IOM pregnancy weight guidelines. Weight gain during pregnancy: Reexamining the guidelines[M]. Washington: National Academies Press (2009).
- Tang XY, Xiao ZY, Li YM. Case-control study of obstetric risk factors in small for gestational age infants. *Chin J Epidemiol*. (2005) 26:915–8.
- Wang HL, Zhao N, Liu R. Effects of maternal education level and frequency of prenatal care on low birth weight and their interaction moderating effect. *J Xi'an Jiaotong Univ*. (2019) 40:144–8.
- Omani-Samani R, Ranjbaran M, Amini P, Esmailzadeh A, Sepidarkish M, Almasi-Hashiani A. Adverse maternal and neonatal outcomes in women with preeclampsia in Iran. *Matern Fetal Neonatal Med*. (2019) 32:212–6.
- Ma YJ, Chen DF. Effect of gestational hypertension on preterm birth and low birth weight. *Chin J Reproductive Health*. (2020) 31:517–21.
- Yue Y, Li YP, Wang SB. Effect of gestational hypertension and health education during pregnancy on low birth weight. *Chin J Public Health*. (2016) 32:1708–11.
- Yan B, Yu Y, Lin M, Li Z, Wang L, Huang P, et al. High, but stable, trend in the prevalence of gestational diabetes mellitus: a population-based study in Xiamen, China. *J Diabetes Invest*. (2019) 10:1358–64. doi: 10.1111/jdi.13039
- Shi P, Liu A, Yin X. Association between gestational weight gain in women with gestational diabetes mellitus and adverse pregnancy outcomes: a retrospective cohort study. *BMC Pregnancy Childbirth*. (2021) 21:508. doi: 10.1186/s12884-021-03982-4
- Chen XJ, Coelho A. Association between body mass index and gestational weight gain with obstetric and neonatal complications in pregnant women with gestational diabetes. *Acta Medica Port*. (2022) 35:718–28. doi: 10.20344/amp.15896
- Han K, Kwak DW, Ryu HM, Park HY. Insufficient weight management in pregnant women with gestational diabetes mellitus. *Osong Public Health Res Perspect*. (2022) 13:242–51. doi: 10.24171/j.phrp.2022.0182
- Choi H, Lim JY, Lim NK, Ryu HM, Kwak DW, Chung JH, et al. Impact of prepregnancy body mass index and gestational weight gain on the risk of maternal and infant pregnancy complications in Korean women. *Int J Obes*. (2022) 46:59–67. doi: 10.1038/s41366-021-00946-8
- Ghio A, Bertolotto A, Resi V, Volpe L, di Cianni G. Triglyceride metabolism in pregnancy. *Adv Clin Chem*. (2011) 55:133–53. doi: 10.1016/B978-0-12-387042-1.00007-1
- Chen HQ, Luo Q, Chen GD. Research progress on the relationship between lipid levels during pregnancy and small for gestational age infants. *Prev Med*. (2021) 33:41–5.
- Chen KY, Lin SY, Lee CN, Wu HT, Kuo CH, Kuo HC, et al. Maternal plasma lipids during pregnancy, insulin-like growth Factor-1 and excess fetal growth. *J Clin Endocr Metab*. (2021) 106:e3461–72. doi: 10.1210/clinem/dgab364
- LaBarre JL, Puttabyatappa M, Song PXX, Goodrich Jaclyn M, Zhou L, Rajendiran TM, et al. Maternal lipid levels across pregnancy impact the umbilical cord blood lipidome and infant birth weight. *Sci Rep*. (2020) 10:14209. doi: 10.1038/s41598-020-71081-z
- Liu PJ, Liu Y, Ma L, Yao AM, Chen XY, Hou YX, et al. The predictive ability of two triglyceride-associated indices for gestational diabetes mellitus and large for gestational age infant among Chinese pregnancies: a preliminary cohort study. *Diabetes Metab Syndr Obes*. (2020) 13:2025. doi: 10.2147/DMSO.S251846
- Jiang ZF (2022). Changes and clinical significance of serum TNF- α and blood lipid levels in pregnant women with gestational diabetes mellitus. Master's thesis, Dalian Medical University
- Fang HX, WJC LHJ. Multiple correspondence analysis of factors associated with neonatal birth weight. *Med Theory Pract*. (2021) 34:1732–4.
- Balachandran VP, Gonen M, Smith JJ, DeMatteo RP. Nomograms in oncology: more than meets the eye. *Lancet Oncol*. (2015) 16:e173–80. doi: 10.1016/S1470-2045(14)71116-7
- Chuangchuang X, Ying G, Xiaolei C. Establishment and validation of a simple nomogram for predicting early postpartum stress urinary incontinence among women with vaginal delivery: a retrospective study. *BMC Womens Health*. (2023) 23. doi: 10.1186/s12905-023-02160-2
- Kang M, Zhang H, Zhang J, Huang K, Zhao J, Hu J, et al. A novel nomogram for predicting gestational diabetes mellitus during early pregnancy. *Front Endocrinol*. (2021) 12:779210. doi: 10.3389/fendo.2021.779210



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Intergenerational crosstalk of brain-gut axis in parental Nd₂O₃ exposure-induced offspring neurotoxicity and cognitive dysfunction: a mechanistic study

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Introduction: Rare earth elements (REEs) are widely used in plenty of fields. REEs have significant neurotoxicity and it may adversely affect the development of cognitive. For example, neodymium will causing neurological damage through penetrate the blood-brain barrier (BBB). However, whether it disrupts the balance of brain-gut axis (BGA) crosstalk and affects the intestinal microecology disorder of host is still unclear. This study investigated the neural damage on children caused by maternal exposure to Neodymium oxide (Nd₂O₃) during pregnancy, and its involved mechanism of BGA injury.

Methods: We used rat model to investigated the mechanisms of the offspring's neural damage that Nd₂O₃ exposure in pregnancy. To verify the neural damage of offspring rats, we examined BBB-related factors, such like glutamate and ROS levels in brain tissue, behavioral tests, hippocampal and cortical damage, as well as changes in gut microbiota, intestinal mucosal barrier, and SCFAs in the intestine. Also, we observed some specific indicators of intestinal immune barrier function and gut nerve-related indicators.

Results: Maternal Nd₂O₃ exposure reduced the content of offspring tight junction proteins, increased BBB permeability, leading to Nd accumulation and brain tissue inflammation, affecting offspring's neural development and weakening their spatial learning ability. Nd₂O₃ also disrupted BBB integrity by regulating SCFAs and BGA. Probiotic intervention in the offspring rats exposed to 2% Nd₂O₃ showed significant recovery of inflammation in both brain and colon tissues, and reduced BBB permeability.

Conclusion: Maternal exposure to Nd₂O₃ affects the offspring's BGA, targeting brain and colon tissues, increasing BBB permeability, affecting neural development, causing damage to the intestinal mucosa, and impacting children's gut development. Probiotics can alleviate these effects. These findings provide valuable insights into understanding the neurodevelopmental and intestinal developmental toxicity of Nd₂O₃ and its prevention and treatment. It also calls for a comprehensive assessment of the health risks of susceptible populations to Nd₂O₃, such as pregnant women. It may providing theoretical basis for preventing and controlling neodymium-induced harm in children by examining the repair mechanism of the damage through probiotic intervention.

KEYWORDS

Nd₂O₃, brain-gut axis, neurotoxicity, cognitive dysfunction, prenatal exposure

1 Introduction

Rare earth elements (REEs) are widely used in many fields such like agriculture, forestry, animal husbandry, fisheries, and pharmaceutical and chemical industries and so on. The environmental residues and accumulation may be the core reasons that caused REEs raising significant public health concerns, especially in children (1). Currently, REEs have been detected in hair, nails, and bodily fluids of human, leading to nephrogenic systemic fibrosis and severe damage to the renal system, as well as neurological damage, fibrotic tissue injury, oxidative stress, pneumoconiosis, cytotoxicity, anti-testicular effects, and male infertility (2). Among the 17 REEs, La, Gd, Ce, and Eu have been extensively studied, while research on Nd is few (2, 3). Neodymium-iron-boron permanent magnet technology is widely used in various fields, making neodymium account for nearly 50% of the major rare earth market share in the world. However, deeply systematic research on the safety of large-scale mining and application of neodymium, particularly concerning the well-being of children living in high-neodymium exposure environments, has not been investigated. Additional, widespread mining and use of rare earths in address developmental impairments in children is urgently necessary.

Epidemiological studies conducted in several major rare earth mining areas in China have shown that the average IQ, cognitive abilities, and learning and memory capabilities of children in these areas are significantly lower than those which in control areas (4). Therefore, REEs have significant neurotoxicity and can have adverse effects on cognitive development (1–4).

Additional, nanometer neodymium oxide (Nano-Nd₂O₃) administered by nasal instillation has a mild stimulating effect on learning and memory in mice by affecting the activity of calcium ion channels (5). Furthermore, studies have found that Nano-Nd₂O₃ can lead to a decrease in the ability of brain tissue to remove lipid peroxides and an increase in oxidative stress levels in mice, demonstrating its toxic effects on the central nervous system (6). Nano-Nd₂O₃ disrupts the oxidation-antioxidant balance in the hippocampus and alters the levels of amino acid neurotransmitters, leading to neuronal damage and impairing learning and memory function in developing rats (7).

The first barrier that rare earth elements must overcome to damage the nervous system is the blood–brain barrier (BBB). The BBB is a multicellular complex composed of brain microvascular endothelial cells (BMECs), tight junctions (TJs) between cells, the basement membrane, and embedded pericytes and astrocyte foot processes. It can prevent certain toxic substances from entering the brain, protecting brain tissue from invasion by toxic substances and pathogens in the blood, providing nutrients to brain tissue, and maintaining the internal environment of the central nervous system (CNS) (8). The immature development of the BBB in early postnatal life provides an opportunity for metals and other toxic substances to enter brain tissue. Additionally, these substances may disrupt TJs, causing the BBB to leak and allowing more toxic substances to enter and accumulate in brain tissue, affecting the proliferation and differentiation of nerve cells and synaptic structure and function, leading to neural developmental damage. However, there have not been researches about whether Nd can break through the BBB as we know.

The human gut is the “secret garden” of 10 trillion diverse symbionts, collectively known as the “microbiota.” Microbiota are 10 times more abundant than our somatic and germ line cells of the body. The collective genes of microbiota are known as the “microbiome” which is 150 times larger than the human genome (9, 10). Certain crucial traits are indispensable for microbes aiming to colonize new environments. These include a comprehensive suite of enzymes that enables them to harness accessible nutrients effectively, a precise configuration of cell-surface molecules that facilitates adherence to suitable niches within their prospective habitats. Additionally, the capacity to circumvent predation by bacteriophages and adaptiveness to counteract the vigilant immune responses of the host organism are paramount. It's also essential for these microorganisms to possess resilience against both the physical and chemical rigors present in the gastrointestinal tract, allowing them to multiply swiftly while resisting expulsion through peristalsis (11).

Significant progress has been made in elucidating the bidirectional interactions between the nervous system, the gut, and the gut microbiota based on studies in experimental animals. Many studies have shown that the gut microbiota can regulate the structure and function of the enteric nervous system, forming a bidirectional connection with the gut-brain axis (GBA), thereby constituting the Brain-Gut-Microbiome (BGM) axis (12). The gut microbiota and its metabolites can influence the brain through neural, immune, and endocrine pathways, and the brain, in turn, regulates the composition of the gut microbiota through this pathway to maintain gut microbial balance. There have been no reports on the effects of rare earth neodymium exposure on the BGM axis in children living in rare earth mining areas. Studies have indicated that signal transduction within the BGM axis is regulated by two dynamic barriers, namely the BBB and the intestinal barrier (13).

Neodymium causes damage to the nervous system, but whether it leads to changes in the balance of BGA crosstalk, affecting the imbalance of the host's gut microbiota and leading to changes in the BGA, has not been reported as we know. Therefore, starting from this specific group of children, it is crucial to study the effects and mechanisms of maternal exposure to Nd₂O₃ during pregnancy on BGA damage, and how to prevent and control the damage caused by neodymium to children, which is of great significance both at the individual and national levels. This study aims to explore the impact of neodymium on the development of the BGA in children, and thus provide a theoretical basis for the prevention and control of neodymium-induced damage during childhood.

2 Materials and methods

2.1 Animals and treatment

Sixty healthy adult female rats and sixty male rats weighing 260 ± 10 g were provided by Sbeifu (Beijing) Biotechnology Co., Ltd. and kept in the animal room for at least 1 week to adapt to the environment. The environmental temperature in the animal room was maintained at 17–23°C, with a relative humidity of 45–55%. The

animal feed was provided by the Animal Experimental Center. Rats were mated in a 1:1 ratio of male to female, and the morning after mating, the presence of a vaginal plug marked as pregnancy day 0. Referring to previous research by Gao et al. (14, 15), the administration of Nd₂O₃ occurred during the gestation and lactation periods (22 days +21 days), with dosing frequencies of 0, 50, 100, and 200 mg/(kg·d). Pregnant rats were randomly divided into control group (distilled water of equal volume), 0.5% Nd₂O₃ group, 1% Nd₂O₃ group, 2% Nd₂O₃ group, and 2% Nd₂O₃ + BTVT (Bifidobacterium tetrad viable tablet, with the main component of Lactobacillus, Hangzhou Yuanda Biopharmaceutical Co., Ltd., 150 mg/kg) group for Nd₂O₃ gavage exposure during pregnancy and lactation, establishing an animal model of offspring exposure (gestation: pregnancy day 22, weaning: pregnancy day 43). All pregnant rats were fed *ad libitum* with food and water until the offspring were fed till adulthood (postnatal day 83) to conclude the animal experiment. Behavioral interventions using the BTVT model commenced on postnatal day 1 (PND 1). Given that the BBB is not yet fully developed in infants under 6 years of age and in rats within 21 days postnatally (specifically during the weaning period at PND 43), the study was conducted on pups at PND 43.

2.2 Nd₂O₃ exposure-induced neurological damage

2.2.1 Detection of BBB-related factors

Ten offspring rats from each of the following groups—pregnant rats exposed to 0.5% Nd₂O₃, 1% Nd₂O₃, 2% Nd₂O₃, 2% Nd₂O₃ + BTVT, and the control group (distilled water of equal volume) - were randomly selected for BBB-related tests on PND43 (postnatal day 43). ICP-MS was used to detect the rare earth neodymium content in the rat brains, the Evans blue method was employed to observe changes in blood–brain barrier (BBB) permeability in offspring rats, and transmission electron microscopy was used to observe ultrastructural changes in the BBB. qPCR was used to detect changes in the expression of TJs such as *Occludin* and *ZO-1* in the brain tissue of offspring rats (primer sequences are listed in Table 1). The study aimed to discuss the impact of Nd₂O₃ exposure on the BBB permeability of offspring rats and its mechanism. Furthermore, relevant issues regarding the damage caused by Nd₂O₃ to the integrity of the BBB in the offspring rat brain were explored.

2.2.2 Behavioral experiments in offspring rats

Five randomly selected offspring rats from pregnant rats exposed to 0.5% Nd₂O₃, 1% Nd₂O₃, 2% Nd₂O₃, 2% Nd₂O₃ + BTVT,

and the control group (distilled water of equal volume) were subjected to relevant behavioral experiments on PND43. The experiments primarily included the Morris water maze test, aiming to investigate changes in learning and memory functions in offspring rats induced by Nd₂O₃ exposure. The Morris water maze consists of two parts: a spatial navigation part for the first 5 days and a spatial exploration part for the 6th day, reflecting the learning and memory ability of the offspring rats. The first 5 days constituted the training period, with the maze being circular and divided into four quadrants, and a small platform placed in one of the quadrants. The offspring rats entered the pool from fixed entry points in each quadrant, and the time taken to find the platform, i.e., the escape latency, was recorded. The mean value was calculated (capped at 60 s if it exceeded 60 s). On the 6th day, the platform was removed, and the offspring rats were once again placed in the pool from the fixed entry points in the four quadrants, and the number of times the offspring rats crossed the platform area within 60 s was recorded. The mean value was calculated.

2.2.3 Cortical damage in offspring rats

HE staining was used to observe changes in the quantity and shape of nerve cells in the cortical region of the rat brain, aiming to explore the pathological basis of cognitive function changes induced by Nd₂O₃ exposure in offspring rats.

2.3 Nd₂O₃-induced intestinal damage of offspring rats

2.3.1 Changes in the intestinal flora

Fecal DNA from experimental animals was extracted, and gene sequencing was performed on the 16S rRNA of offspring rats in the Nd₂O₃ exposed group and the non-Nd₂O₃ exposed group. PCR amplification and library construction of the target segments were conducted, followed by sequencing and bioinformatics analysis using the Greengenes database. The QIIME2 software was used with the classify-sklearn algorithm to annotate species using a pre-trained Naive Bayes classifier. Alpha diversity and beta diversity assessment of the abundance of the two groups were measured using various indices such as Chao1, Observed species, Shannon, Simpson, Faith's PD, Pielou's evenness, and Good's coverage. Principal coordinate analysis (PCoA) was used to analyze beta diversity, and statistical tests like PERMANOVA, anosim, and permdisp were employed for validation, exploring the impact of Nd₂O₃ exposure on the diversity and abundance of intestinal flora. Random forest analysis with LDA and

TABLE 1 Primer sequences of genes.

Gene	Forward (5'-3')	Reverse (5'-3')
<i>Occludin</i>	GGTGCCATAGAAATGAGATGTTGGA	CCAATGGGCACACCCTGATAC
<i>ZO-1</i>	TTCATCGGTGAAGTAGCCACCA	GACATTAAGGCAGCATCCAGCA
<i>Hrt3a</i>	AACAAGACTGATGACTGCTCAG	GATGGAGGATAGCTCTTGCAAG
<i>Hrt4</i>	AGGTCCGTGGAGAAGGTCGTG	CACAGCCACCATCACCAGCAG
<i>Sst</i>	CCAACCAGACAGAGAATG	ACAGGATGTGAATGTCTTC
<i>β-actin</i>	CCTAAGGCCAACCGTGAAAA	CAGAGGCATACAGGGACAACAC

OPLS-DA was used to identify biomarkers. Community analysis was conducted using a Venn diagram to compare the members and shared ASV/OTU numbers among different groups.

2.3.2 Alterations in the intestinal mucosal barrier

Macroscopic observation included measuring intestinal length, surface color, and integrity changes, while histological observations with HE staining and AB-PAS staining focused on inflammatory cell infiltration, villi, and goblet cell alterations. AB-PAS staining colored goblet cells in the intestine, where the colors represented different substances secreted by the cells. The thickness of the mucous layer was measured at five locations on each slide and averaged. The study discussed the pathological changes in the offspring rat intestines due to Nd₂O₃ exposure.

2.3.3 Impact on SCFAs in the intestines

Fecal samples from experimental animals were analyzed using GC-MS to detect changes in acetic acid, propionic acid, butyric acid, valeric acid, isovaleric acid, and isobutyric acid. The study explored how changes in the intestinal flora due to Nd₂O₃ exposure affected microbial metabolism.

2.4 Nd₂O₃-induced the BGA damage

Detection of intestinal neurogenic markers: Using β -actin as an internal reference, RT-PCR was employed to determine the expression of major intestinal neurotransmitters *Hrt3a* and *Hrt4*, as well as intestinal peptide *Sst* (primer sequences are listed in Table 1). This exploration aims to provide a theoretical basis for understanding the imbalance of the BGA due to Nd₂O₃ exposure.

2.5 Statistical methods

Experimental data were expressed as mean $\pm$ standard deviation and analyzed using SPSS 25.0 statistical software. When the data followed a normal distribution, comparisons of means or one-way analysis of variance (ANOVA) were conducted. When the data did not follow a normal distribution, the Mann-Whitney U test was employed. A significance level of $p < 0.05$ was set to indicate statistical significance.

3 Results

3.1 Mechanism of neurological damage induced by Nd₂O₃ exposure

3.1.1 Detection of neodymium content in the brains of offspring rats

Neodymium content in the brains of offspring rats was measured using ICP-MS. By comparing with the control group, it was observed that as the concentration of parental Nd₂O₃ increased (0.5–2%), the Nd content in the brain tissues of the offspring rats significantly increased ($p < 0.05$). After intervention with Lactobacillus, the Nd content notably decreased ($p < 0.05$) (see Figure 1A). This indicates that parental rat exposure to Nd₂O₃ can lead to Nd accumulation in offspring rats, and Lactobacillus can reduce the accumulation of Nd in offspring.

3.1.2 Observing changes in blood–brain barrier permeability in offspring rats

Using the Evans Blue method, we found that the permeability of Evans Blue in offspring PND43 ($n = 3$) gradually increased with increasing concentrations of maternal Nd₂O₃ ($p < 0.05$). However, following Lactobacillus intervention (2% Nd₂O₃ + BTVT group), there was a significant decrease in Evans Blue permeability ($p < 0.05$) (see Figure 1B). This suggests that maternal exposure to Nd₂O₃ can increase blood–brain barrier permeability in offspring rats, while probiotics reduce its impact on blood–brain barrier permeability.

3.1.3 BBB related factors detection

Detecting the expression changes of TJs (*Occludin*, *ZO-1*) in offspring rat brain tissues. Among them, there was no significant difference in the content of *Occludin* between the control group and the 0.5% Nd₂O₃ group ($p > 0.05$). However, there were significant differences in the comparison between the other groups ($p < 0.05$). As the concentration of Nd₂O₃ increased, the content of *Occludin* decreased. After intervention with Lactobacillus, the content of Nd₂O₃ increased ($p < 0.05$) (see Figure 1C).

Comparing the content of *ZO-1* among groups, except for the 2% Nd₂O₃ + BTVT group, which showed no significant difference compared to the control group ($p > 0.05$), there were significant differences in the remaining groups ($p < 0.05$). Moreover, as the concentration of Nd₂O₃ increased, the content of *ZO-1* gradually

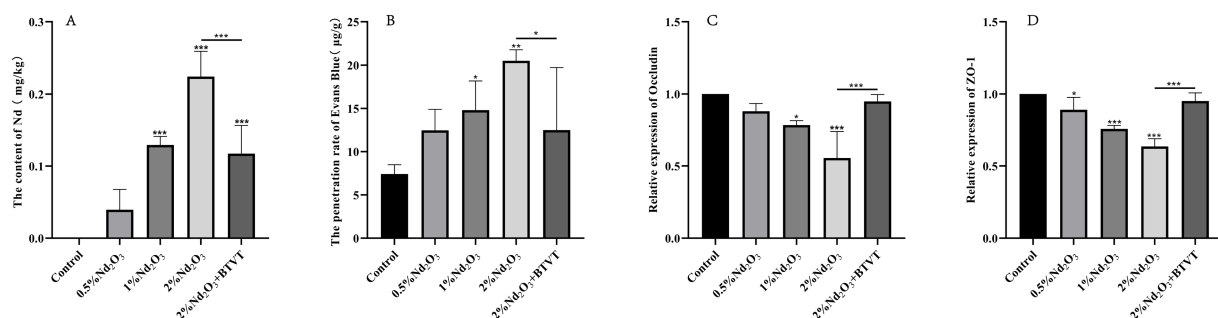


FIGURE 1

Detection of offspring rats exposed to different Nd concentrations in brain tissue and related factors. (A) Evans Blue permeability. (B) Bar graph of Nd concentration in brain tissue. (C) *Occludin* content. (D) *ZO-1* content. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

decreased. After intervention with *Lactobacillus*, the content of ZO-1 in offspring rats treated with 2% Nd₂O₃ significantly increased ($p < 0.01$) (see Figure 1D).

3.1.4 BBB ultrastructural changes

Observation of BBB ultrastructure in 5 groups by transmission electron microscopy revealed that, compared to the negative control group, with the increase in Nd₂O₃ concentration (0.5–2%), the blood–brain barrier structure gradually became irregular. Some areas showed unclear basal membrane structure, local thinning, and rupture. Endothelial cells exhibited swelling, irregular nuclear morphology, significant increase in heterochromatin within the nucleus, swelling of some mitochondria in the cytoplasm, decreased electron density of the matrix with vacuolization, and fragmentation or disappearance of mitochondrial cristae. Tight junction structures were clear, cell membrane structures were blurry, lumens were narrowed, surfaces were not smooth, and partial demyelination was observed around blood vessels, indicating obvious demyelination. After addition of 2% Nd₂O₃ with probiotics, the blood–brain barrier structure within the field of view became regular, mitochondria in the cytoplasm appeared oval or short rod-shaped, the double-layer membrane structure was intact, and the ridge was vague. The cell membrane structure was intact, the surface was relatively smooth, the lumen was rounded, and compared to the pure 2% Nd₂O₃ group, the damage to the blood–brain barrier was significantly reduced (see Figure 2).

3.1.5 Morris water maze experiment

In the spatial exploration experiment, as the days progressed, the number of times each group crossed the platform decreased. As the concentration of Nd₂O₃ increased, the offspring rats showed more and more the escape latency, while the number of crossings decreased after *Lactobacillus* intervention ($p < 0.05$) (see Figure 3A). With the increase of Nd₂O₃ concentration, the frequency of crossing numbers decreased, and the frequency of crossing platform increased after *Lactobacillus* intervention ($p < 0.05$) (see Figure 3B), indicating learning, memory and special function. With the increase in Nd₂O₃ concentration, the trajectories of the offspring rats' location navigation became gradually more complex, the number of deviations increased, and the areas outside the target route gradually increased. However, after adding

Lactobacillus intervention, the offspring rats only deviated from the course once, returned to the predetermined course, and successfully reached the target (see Figure 3C).

3.1.6 Brain tissue structure

Through observation of HE-stained brain tissue sections of the offspring rats, the control group's brain tissue structure was basically normal. In the field of view, the neurons in the cerebral cortex were arranged regularly, abundant in number, with round nuclei, and a tight tissue structure. With the increase in Nd₂O₃ concentration, the tissue structure of the offspring rats gradually became abnormal. Within the field of view, the neurons in the cerebral cortex showed degeneration, deepened staining, and the cell bodies gradually became unclear (see Figure 4).

3.2 Mechanisms of intestinal damage induced by Nd₂O₃ exposure

3.2.1 Sequencing of the intestinal microbiota

Fecal DNA was separately extracted from offspring rats in the non-Nd₂O₃ exposure group (Control group, E1–E6) and Nd₂O₃ exposure group (Nd₂O₃ group, H1–H8). From the perspective of ASV/OTU numbers and Taxa numbers at various classification levels in each sample, columns representing genus and species levels were relatively long, while those representing phylum level were shorter, indicating a higher resolution of annotation included (see Figures 5A,B). After parental rats were exposed to Nd₂O₃, the content of orders Clostridiales, Lactobacillales, and Bacteroidales in the intestinal microbiota of offspring rats increased, while the content of orders Verrucomicrobiales and Enterobacteriales decreased (see Figure 5C). At the species level, Bacteroides, Escherichia, and Akkermansia decreased, while *Lactobacillus*, *Prevotella*, *Parabacteroides*, and *Blautia* increased (see Figures 5D–F).

In terms of diversity, our study utilized multiple indices to evaluate the *alpha* diversity of offspring rats after Nd₂O₃ exposure from various dimensions. In this research, only Faith's PD index showed statistical significance between the two groups ($p < 0.05$) (see Figure 6F), indicating differences in evolution-based *alpha* diversity between the two groups.

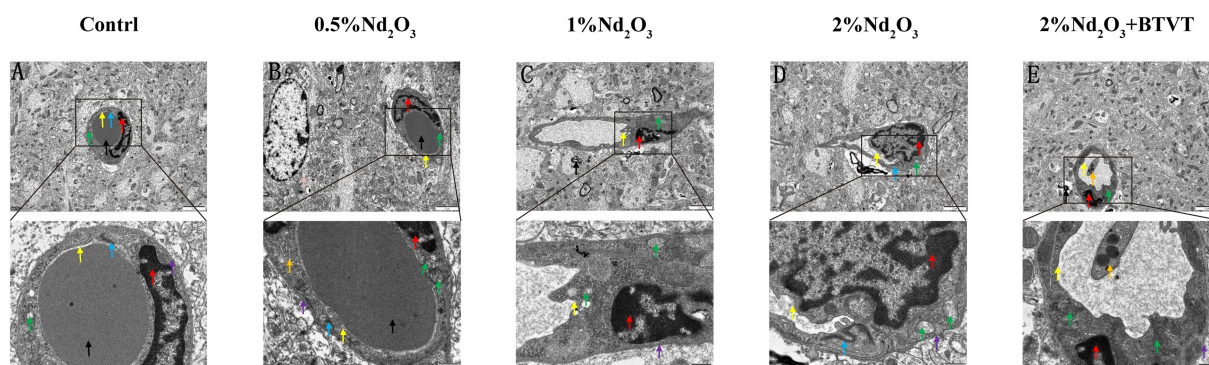


FIGURE 2

Ultrastructural observations of brain tissue under electron microscopy. (A) Control group. (B) 0.5% Nd₂O₃ group. (C) 1% Nd₂O₃ group. (D) 2% Nd₂O₃ group. (E) 2% Nd₂O₃ + BTVT group. Red arrows indicate: endothelial cell nucleus structure. Purple arrows indicate: basement membrane structure. Green arrows indicate: mitochondrial structure. Blue arrows indicate: tight junction structure. Yellow arrows indicate: cell membrane structure. Black arrows indicate: perivascular region. Pink arrows indicate: astrocyte. Orange arrows indicate: platelet.

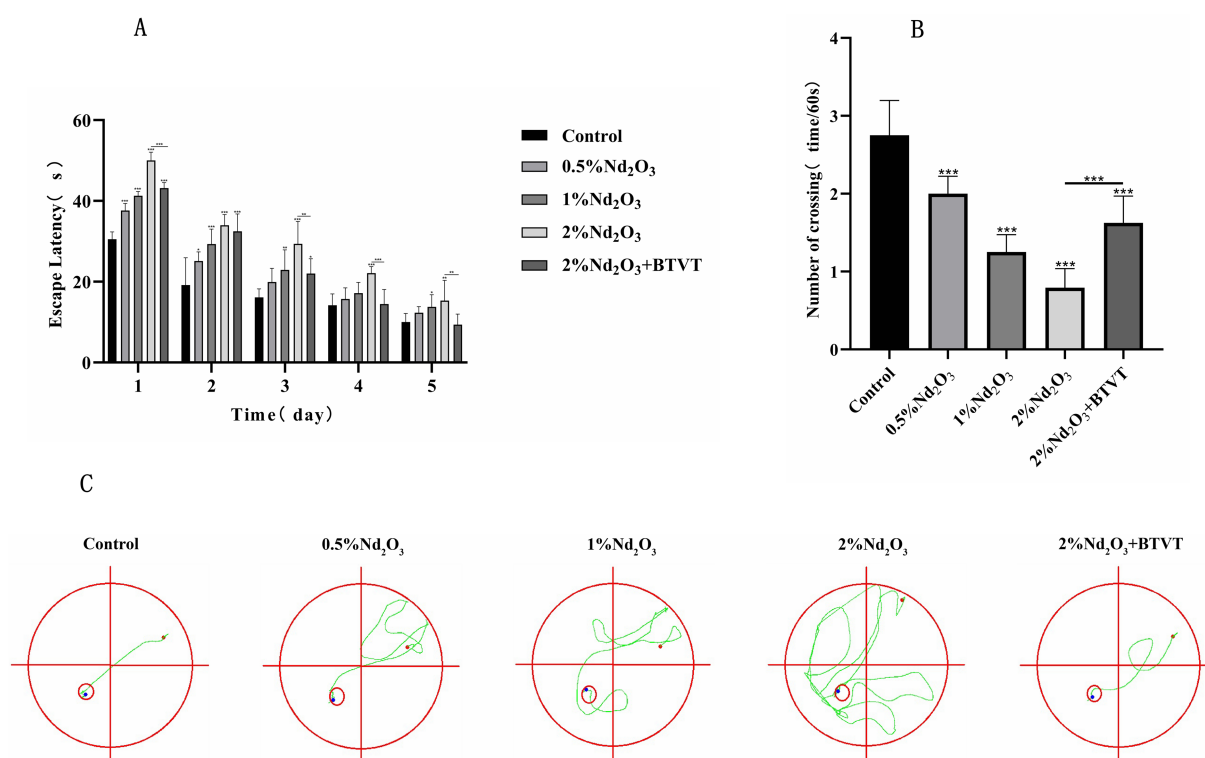


FIGURE 3 Morris water maze experiment of each group of offspring rats. **(A)** Escape latency, **(B)** number of crossings, **(C)** trajectory of crossing. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

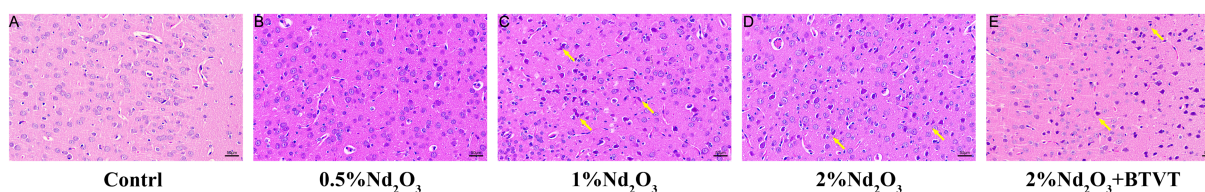


FIGURE 4 HE staining of offspring rat brain tissues in each group (200x). **(A)** Control group, **(B)** 0.5%Nd₂O₃ group, **(C)** 1%Nd₂O₃ group, **(D)** 2%Nd₂O₃ group, **(E)** 2%Nd₂O₃ + BTVT group. Yellow arrows indicate the denatured neuron cells.

However, the indices for Chao1, Simpson, Shannon, Pielou's evenness, Observed species, and Good's coverage showed no statistical significance ($p > 0.05$) (see Figures 6A–E,G), suggesting no significant differences in richness, evenness, and coverage between the two groups.

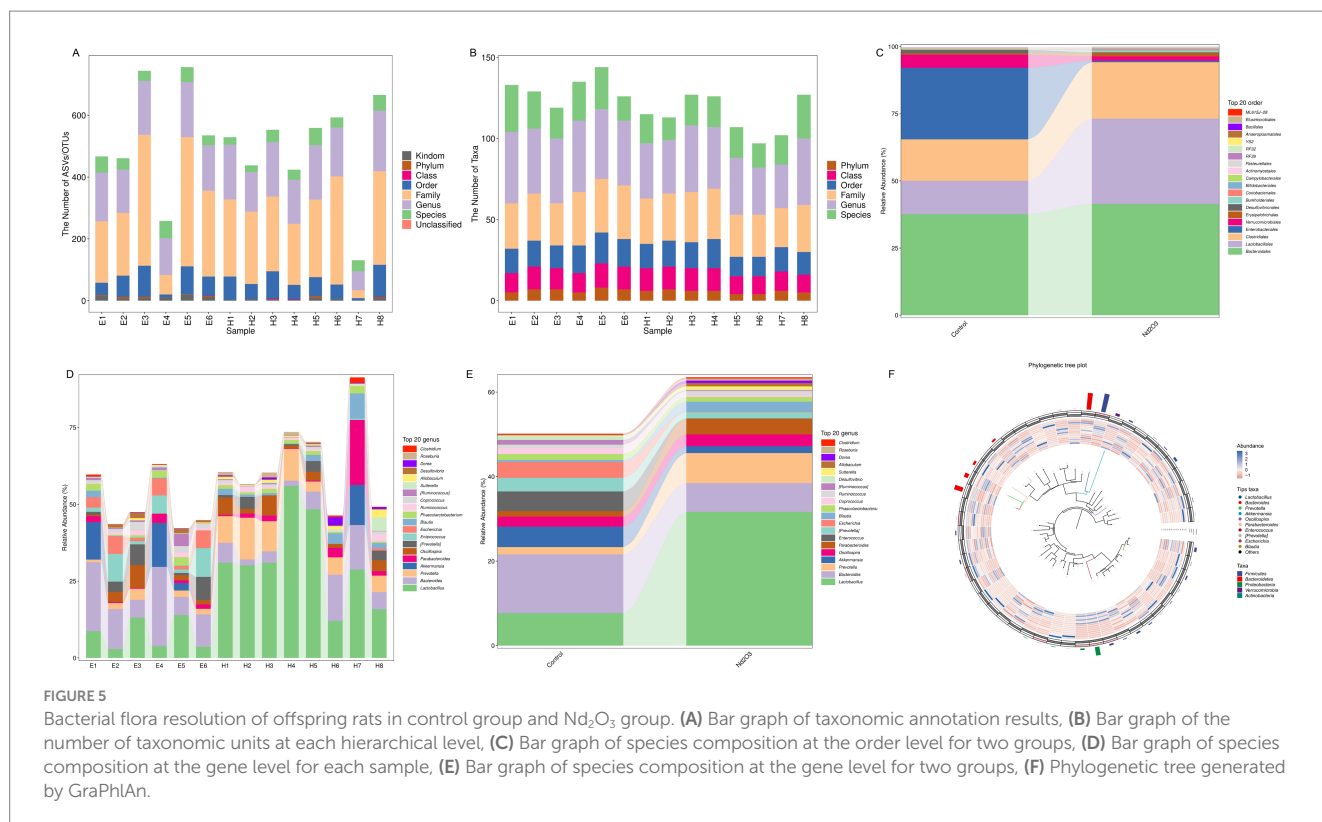
PCoA was employed to reduce the dimensionality of multidimensional microbiota data (see Figure 7A). Analysis of the distribution along the principal axis revealed significant differences in beta diversity between the two groups of samples (Control and Nd₂O₃ groups) (see Figure 7B). Through PCoA analysis of the multidimensional microbial data and subsequent validation using PERMANOVA, anosim, and permdisp., it was found that there were differences in beta diversity between the two groups (all three validation results showed $p < 0.05$) (see Figures 7C–H).

Using LDA and OPLS-DA for random forest analysis screening, ASV_349 was identified as the most important inter-group differentiating bacterial species (see Figures 8A,B). The sub network of Control and Nd₂O₃ groups shows the gene with the highest similarity between the two groups

is Lactobacillus (see Figure 8C). The similarity of the two groups Community analysis using a Venn diagram revealed that the proportion of shared bacterial species between the two groups was 10.83% (467 species) (see Figure 8D). In terms of both the number and abundance values of ASV/OTU, Bacteroidetes and Firmicutes were the highest (see Figure 8E). In quantitative terms, the content of Lactobacillus was the highest in both groups, and the top five abundant species were Oscillopsia, Bacteroides, Lactobacillus, Ruminococcus, and Parabacteroides (see Figure 8F).

3.2.2 Alterations of the intestinal mucosal barrier

After dissecting the offspring rats on PND 43d, observations were made regarding the length and surface color changes of the colon. Regardless of Nd₂O₃ intervention, there were no significant differences observed in the length or surface color of the colon. Upon selecting and fixing colonic segments for each group and staining with HE, it was found that with increasing Nd₂O₃ concentration, the colonic tissue structure gradually became abnormal, lymph nodes enlarged, crypt numbers



decreased, and were accompanied by a small amount of inflammatory cell infiltration. However, the epithelial cells of the mucosal layer were closely arranged and not shed. Following intervention with *Lactobacillus* after Nd_2O_3 exposure, the colonic tissue structure of the offspring rats was essentially normal. The epithelial cells of the mucosal layer were closely arranged without shedding in the field of view, the crypt structure was intact and orderly, and there was no apparent infiltration of inflammatory cells in the tissue (see Figure 9). After AB-PAS staining, it was discovered that with increasing Nd_2O_3 concentration, the number of goblet cells in each group gradually decreased, showing a significant difference ($p < 0.05$). The number of goblet cells in the 2% Nd_2O_3 + BTVT group did not show a significant difference compared to the pure 2% Nd_2O_3 group ($p > 0.05$). In comparison to the control group, the thickness of the colonic mucus layer increased significantly in all groups exposed to Nd_2O_3 ($p < 0.05$), but there was no significant difference between the different Nd_2O_3 -exposed groups ($p > 0.05$). The addition of *Lactobacillus* intervention resulted in a thinner colonic mucus layer compared to the Nd_2O_3 -exposed group ($p < 0.05$), with no significant difference compared to the control group ($p > 0.05$) (see Figure 10).

3.2.3 Affection of the SCFAs in the intestines

The feces of experimental animals were extracted, and GC-MS was used to detect changes in the content of acetic acid, propionic acid, butyric acid, valeric acid, isovaleric acid, and isobutyric acid in the feces. It was found that after Nd_2O_3 intervention, the acetic acid content decreased significantly ($p < 0.01$). There was no significant difference in acetic acid content with increasing Nd_2O_3 concentration ($p > 0.05$), and the addition of *Lactobacillus* increased the acetic acid content in the offspring rats exposed to Nd_2O_3 ($p < 0.05$) (see Figure 11A). After Nd_2O_3 intervention, the propionic acid content decreased ($p < 0.01$), and with increasing Nd_2O_3 concentration, the propionic acid content significantly decreased ($p < 0.05$). The addition of *Lactobacillus* increased the propionic acid

content in the offspring rats exposed to Nd_2O_3 ($p < 0.05$) with no significant difference compared to the control group ($p > 0.05$) (see Figure 11B). After Nd_2O_3 intervention, the butyric acid content decreased ($p < 0.05$), and there was no significant difference in butyric acid content with increasing Nd_2O_3 concentration ($p > 0.05$). The addition of *Lactobacillus* increased the butyric acid content in the offspring rats exposed to 2% Nd_2O_3 ($p < 0.05$) with no significant difference compared to the control group ($p > 0.05$) (see Figure 11C). Compared to the control group, there was no significant difference in valeric acid content after intervention with 0.5% Nd_2O_3 ($p > 0.05$), while the valeric acid content increased after intervention with 1% Nd_2O_3 and 2% Nd_2O_3 ($p < 0.05$). There was no significant difference between the two, and the addition of *Lactobacillus* resulted in a decrease in valeric acid content in the offspring rats exposed to 2% Nd_2O_3 , with no significant difference compared to the control group (see Figure 11D). There was no significant change in isovaleric acid content in the intestines of offspring rats after intervention with 0.5% Nd_2O_3 ($p < 0.05$). After intervention with 1% Nd_2O_3 , the isovaleric acid content increased ($p > 0.05$), however, there was no significant change in isovaleric acid content compared to the control group after intervention with 2% Nd_2O_3 ($p > 0.05$). Additionally, the addition of *Lactobacillus* did not result in a significant difference in isovaleric acid content in the intestines of the offspring rats exposed to 2% Nd_2O_3 compared to the group exposed to 2% Nd_2O_3 without *Lactobacillus* intervention ($p > 0.05$) (see Figure 11E). There was no significant difference in isobutyric acid content in the intestines of the offspring rats after intervention with 0.5% Nd_2O_3 compared to the control group ($p > 0.05$). The isobutyric acid content decreased after intervention with 1% Nd_2O_3 and 2% Nd_2O_3 ($p < 0.05$), and the addition of *Lactobacillus* increased the isobutyric acid content in the offspring rats exposed to 2% Nd_2O_3 ($p < 0.05$), with no significant difference compared to the control group ($p > 0.05$) (see Figure 11F). There was no significant difference of total SCFAs content among the five groups ($p > 0.05$) (see Figure 11G).

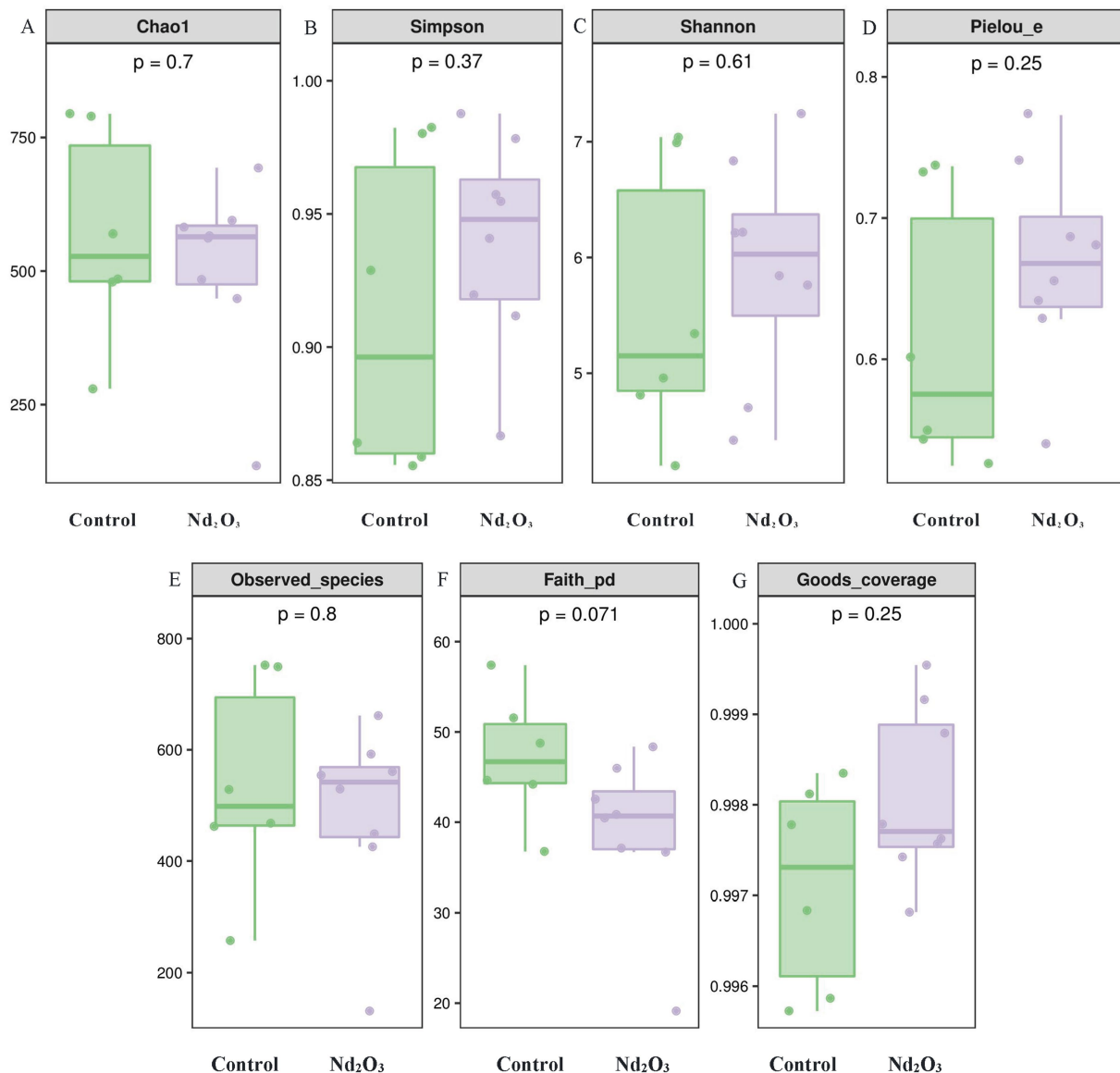


FIGURE 6

Alpha diversity of intestinal flora in offspring rats. (A) Comparison of Chao1 index between the control group and the Nd_2O_3 group, (B) Comparison of Simpson index between the control group and the Nd_2O_3 group, (C) Comparison of Shannon index between the control group and the Nd_2O_3 group, (D) Comparison of Pielou's evenness index between the control group and the Nd_2O_3 group, (E) Comparison of Observed species index between the control group and the Nd_2O_3 group, (F) Comparison of Faith's PD index between the control group and the Nd_2O_3 group, (G) Comparison of Good's coverage index between the control group and the Nd_2O_3 group.

3.3 The impact of Nd_2O_3 exposure on the BGA

Comparison of mRNA expression levels of *Hrt3a*, *Hrt4*, and *Sst* among different groups: The expression level of *Hrt3a*, except for no significant difference between the control group and the 0.5% Nd_2O_3 group ($p > 0.05$), showed significant differences in pairwise comparisons between the other groups ($p < 0.05$) (see Figure 12A). For the expression level of *Hrt4*, there was no significant difference between the control group and the 0.5% Nd_2O_3 group ($p > 0.05$). In pairwise comparisons, there were no significant differences between the 1% Nd_2O_3 group, 2% Nd_2O_3 group, and 2% Nd_2O_3 + BTVT group

($p > 0.05$), while significant differences were observed in pairwise comparisons between the remaining groups ($p < 0.05$) (see Figure 12B). As for the expression level of *Sst*, except for no significant difference between the 0.5% Nd_2O_3 group and the 2% Nd_2O_3 + BTVT group ($p > 0.05$), significant differences were observed in pairwise comparisons between the other groups ($p < 0.05$) (see Figure 12C). This indicates that the mechanism of BGA damage caused by Nd_2O_3 exposure is inversely correlated with the mRNA expression of intestinal neurotransmitters *Hrt3a*, *Hrt4*, and *Sst*, and the exposure of parental rats to Nd_2O_3 can promote the expression of *Hrt3a* and *Sst* in offspring rats after intervention with *Lactobacillus*.

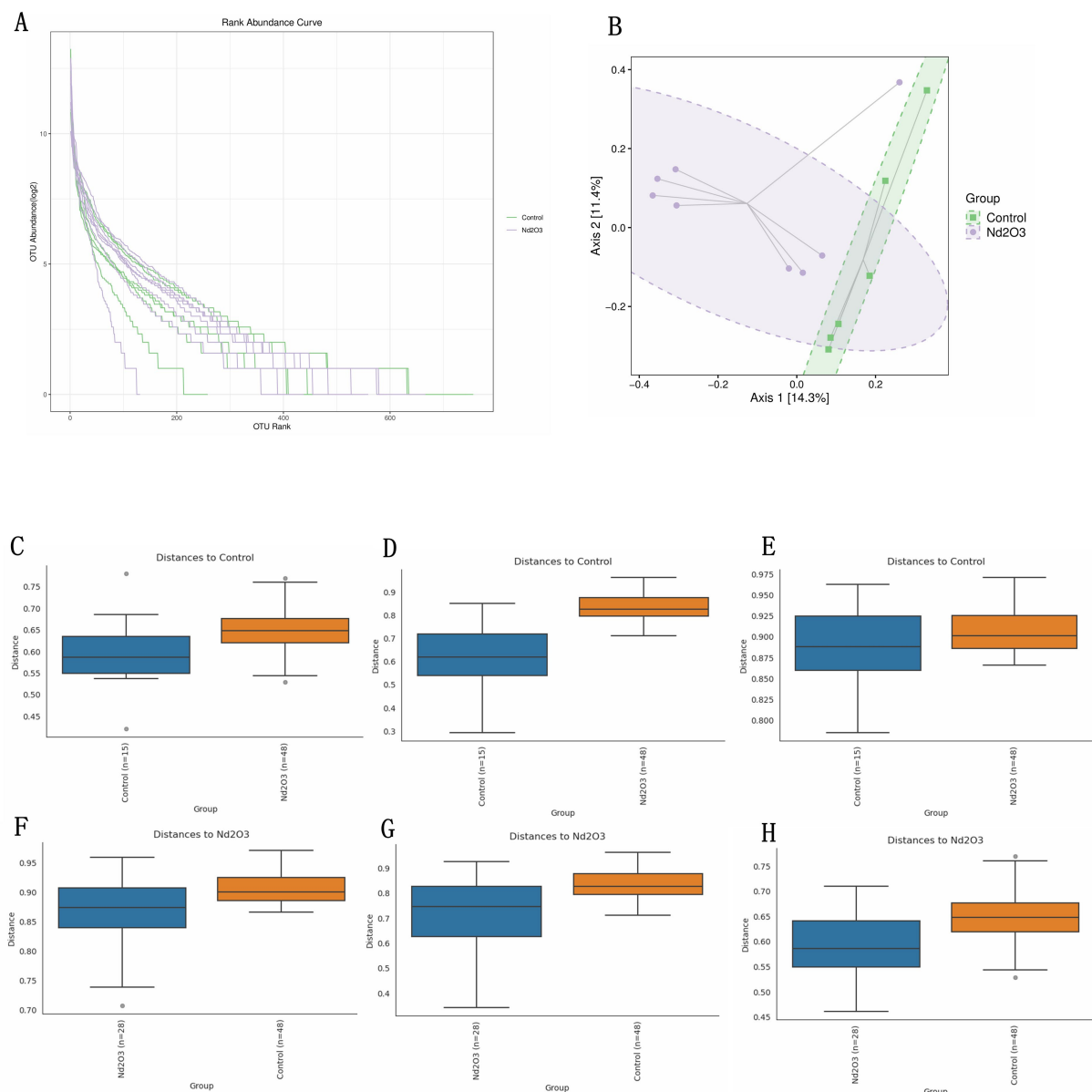


FIGURE 7

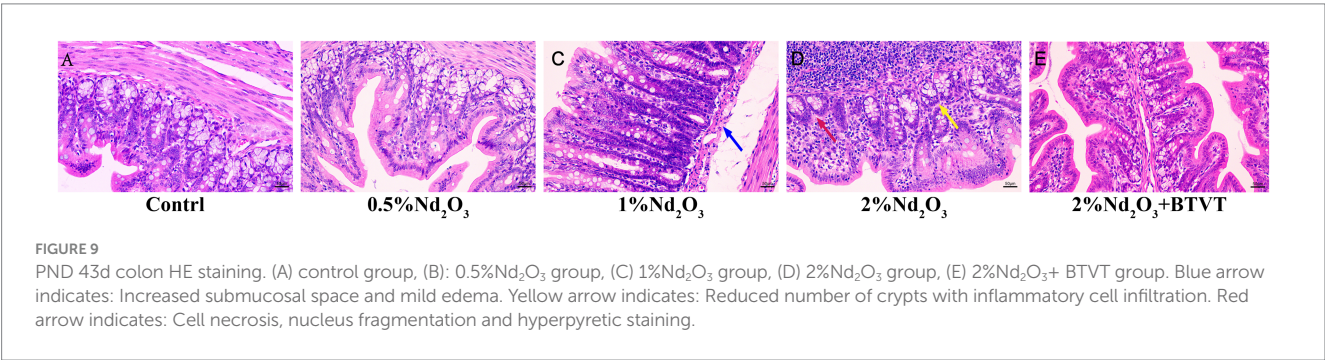
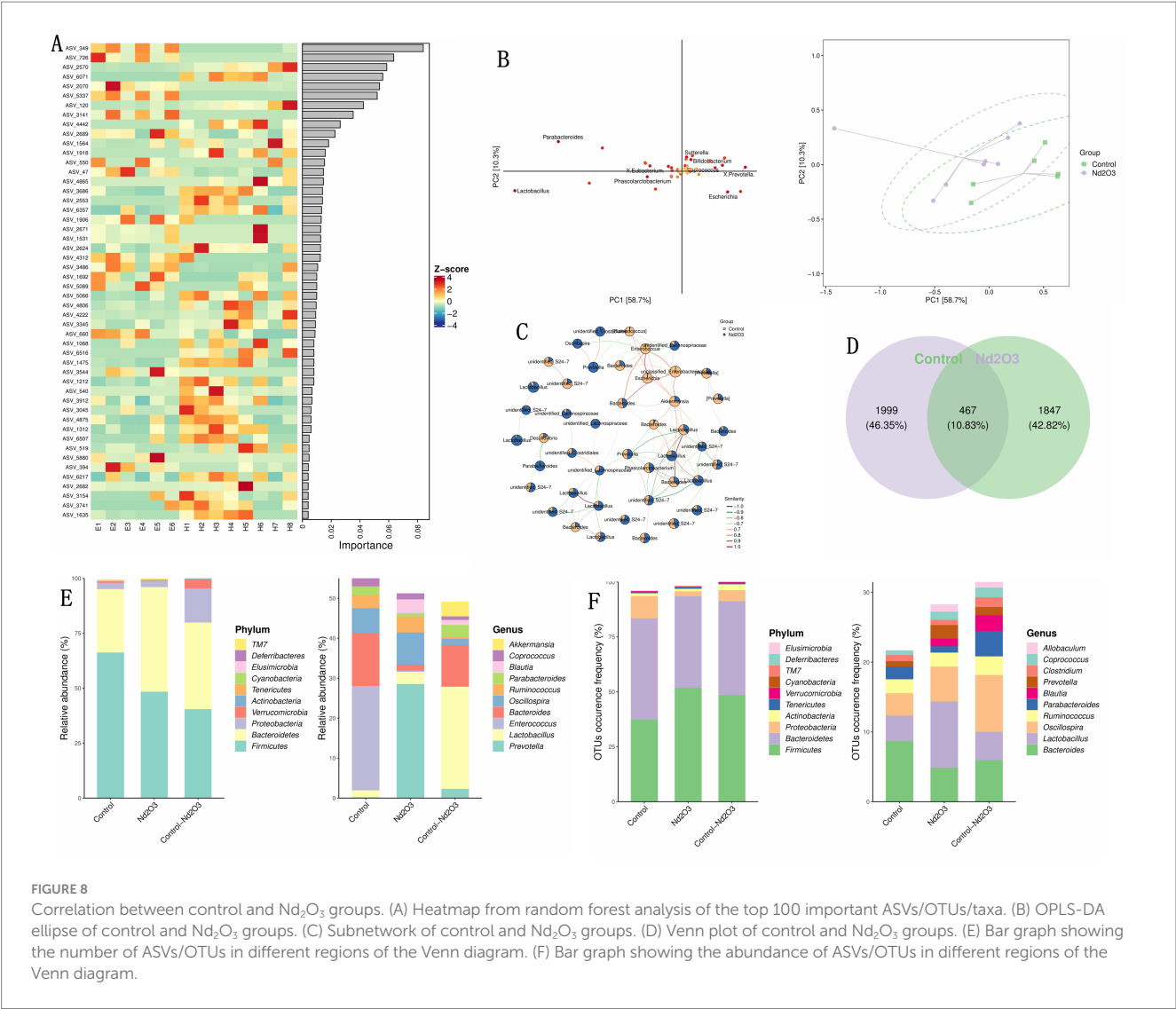
Beta diversity of intestinal flora in offspring rats. (A) OTU rank abundance curve of two groups. (B) The distribution of two groups of samples on the sequential ordering axis. (C–H) Beta diversity results validation. (C,F) Pairwise anosim results, (D,G) pairwise permanova results, (E,H) pairwise permdisp results.

4 Discussion

4.1 Nd₂O₃'s destruction of the BBB

Research has shown that increased BBB permeability is a critical threshold for toxic and harmful factors in the environment to enter the central nervous system and cause neurodevelopmental damage. For example, when pregnant and lactating rats drink water containing REEs, the brains of their offspring can exhibit rare earth accumulation that is several times higher than that of the control group (16). When male Sprague–Dawley rats were intravenously injected with 10 mg/kg body weight of neodymium chloride (NdCl₃), dissection after 7 days revealed significant absorption and retention of neodymium in the rat

brain, indicating that neodymium can cross the BBB, and the brain has an accumulative effect on neodymium (17). The above studies indicate that Nd can penetrate the BBB, thereby causing damage to the nervous system. Therefore, the brain serves as both a storage organ and a target organ for neodymium damage. Furthermore, our research has found that exposure of parental rats to Nd₂O₃ can reduce the content of TJs in the offspring rats, increase the BBB permeability in the offspring rats, leading to neodymium accumulation in the offspring rats, and this accumulation is positively correlated with the concentration of Nd₂O₃. However, after the intervention of probiotics, the content of TJs in the BBB of the offspring rats increased, the BBB permeability decreased, and likewise, the accumulation of neodymium in the offspring rats decreased. After staining the brain tissue of the



offspring rats with HE, it was found that the inflammation of the brain tissue gradually intensified after parental Nd_2O_3 exposure, but the addition of probiotics reduced the inflammation in the brain tissue of the offspring rats. The above results indicate that exposure of parental rats to Nd_2O_3 can lead to reduced content of TJs in the offspring, increased BBB permeability, neodymium accumulation, occurrence of brain tissue inflammation, and thus affect the neurodevelopment of the offspring. However, probiotics can alleviate the aforementioned

effects. The Morris water maze experiment revealed that exposure of parental rats to Nd_2O_3 can lead to reduced spatial orientation ability in the offspring rats. However, after parental rats were intervened with Nd_2O_3 with BTVT, there was no significant change in the spatial orientation ability of the offspring rats compared to the control group, indicating that the intervention of probiotics in parental rats can mitigate the effect of Nd_2O_3 on the spatial orientation ability of the offspring rats.

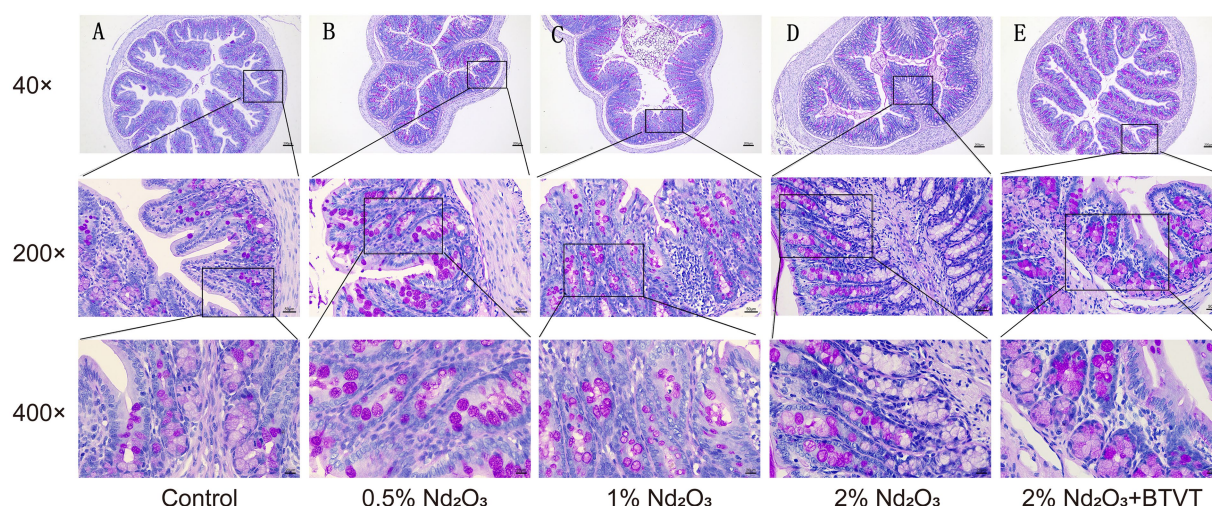


FIGURE 10

PND 43d Rat Colon AB-PAS Staining: As Nd_2O_3 concentration increases, the number of goblet cells (stained pink with AB-PAS) gradually decreases among the groups. Following intervention with probiotics, there is no significant change in the number of goblet cells in the colon of rats treated with 2% Nd_2O_3 . Post-intervention with Nd_2O_3 , offspring rat intestinal mucus thickens, which is attenuated with probiotic intervention, resulting in thinner mucus. (A) Control group, (B) 0.5% Nd_2O_3 group, (C) 1% Nd_2O_3 group, (D) 2% Nd_2O_3 group, (E) 2% Nd_2O_3 + BTVT group.

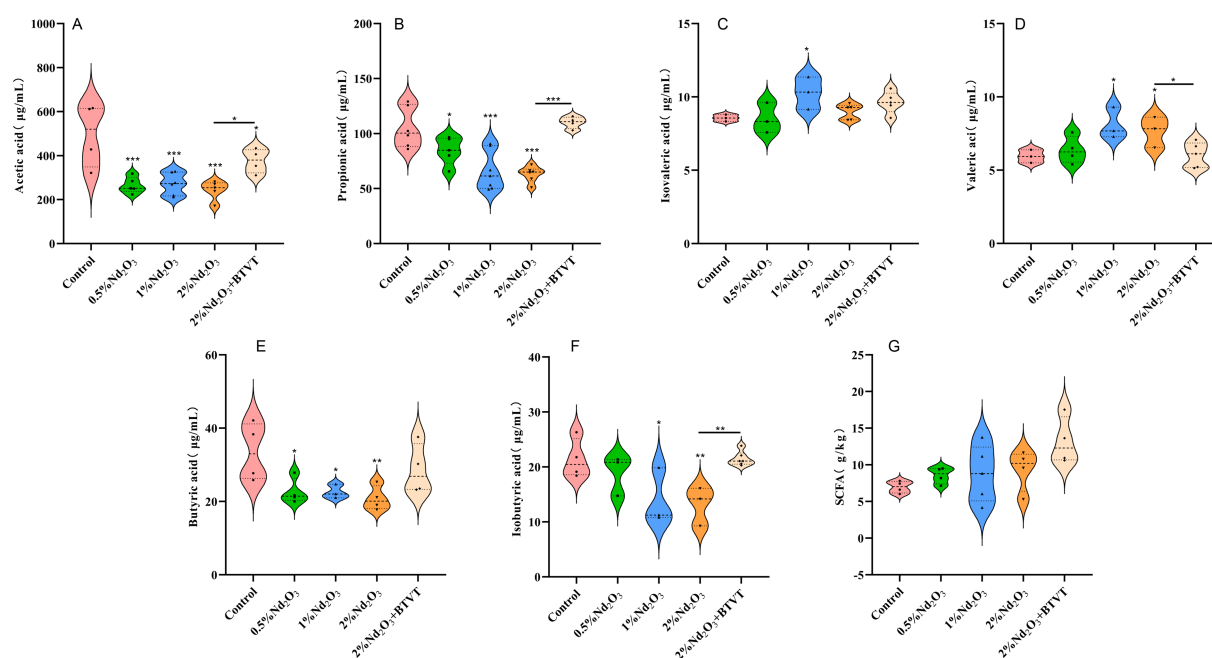


FIGURE 11

Changes in SCFAs (short-chain fatty acids) in the intestines of offspring rats exposed to various concentrations of Nd_2O_3 . (A) Acetic acid content, (B) propionic acid content, (C) butyric acid content, (D) valeric acid content, (E) isovaleric acid content, (F) isobutyric acid content, (G) total SCFAs content. * $p<0.05$, ** $p<0.01$, *** $p<0.001$.

4.2 Destruction of the intestinal barrier by Nd_2O_3

The intestinal epithelial barrier consists of tightly connected basal layer cells and a dynamic mucus layer containing secretory IgA (sIgA) and antimicrobial peptides. The main function of the intestinal epithelial barrier is to regulate the absorption of nutrients, electrolytes,

and water from the lumen into circulation, prevent pathogenic microorganisms and luminal toxins from entering, regulate molecular exchange between the environment and the host through the intestinal barrier, and affect the balance between tolerance to self and non-self antigens and immunity (18). The permeability of the intestinal barrier can be influenced by inflammatory mediators and activity of the sympathetic nervous system (19). Metabolites produced by gut

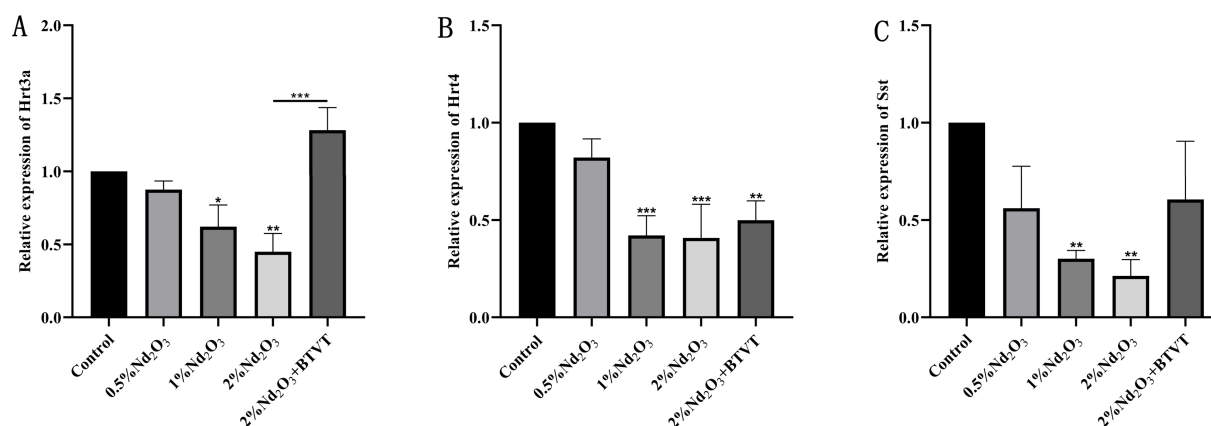


FIGURE 12

mRNA expression of intestinal neurotransmitters and neuropeptides in offspring rats following exposure to different concentrations of Nd₂O₃.

(A) Expression of *Hrt3a* in offspring rats after exposure to different concentrations of Nd₂O₃. (B) Expression of *Hrt4* in offspring rats after exposure to different concentrations of Nd₂O₃. (C) Expression of *Sst* in offspring rats after exposure to different concentrations of Nd₂O₃. **p*<0.05, ***p*<0.01, ****p*<0.001.

microbiota in the intestine can interact with immune cells to influence host health, and these metabolites can significantly affect the integrity of the intestinal epithelial barrier and regulate the maintenance of intestinal homeostasis (20). Existing research shows that heavy metals promote oxidative stress, thereby altering the permeability of the intestinal barrier, leading to inflammation, and facilitating the absorption of heavy metals into the brain. Humans ingest various nutrients, vitamins, and active metals through contaminated food or water every day, and interventions to reduce toxic metals in the environment may reduce the inflammatory burden of the gut microbiota and the occurrence of potential neurological disorders (21). The global industrial influx of heavy metals into the environment is associated with brain pathology from environmental sources, suggesting that initial environmental exposures may interact with gut-related microbiota before reaching the brain. However, research on the damage to the intestinal epithelial barrier caused by low-dose, long-term exposure to rare earth elements is limited. In this study, as the concentration of parental Nd₂O₃ exposure increased, mucosal inflammation in the offspring's intestines gradually worsened, and the number of goblet cells decreased. After parental rats were intervened with probiotics, no significant inflammation was observed in the offspring's intestinal mucosa, but there was no significant change in the reduction of goblet cell numbers. Parental Nd₂O₃ exposure resulted in thickening of the mucous layer in the offspring's intestines, which was reversed to thinner mucus with probiotic intervention. These results suggest that the intestine may also be one of the target organs damaged by parental Nd₂O₃ exposure, causing injury to the intestinal mucosa and affecting childhood intestinal development.

4.3 Relationship between Nd₂O₃ and the BGA

The human intestines harbor approximately 10¹³ to 10¹⁴ microbes, with the gut microbiome possessing over 150 times the total number of genes found in the human genome (9). It is widely acknowledged that there is bidirectional communication and interaction between the

gut and the brain (22). The enteric nervous system and the central nervous system serve as crucial bidirectional regulatory channels. The intestinal wall contains numerous sensory neurons that can perceive changes in the intestinal environment, autonomously regulating metabolic and endocrine activities within the intestines in response to physicochemical alterations, a system referred to as the enteric nervous system or the “gut-brain axis,” also known as the “second brain” of the body (23).

The gut microbiome can influence the permeability of the blood–brain barrier (BBB) by regulating the expression of tight junction proteins (24). Short-chain fatty acids (SCFAs) act as the primary signaling molecules for host-microbe communication mediated by enteroendocrine cells and intestinal enterochromaffin cells, participating in various host processes such as gastrointestinal function, blood pressure regulation, circadian rhythms, neuroimmune function, enhancing intestinal epithelial integrity, increasing mucus production, regulating intestinal motility, and exerting anti-inflammatory effects (25). There is evidence suggesting that SCFAs may serve as crucial signaling metabolites, influencing the development and maintenance of the BBB through epigenetic modifications (13).

Research has reported that SCFAs, mainly acetate, propionate, and butyrate, play a protective role in maintaining BBB integrity within the BGA (26). This protective mechanism is mediated through G-protein-coupled receptor signaling, involving the inhibition of histone deacetylase activity, interference with the signaling pathways of transcription factors NF-κB and Nrf2. Bacterial metabolites, particularly SCFAs were shown to induce tryptophan hydroxylase 1 in enterochromaffin cells to release serotonin in the gut. Serotonin can stimulate the sympathetic nervous system to influence memory and learning process. Emerging data supports the fact that dysbiosis in gut microbiota during functional GI disorders disrupts the GBA and leads to mood disorders. Experimental evidences also suggested that probiotic can induce brain derived neurotrophic factors in the hippocampus and cerebral cortex and regulate cognitive functions as well as muscle repair, regeneration, and differentiation (27). Our study found that after parental rats were exposed to Nd₂O₃, the feces of their

offspring exhibited decreased levels of acetate, propionate, and butyrate, while there was an increase in valerate and isovalerate. However, after treatment with probiotics, the levels of acetate and propionate in the offspring increased, demonstrating that Nd_2O_3 can disrupt BBB integrity and affect the BGA by modulating SCFAs. The mechanism of action for Nd_2O_3 -induced BGA damage is inversely correlated with the mRNA expression of gut-derived neurotransmitters *Hrt3a*, *Hrt4*, and BG peptide *Sst*. Additionally, after intervention with probiotics, the parental rats exposed to Nd_2O_3 promoted the expression of *Hrt3a* and *Sst* in their offspring.

4.4 The prevention and repair of Nd_2O_3 damage by probiotics

Early life, including the prenatal period, is a particularly important developmental window for the central nervous system, with widespread synaptogenesis and myelination occurring. It is also an important period for the development of the intestinal microbiota, as the energy produced by microorganisms plays a crucial role in brain development. During this period, exposure to different microorganisms, diets, stressors, antibiotics, and other factors not only affects communication within the developing central nervous system but also influences the structure and function of the microbiota. Through these mechanisms, various influences during early life events play a key role in programming the gut microbiota and the brain, and may be implicated in the etiology of several neurodevelopmental disorders (28).

The diversity of the gut symbiotic microbiota plays an important regulatory role in infant neurodevelopment. Research has shown that bacterial metabolic products (bacterial peptidoglycans) in the mother's body can affect fetal neurodevelopment and cognitive function through the placenta (29), and may also disrupt the integrity of the blood–brain barrier (BBB) (23). This could lead to the infiltration of inflammatory factors and the pro-inflammatory effects of microbial-derived metabolites (such as phenylalanine or isoleucine), affecting the occurrence of diseases in offspring such as psychological, behavioral, cognitive, emotional, and neurological disorders (30).

For example, Ganai-Vonarburg et al. (31), researchers have confirmed that the mother's gut microbiota plays a crucial role in promoting infant development and maintaining their normal physiological activities. The mother's diet and stress exposure during pregnancy can affect the composition and function of the infant's gut microbiota. The infant's gut microbiota is relatively unstable in the early stages, gradually gaining stability and diversity during the growth process. Most of the infant's gut microbiota is colonized at birth, with the mode of delivery, breastfeeding, premature birth, environment, host genetics, antibiotic exposure, infection status, and stress exposure all influencing the complex microbiota that the infant is exposed to the environment (32).

A study of 89 infants found that the composition of the gut microbiota at 1 year of age was related to cognitive performance 1 year later, further emphasizing the importance of this early period in the interaction between the gut microbiota and brain development (33).

In our study, we found that the levels of *Escherichia coli*, *Akkermansia*, and *Bacteroides* decreased, while *Lactobacillus*, *Prevotella*, *Parabacteroides*, and *Blautia* increased in the feces of

offspring rats through 16S RNA gene detection. Among them, the increase in *Lactobacillus* was the most significant. Using random forest analysis with LDA and OPLS-DA, ASV_349 was identified as the most important inter-group differentiating bacteria. Community analysis using a Venn diagram showed that the proportion of intersecting bacteria between the two groups was 10.83% (467 species). The content of *Lactobacillus* was the highest among the ASV/OTU in both groups.

After intervening with the parent rats exposed to 2% Nd_2O_3 by adding *Lactobacillus*, we found significant recovery of inflammation in both brain and colon tissues, and a decrease in BBB permeability. This indicates that *Lactobacillus* has a dual repair effect on the damage to brain and colon tissues caused by Nd_2O_3 in the BGA. The specific mechanism of this action will provide direction for further research.

5 Conclusion

Our research showed that parental exposure to Nd_2O_3 during pregnancy can affect the offspring's BGA, targeting the brain and colon tissues, leading to increased BBB permeability in offspring and affecting their neurodevelopment. It also causes damage to the intestinal mucosa, impacting children's intestinal development. However, *Lactobacillus* can alleviate the aforementioned effects. These findings will provide valuable insights for understanding the neurodevelopmental and intestinal developmental toxicity of Nd_2O_3 and related damage, and call for a comprehensive assessment of the health risks for susceptible populations (such as pregnant women) exposed to Nd_2O_3 .

Data availability statement

The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding authors.

Ethics statement

The animal study was approved by The Animal Ethics Review Committee at Baotou Medical College, Inner Mongolia University of Science and Technology, affiliated to Baotou Medical College, Inner Mongolia University of Science and Technology. The study was conducted in accordance with the local legislation and institutional requirements.

Author contributions

YJ: Writing – original draft, Methodology, Data curation, Formal analysis. JC: Methodology, Data curation, Formal analysis, Writing – original draft. YG: Data curation, Writing – review & editing. LW: Data curation, Writing – review & editing. XD: Data curation, Writing – review & editing. BT: Conceptualization, Methodology, Supervision, Writing – review & editing. BX: Conceptualization, Methodology, Supervision, Writing – review & editing. YD: Conceptualization, Methodology, Supervision, Writing – review & editing.

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References

1. Zhao Y, Liang J, Meng H, Yin Y, Zhen H, Zheng X, et al. Rare earth elements lanthanum and praseodymium adversely affect neural and cardiovascular development in zebrafish (*Danio rerio*). *Environ Sci Technol*. (2021) 55:1155–66. doi: 10.1021/acs.est.0c06632
2. Gwenzi W, Mangori L, Danha C, Chaukura N, Dunjana N, Sanganyado E. Sources, behaviour, and environmental and human health risks of high-technology rare earth elements as emerging contaminants. *Sci Total Environ*. (2018) 636:299–313. doi: 10.1016/j.scitotenv.2018.04.235
3. Egler SG, Niemeyer JC, Correia FV, Saggioro EM. Effects of rare earth elements (REE) on terrestrial organisms: current status and future directions. *Ecotoxicology*. (2022) 31:689–99. doi: 10.1007/s10646-022-02542-6
4. Huang FL, Wang H, Chen L, Wang YW. Effects of rare earth elements and lead exposure on children's intelligence. *J Mod Med Health*. (2020) 36:2534–8. doi: 10.3969/j.issn.1009-5519.2020.16.016
5. Song Y. Effects of in utero exposure to lanthanum on neurological behavior in rat offspring. *Neurotoxicol Teratol*. (2020) 77:106854. doi: 10.1016/j.ntt.2019.106854
6. Jin Y, Phillips B. A pilot study of the use of EEG-based synchronized transcranial magnetic stimulation (sTMS) for treatment of major depression. *BMC Psychiatry*. (2014) 14:13. doi: 10.1186/1471-244X-14-13
7. Yang N, Yang J, Liu Y, Fan H, Ji L, Wu T, et al. Impaired learning and memory in mice induced by nano neodymium oxide and possible mechanisms. *Environ Toxicol*. (2021) 36:1514–20. doi: 10.1002/tox.23148
8. Heithoff BP, George KK, Phares AN, Zuidhoek IA, Munoz-Ballester C, Robel S. Astrocytes are necessary for blood-brain barrier maintenance in the adult mouse brain. *Glia*. (2021) 69:436–72. doi: 10.1002/glia.23908
9. Qin J, Li R, Raes J, Arumugam M, Burgdorf KS, Manichanh C, et al. A human gut microbial gene catalogue established by metagenomic sequencing. *Nature*. (2010) 464:59–65. doi: 10.1038/nature08821
10. Bäckhed F, Roswall J, Peng Y, Feng Q, Jia H, Kovatcheva-Datchary P, et al. Dynamics and stabilization of the human gut microbiome during the first year of life. *Cell Host Microbe*. (2015) 17:690–703. doi: 10.1016/j.chom.2015.04.004
11. Ley RE, Peterson DA, Gordon JI. Ecological and evolutionary forces shaping microbial diversity in the human intestine. *Cell*. (2006) 124:837–48. doi: 10.1016/j.cell.2006.02.017
12. Martin CR, Osadchiv V, Kalani A, Mayer EA. The brain-gut-microbiome Axis. *Cell Mol Gastroenterol Hepatol*. (2018) 6:133–48. doi: 10.1016/j.jcmgh.2018.04.003
13. Osadchiv V, Martin CR, Mayer EA. The gut-brain Axis and the microbiome: mechanisms and clinical implications. *Clin Gastroenterol Hepatol*. (2019) 17:322–32. doi: 10.1016/j.cgh.2018.10.002
14. Lei G, Weidong H, Hailian J, Lixia Z, Reihong M, Jianrong C, et al. Effects on neodymium nitrate on learning and memory function and oxidative damage to the hippocampus in developing rats. *Prev Med Forum (Chinese)*. (2020) 26:817–820, 823. doi: 10.16406/j.pmt.issn.1672-9153.2020.11.006
15. Lei G, Lixia Z, Hailian J, Haijing Y, Mingjie G, Jun C, et al. Influence of neodymium nitrate on learning and memory function and oxidative damage to the hippocampus in developing rats. *Prev Med Forum (Chinese)*. (2019) 25:331–333, 337. doi: 10.16406/j.pmt.issn.1672-9153.2019.05.005
16. Estevez AY, Pritchard S, Harper K, Aston JW, Lynch A, Lucky JJ, et al. Neuroprotective mechanisms of cerium oxide nanoparticles in a mouse hippocampal brain slice model of ischemia. *Free Radic Biol Med*. (2011) 51:1155–63. doi: 10.1016/j.freeradbiomed.2011.06.006

Conflict of interest

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17. Kim YS, Lim CH, Shin SH, Kim JC. Twenty-eight-day repeated inhalation toxicity study of Nano-sized neodymium oxide in male Sprague-Dawley rats. *Toxicol Res*. (2017) 33:239–53. doi: 10.5487/TR.2017.33.3.239
18. Kelly JR, Kennedy PJ, Cryan JF, Dinan TG, Clarke G, Hyland NP. Breaking down the barriers: the gut microbiome, intestinal permeability and stress-related psychiatric disorders. *Front Cell Neurosci*. (2015) 9:392. doi: 10.3389/fncel.2015.00392
19. Li Z, Quan G, Jiang X, Yang Y, Ding X, Zhang D, et al. Effects of metabolites derived from gut microbiota and hosts on pathogens. *Front Cell Infect Microbiol*. (2018) 8:314. doi: 10.3389/fcimb.2018.00314
20. Alam A, Neish A. Role of gut microbiota in intestinal wound healing and barrier function. *Tissue Barriers*. (2018) 6:1539595. doi: 10.1080/21688370.2018.1539595
21. Rolli-Derkinderen M, Leclair-Visonneau L, Bourreille A, Coron E, Neunlist M, Derkinderen P. Is Parkinson's disease a chronic low-grade inflammatory bowel disease? *J Neurol*. (2020) 267:2207–13. doi: 10.1007/s00415-019-09321-0
22. Mayer EA, Nance K, Chen S. The gut-brain Axis. *Annu Rev Med*. (2022) 73:439–53. doi: 10.1146/annurev-med-042320-014032
23. Cryan JF, O'Riordan KJ, Cowan CSM, Sandhu KV, Bastiaansen TFS, Boehme M, et al. The microbiota-gut-brain Axis. *Physiol Rev*. (2019) 99:1877–2013. doi: 10.1152/physrev.00018.2018
24. Braniste V, Al-Asmakh M, Kowal C, Anuar F, Abbaspour A, Tóth M, et al. The gut microbiota influences blood-brain barrier permeability in mice. *Sci Transl Med*. (2014) 6:263ra158. doi: 10.1126/scitranslmed.3009759
25. Doroszkiwicz J, Groblewska M, Mroczko B. The role of gut microbiota and gut-brain interplay in selected diseases of the central nervous system. *Int J Mol Sci*. (2021) 22:10028. doi: 10.3390/ijms221810028
26. Fock E, Parnova R. Mechanisms of blood-brain barrier protection by microbiota-derived short-chain fatty acids. *Cells*. (2023) 12:657. doi: 10.3390/cells12040657
27. Carabotti M, Scirocco A, Maselli MA, Severi C. The gut-brain axis: interactions between enteric microbiota, central and enteric nervous systems. *Ann Gastroenterol*. (2015) 28:203–9.
28. Kempermann G. Environmental enrichment, new neurons and the neurobiology of individuality. *Nat Rev Neurosci*. (2019) 20:235–45. doi: 10.1038/s41583-019-0120-x
29. Humann J, Mann B, Gao G, Moresco P, Ramahi J, Loh LN, et al. Bacterial peptidoglycan traverses the placenta to induce fetal Neuroproliferation and aberrant postnatal behavior. *Cell Host Microbe*. (2016) 19:388–99. doi: 10.1016/j.chom.2016.02.009
30. Kigerl KA, Zane K, Adams K, Sullivan MB, Popovich PG. The spinal cord-gut-immune axis as a master regulator of health and neurological function after spinal cord injury. *Exp Neurol*. (2020) 323:113085. doi: 10.1016/j.expneurol.2019.113085
31. Ganai-Vonarburg SC, Horneff MW, Macpherson AJ. Microbial-host molecular exchange and its functional consequences in early mammalian life. *Science*. (2020) 368:604–7. doi: 10.1126/science.aba0478
32. Coley EJJ, Hsiao EY. Malnutrition and the microbiome as modifiers of early neurodevelopment. *Trends Neurosci*. (2021) 44:753–64. doi: 10.1016/j.tins.2021.06.004
33. Carlson AL, Xia K, Azcarate-Peril MA, Goldman BD, Ahn M, Styner MA, et al. Infant gut micro-biome associated with cognitive development. *Biol Psychiatry*. (2018) 83:148–59. doi: 10.1016/j.biopsych.2017.06.021



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Early postnatal care uptake and its associated factors following childbirth in East Africa—a Bayesian hierarchical modeling approach

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Background: The postnatal period is a critical period for both mothers and their newborns for their health. Lack of early postnatal care (PNC) services during a 2-day period is a life-threatening situation for both the mother and the babies. However, no data have been examined for PNCs in East Africa. Hence, using the more flexible Bayesian multilevel modeling approach, this study aims to investigate the pooled prevalence and potential factors for PNC utilization among women after delivery in East African countries.

Methods: We retrieved secondary data from the Kids Record (KR) demographic and health surveys (DHS) data from 2015 to 2022 from 10 East African countries. A total of 77,052 weighted women were included in the study. We used R 4.3.2 software for analysis. We fitted Bayesian multilevel logistic regression models. Techniques such as Rhat, effective sample size, density, time series, autocorrelation plots, widely applicable information criterion (WAIC), deviance information criterion (DIC), and Markov Chain Monte-Carlo (MCMC) simulation were used to estimate the model parameters using Hamiltonian Monte-Carlo (HMC) and its extensions, No-U-Turn Sampler (NUTS) techniques. An adjusted odds ratio (AOR) with a 95% credible interval (CrI) in the multivariable model to select variables that have a significant association with PNC was used.

Results: The overall pooled prevalence of PNC within 48 hrs. of delivery was about 52% (95% CrI: 39, 66). A higher rate of PNC usage was observed among women aged 25–34 years (AOR = 1.21; 95% CrI: 1.15, 1.27) and 35–49 years (AOR = 1.61; 95% CrI: 1.5, 1.72) as compared to women aged 15–24 years; similarly, women who had achieved primary education (AOR = 1.96; 95% CrI: 1.88, 2.05) and secondary/higher education (AOR = 3.19; 95% CrI: 3.03, 3.36) as compared to uneducated women; divorced or widowed women (AOR = 0.83; 95% CrI: 0.77, 0.89); women who had currently working status (AOR = 0.9; 95% CrI: 0.87, 0.93); poorer women (AOR = 0.88; 95% CrI: 0.84, 0.92), middle-class women (AOR = 0.83; 95% CrI: 0.79, 0.87), richer women (AOR = 0.77; 95% CrI: 0.73, 0.81), and richest women (AOR = 0.59; 95% CrI: 0.55, 0.63) as compared to the poorest women; women who had media exposure (AOR = 1.32; 95% CrI: 1.27, 1.36), were having 3–5 children (AOR = 0.89; 95% CrI: 0.84, 0.94), had

>5 children (AOR = 0.69; 95% CrI: 0.64, 0.75), had first birth at age <20 years (AOR = 0.82; 95% CrI: 0.79, 0.84), had at least one ANC visit (AOR = 1.93; 95% CrI: 1.8, 2.08), delivered at health facilities (AOR = 2.57; 95% CrI: 2.46, 2.68), had average birth size (AOR = 0.94; 95% CrI: 0.91, 0.98) and small birth size child (AOR = 0.88; 95% CrI: 0.84, 0.92), had twin newborns (AOR = 1.15; 95% CrI: 1.02, 1.3), and fourth and above birth order (AOR = 0.88; 95% CrI: 0.82, 0.95) were individual-driven women who have been independently associated with PNC, respectively. Regarding community-level variables, rural women (AOR = 0.76; 95% CrI: 0.72, 0.79), high media exposure communities (AOR = 1.1; 95% CrI: 1.04, 1.18), communities with high wealth levels (AOR = 0.88 95% CrI: 0.83, 0.94), communities with high antenatal care (ANC) utilization (AOR = 1.13, 95% CrI: 1.07, 1.19), and long distance to health facilities (AOR = 1.5; 95% CrI: 1.38, 1.63) were among the community factors associated with PNC, respectively.

Conclusion: One of the significant public health priorities in East Africa continues to be the underutilization of immediate PNC. The government ought to prioritize improving maternity and child health services, collaborating with interested parties in the area, reducing health disparities, educating mothers about child health, and other connected issues that are very beneficial.

KEYWORDS

Bayesian hierarchical model, East Africa, factors, newborns, postnatal care, women

Introduction

According to the various wide range of reports, the damage caused by the world's health system—especially to the health of mothers and children—continues to be very serious. To achieve Sustainable Development Goal 3 (SDG 3), that is, ensuring healthy lives and promoting wellbeing at all ages, efforts on the mother's health during pregnancy, childbirth, and the postpartum period are the main agenda (1). The WHO, and United Nations Children's Fund (UNICEF) advise that women who give birth in medical facilities should have their babies and themselves examined for any health-related challenges within 24 h, considering a date to bring them back for additional postnatal care (PNC) even when everything seems to be going well (2, 3). Furthermore, women should be counseled to return back immediately if they notice any warning signs (4). The initial PNC contact should also be held as soon as practicable, ideally within 24 h of the birth, if the delivery occurs at home. Ultimately, it is advocated that all mothers and newborns receive a minimum of three more postnatal examinations: on day 3 (48–72 h), within days 7–14 immediately after delivery, and 6 weeks later (5–7). Globally, although the number of maternal and infant deaths is decreasing, developing countries, especially, sub-Saharan African (SSA) countries, have a significant share in the failure of the sustainable development goal to reduce 70 maternal deaths per 100,000 live births and 12 neonatal deaths per 1,000 live births by 2030 (8, 9). Since the year 2017, pieces of evidence show that globally, 66% of maternal deaths occur in SSA only (10–12), and the issue is more massive and awful. Inaccessibility to healthcare and inadequate use of postnatal care (PNC) contribute to 99% of maternal mortality in low- and middle-income countries (LMICs), including SSA. These issues are particularly concerning because the majority of the deliveries in these regions occur at home, leading to tragic outcomes that affect public health significantly (9, 12, 13). In comparison to the 230 fatalities per 100,000 live births that occurred in LMICs, the

maternal mortality ratio similarly remained unacceptably high at 433 (14, 15). All these gaps could be eliminated by integrating maternal child health service care at a high range (16). Therefore, if women can receive the early postnatal care check-up suggested by the WHO, it could significantly reduce the risk of complications and maternal mortality (6, 17). The SSA countries can avoid greater maternal morbidity and related mortality, which could also help the countries achieve SDG 3.

There are significant gaps in understanding early PNC in East Africa. Key issues include outdated knowledge, lack of region-specific studies, insufficient detail on influencing factors, limited use of advanced statistical methods, and large sample sizes. Addressing these gaps with current, localized, and methodologically robust research is crucial for improving PNC outcomes in the region. Although studies were not conducted under large study settings, numerous studies have found links between the continuum of care and factors such as socioeconomic status, family and individual characteristics, community features, characteristics of the newborn, and interactions with the healthcare system (18, 19). For instance, the age of the mother (20, 21), her marital status (22), her education level (20, 21, 23), occupation (23), the order in which her children were born (20), her access to media (18, 21), residence, health insurance, family number, her ability to make decisions, and her wealth index (19, 21, 24) were found to be the determinants of the continuum of maternal and child care.

Therefore, this study aimed to ascertain the number of reproductive-age women who received each of the chosen functions of the PNC during the first 2 days after birth, as well as its predictors of the number of last live births in the 2 years prior to the survey by applying more advanced and flexible modeling approach to the data. As the Bayesian multilevel approach incorporates prior information, allows for more model flexibility, and is a natural approach to expressing uncertainty, this study benefits the East African countries by identifying key factors—both individual and community-level factors—that influence postnatal care use in the region. It is crucial to

enhance PNC and lower rates of child morbidity and mortality. Although studies have not been performed to clarify the elements that support or obstruct PNC at the national level, East African countries continue to be one of the leading causes of mother and infant mortality worldwide (25). The results of this study will provide preliminary information for the upcoming researchers in the area, and policymakers and other stakeholders working on issues related to both women's and children's health with an up-to-date multicounty result from which they can build, enhance, and implement their plans.

Materials and methods

Study setting and period

For a cross-sectional study design conducted nationwide, data were gathered in East African countries for the period from 2015 to 2022. The study encompassed communities from 10 countries: Burundi, Ethiopia, Kenya, Madagascar, Malawi, Rwanda, Uganda, Tanzania, Zambia, and Zimbabwe. The demographic and health surveys (DHS) Program, funded by the United States Agency for International Development (USAID), provided both financial support and technical assistance for population and health surveys conducted globally. The most recent DHSs dataset encompassing the last 7-year period (2015–2022) in East African nations served as this study's primary source of information. A standardized dataset was employed (26) to collect a sizable sample size that is representative of the population source and all factors. DHSs gather comparable data on a global scale. The surveys have huge sample sizes, are population-based, and are nationally representative of each nation (26). The 14 nations that make up Eastern Africa are spread throughout the Horn of Africa, the Indian Ocean islands, and the Great Lakes region. These nations struggle with comparable economic, social, and environmental problems and worry that they would not achieve all of the sustainable development objectives (27) East Africa refers to the region of the African continent situated in the Horn and Eastern regions of the Sahara Desert. It is estimated that approximately 486,766,759 individuals inhabit this region, and it spans an area of 6,667,493 km² (2,574,332 sq. mi), constituting around 6.03% of the global population.

Sample size determination and sampling methods

In every country, the DHSs followed the stratified multistage sampling method, which involves stratification, clustering, and sample selection over two stages. Urban and rural areas were grouped into separate clusters to form the basis for stratification. The administered questionnaire was responded to by women who consented and agreed to participate in the study. Enumeration areas (EAs) inside each sampling stratum were initially chosen with a probability proportional to their size. The households were carefully sampled in the second step. Each of the chosen clusters underwent a household listing operation (28). Demographic and health survey reports were accessible for approximately 10 out of the 13 East African nations. Periodically, every 5 years, a systematic gathering of DHSs surveys is

carried out in low- and middle-income countries, utilizing pretested, validated, and structured questionnaires. Using a standardized approach for sampling, questionnaires, data collection, and coding across DHSs surveys enables the possibility of conducting multicountry analyses. In each of the surveys conducted in the specified nations, the most recent conventional census frame was utilized.

The DHSs' samples are often divided into urban and rural areas within each administrative geographic region. The DHSs employ a stratified two-stage cluster sampling technique. In the first stage, clusters and enumeration areas (EAs) are randomly selected from the sample frame, typically derived from the most recent national census available. Subsequently, systematic sampling is utilized in the second stage to select households within each cluster or EA. During the initial sampling round, EAs are chosen with a probability proportional to the size of each stratum. A predetermined number of households is systematically selected within designated EAs in the second stage. Following the listing of households, equal probability systematic sampling is employed to select a specific number of households within the defined cluster (26).

Data source and study population

For this study, we utilized DHSs that were conducted over the span of the last 7 years, from 2015 to 2022. Among the approximately 14 countries in East Africa that carried out DHSs during this period, only approximately 10 countries' surveys contained the necessary information on the outcome variable. Thus, they were included in our analysis. After appending the data from each country, the final analysis included a total weighted sample of 78,213 women and a total unweighted sample of 78,536 women (refer to Table 1). The source population consisted of mothers who had given birth 2 years prior to the survey. Therefore, only mothers who met this criterion were included in the analysis. To account for any unequal sample distributions during the data collection process, weightings were applied to the children's samples during the estimation process. This adjustment ensured that the results were representative and accurately reflected the studied population.

Data quality control

To ensure data quality in each country, the DHSs implemented several measures. These included providing comprehensive training to data collectors, supervisors, and field editors, as well as conducting ongoing supervision to maintain high standards. Standardized questionnaires were used, which were translated into national and local languages to accommodate participants' preferred languages. Data processing specialists were involved in the data entry and management phase, ensuring accurate and efficient handling of the collected data. Systematic biases were carefully addressed during this phase to minimize their impact on the results. Once the data were obtained from the DHSs, proper data management procedures were followed. This involved appending women's and men's data, addressing missing

TABLE 1 List of countries, survey years, and sample size distribution for PNC uptake in East African countries from 2015–2022.

Countries	Survey year	Sample size distributions		
		Unweighted	weighted	Weighted percentage
Burundi	2016/17	8,660	8,821	11.28
Ethiopia	2016	7,193	7,132	9.12
Kenya	2022	5,460	5,486	7.01
Madagascar	2021	9,315	9,176	11.73
Malawi	2015/16	13,448	13,079	16.72
Rwanda	2019/20	6,167	6,313	8.07
Tanzania	2022	5,825	5,963	7.62
Uganda	2016	10,263	9,973	12.76
Zambia	2018	7,372	7,509	9.6
Zimbabwe	2015	4,833	4,761	6.09
Total sample size		78,536	78,213	100

observations through appropriate techniques such as missing completely at random, and conducting necessary recoding and variable recategorization. These rigorous data management practices were consistently implemented across all countries with similar working systems, ensuring a standardized and reliable approach to data handling and analysis. The DHSs guidance provides additional details regarding the data-collection process. Details can be accessed from the Guide to DHSs statistics (26).

Variables of the study

Dependent variable

The study's outcome variable is early postnatal care (PNC) within the first 2 days of delivery. To calculate the desired measure of PNC for newborns within the first 2 days after birth, along with the associated variables, the under-five datasets (KR files) from DHSs data of 10 East African countries were utilized as the data source for this analysis. The factors considered for computation included cord examination (m78a), temperature measurement (m78b), counseling on danger symptoms (m78c), breastfeeding counseling (m78d), and nursing observation (m78e) (29). All of these were summed up, and if a newborn did not receive a postnatal check within 2 days of birth, it was recorded as “No (0).” Conversely, if a newborn did receive a postnatal check within 2 days, it was recorded as “Yes (1).”

Independent variables

Both individual and community-level factors that have been identified by earlier researchers and scientific backgrounds as potential factors of PNC checkups were included in this study (Table 2).

Data management and analysis process

We conducted a secondary study using the Kids Records (KR) dataset, which involved analyzing the data from the DHSs. To carry out the analysis, we utilized R 4.3.2 software (68, 69) and Microsoft Excel version 19 for tasks such as data downloading, appending, cleaning, recoding, and handling missing values. In the DHSs' data, infants were nested within clusters, and neonates within the same cluster showed more remarkable similarity than those in different

clusters. This violated the assumptions of independence of observations and equal variance across clusters in the classical logistic regression model. Therefore, a more sophisticated modeling approach was required to account for between-cluster factors. We constructed a Bayesian multilevel random logistic regression model to investigate the relationship between individual- and community-level variables and the risk of not receiving immediate PNC within 2 days of birth. In total, four models were developed. The first model, known as the empty or null model, was fitted without any explanatory variables. This model helped reduce community differences and served as a baseline for understanding community variances. It also assisted in determining whether a multilevel statistical framework should be used instead of a standard logistic regression model. The null model was evaluated using various measures, including the log-likelihood ratio (LLR), median odds ratio (MOR), intraclass correlation coefficient (ICC), proportional change of variance (PCV), and the widely applicable information criterion (WAIC). The second model included only individual or household-level characteristics, while the third included only community-level factors without individual-level factors. Finally, the fourth and final model included components from both the individual and community levels. These models were constructed to assess the impact of individual and community factors on mothers' behavior regarding immediate PNC. Then, we conducted a Bayesian meta-analysis to compute the pooled prevalence and construct the forest plot (30). Subsequently, a two-level Bayesian logistic regression was employed to identify the determinants of PNC.

Bayesian mixed model and convergence of algorithm

To identify the factors influencing early PNC uptake, we utilized multilevel mixed-effects logistic regression analysis employing the Bayesian approach. The Bayesian approach to credible intervals serves a similar purpose to classical confidence intervals (CIs); however, their composition and interpretation philosophies differ significantly (31). The Bayesian statistical approach offers the ability to incorporate additional prior information external to the data through prior distributions. By leveraging this additional prior information, the accuracy and credibility of effect size estimations can be improved. Consequently, applying the classical confidence interval interpretation

TABLE 2 Shows independent variable categorizations among women in East Africa countries, 2015–2022.

Individual level variables	
Variable	Description
Age of the mother	15–24, 25–34, 35–49
Maternal education	no education, primary, secondary and above
Mother working status	Not working, working
Marital status	unmarried, married, Others
Wealth index	Poorest, poorer, middle, richer, richest
Mass media exposure (either watching to television, listening to radio or reading to newspapers/magazines)	No, Yes
Total children ever born	1–2, 3–5, 6 and above
Place of delivery	Home, Health facility
At least one ANC visit	No, Yes
Women perception to distance to the health facility	Not big problem, big problem
Weight at birth	Small, average, and large
Sex of a child	Male, Female
Twin	Single, Multiple
Birth order	1st, 2nd to 3rd, ≥ 4 th
Community level variables	
Residence	Urban, Rural
Community women education	Low, High
Community wealth level	Low, High
Community media exposure	Low, High
Community ANC utilization	Low, High
Community level distance to health facility	Not big problem, big problem

is inappropriate, as the Bayesian statistical approach provides a more reasonable alternative. The Bayesian credible interval interpretation is more intuitive in this context, while frequentist confidence intervals are often misinterpreted as Bayesian credible intervals.

We used the random variable EAs to account for the variation of early postnatal care (PNC) utilization across different EAs within the country. An ICC value $>5\%$ was used as a threshold to consider the variation across EAs. Since the outcome variable was dichotomized (no/yes), children within households were treated as level-1 unit, while EAs were considered as level-2 units. This hierarchical structure resulted in children being nested within EAs. We employed a Bayesian multilevel logistic regression model to address the hierarchical nature of the data and account for the dependency of observations within the same cluster. This approach allowed us to obtain accurate and credible estimates of effect sizes, considering the clustering of children within EAs and the potential impact of the EA on the outcome variable.

Hence, the dependent variable was represented by:

$$Y_{ij} = \begin{cases} 1, & \text{if the } i\text{th women in the } j\text{th EA received early PNC} \\ 0, & \text{if the } i\text{th women in the } j\text{th EA have not received early PNC} \end{cases}$$

The likelihood function

The key ingredients to a Bayesian analysis are the likelihood function, which reflects information about the parameters contained

in the data, and the prior distribution, which quantifies what is known about the parameters before observing data. The prior distribution and likelihood can be easily combined to form the posterior distribution, which represents total knowledge about the parameters after the data have been observed. Bayesian multilevel logistic analysis specifies a dichotomous dependent variable as a function of a set of explanatory variables (32, 33).

Likelihood contribution from the i th subject in the j th group is Bernoulli:

$$\mathcal{L}(\theta_i) = \theta_i^{y_i} (1 - \theta_i)^{1 - y_i},$$

where θ_i represents the probability of the event for subject i in group j that has a covariate vector x_i and y_i indicates the presence ($y_i = 1$) or absence ($y_i = 0$) of the event for that subject. In multilevel logistic regression, we know that

$$\theta_i = \text{logit}^{-1}(\beta_0 + \beta_1 x_{i1} + \beta_2 x_{i2} + \dots + u_{0j} + \gamma_0 + \gamma_1 x_{i1} + \gamma_2 x_{i2} + \dots + v_{0j}),$$

where $\beta_0 + \beta_1 x_{i1} + \beta_2 x_{i2} + \dots + \beta_k x_{ijk}$ is a fixed part of the model and u_{0j} is a random part of the model and $u_{0j} \sim N(0, \sigma_u^2)$. θ_i is the probability of the i th child in the j th the group having PNC uptake so that the likelihood contribution to the i th subject in the j th group is

where $\sigma^2\mu$ is the variance of the random parameter at the cluster level representing the amount of unobserved heterogeneity between clusters; and $\frac{\sigma^2}{3}$ is a parameter representing the amount of unobserved heterogeneity between women (individual-level variance).

Median Odds Ratio (MOR): The MOR measures how much variability in the early PNC uptake exists between EAs (i.e., clusters) by comparing two persons from two randomly chosen, different EAs (42). Consider two persons chosen randomly from two different EAs but with the same values of covariates in the model. The MOR is the median odds ratio between the person at EA with a higher probability of receiving early PNC services and the person at Survey EA with a lower probability of receiving early PNC services. It is a function of the estimated EAs, that is, cluster, variance $\sigma^2\mu$ and is given by

$$\text{MOR} = \exp\left(\sqrt{2\sigma^2} \times f^{-1}\left(\frac{3}{4}\right)\right),$$

where σ^2 is the variance of each model, and Φ^{-1} is the inverse of the standard normal cumulative distribution function $f^{-1}(0.75)$ is the 75th percentile, and $\exp(\cdot)$ is the exponential function (42, 43).

Proportional change in variance (PCV) was calculated as $\text{PCV} = \frac{(V_0 - V_x) \times 100}{V_0}$, where V_0 is the variance of the null model, and V_x is the variance of each model at each level with variables (41).

Operational definitions for community-level factors

Community women education

This metric reflects the collective value of women's educational attainment, which is determined based on the median distribution of educational levels within the neighborhood. If the proportion of women in the community with at least a secondary education fell below the median, it was considered low, while if it exceeded the median, it was considered high. On average, the median proportion was 0.50.

Community media exposure

This variable was created based on individual responses regarding exposure to radio or television media. If the proportion of women in the community who reported media exposure was between 0 and 48%, it was classified as low. Conversely, if the proportion ranged from 49 to 100%, it was considered high.

Community ANC utilization rate

This variable is derived from individual data on antenatal care (ANC) utilization. If the proportion of women in the community who attended at least one ANC visit fell between 0 and 50%, it was classified as low. The median value for this proportion was 0.51.

Community perception distance to health facility

This community-level variable was constructed based on individual responses regarding the major challenge in accessing health facilities, specifically related to the distance to the nearest facility. If the proportion of women in the community who perceived distance as a significant problem to visit health facilities ranged from 0 to 14%, it was categorized as a low problem. The median value for this proportion was 0.15.

Community wealth

The procedure employed to obtain this variable was similar to that used for the household's wealth index. If the proportion of women in a community belonging to the two lowest wealth quintiles ranged from 50 to 100%, it was classified as high. Conversely, if the proportion fell between 0 and 49%, it was considered low.

Results

Sociodemographic characteristics of the study participants

In this analysis, a total of 78,213 weighted numbers of mothers were included. Out of the total mothers interviewed 44.7% of them were between 25 and 34 years of age. Close to 49% of the women had primary education, while 29% had secondary and above education. The majority (64%) of mothers were employed, and 67% were married. In addition, 45.67% of the participants were poor, and about 57% had media exposure. Nearly 93% of the women had ANC visits during their pregnancy time. Moreover, 77% of them gave birth at a health facility. About 58% of mothers give birth for the first time at the age of 19 years and below. Only 20% of the households had a number of under-5-year-old children above the age of 5 years. Close to half (51%) of the children were males, and only 1.7% were twins. Approximately 53.47% of the children had average size, and 41% of the children were the fourth or above child in the family. Regarding community-level variables, nearly 53% of the participants were from four countries (namely, Burundi, Madagascar, Malawi, and Uganda), and 77% were rural residents. Approximately 53% of the population had low exposure to mass media. Nearly 51% of women in the community had low educational levels. Regarding the community utilization of health facility delivery was low at 52%. Approximately 52% of the community had low ANC utilization and poverty level, respectively (Table 3).

Pooled magnitude of early PNC uptake in East Africa

The pooled magnitude of early PNC uptake in the East African countries was 52% (95% CI: 39, 66). The highest magnitude of early PNC uptake was found in Zimbabwe (71%), followed by Kenya (69%) and Rwanda (63%). The lowest magnitude of early PNC utilization was reported in Uganda (40%). The between-country difference in magnitude of early PNC uptake (τ) was 22% (95% CI: 11, 44) (Figure 1).

Measures of variation (random effect estimates) analysis

The model with both individual and community-level factors has the smallest Widely Applicable Information Criteria (WAIC = 98,050.2) compared to the random intercept-only model (WAIC 107,081.7), the model with only individual-level factors (WAIC = 98,361.9), and the model with only community-level factors (WAIC = 105,612). Therefore, this model is the best fitted model for the data because it has the smallest WAIC compared to the other

TABLE 3 Participant characteristics early PNC uptake and its associated factors following child birth in East Africa: using recent DHS data from 2015 to 2022.

Variables	Frequency (weighted)	Percentage (weighted)
Maternal age		
15–24	24,662	31.53
25–34	34,960	44.7
35–49	18,590	23.77
Maternal education		
Not primary education	16,954	21.68
Primary education	38,488	49.21
secondary and Higher	22,771	29.11
Marital status		
Unmarried	5,441	6.96
Married	52,648	67.31
Others*	20,124	25.73
Wealth index		
Poorest	19,318	24.7
Poorer	15,637	19.99
Middle	14,470	18.5
Richer	14,228	18.19
Richest	14,560	18.62
Media exposure		
No	44,545	56.95
Yes	33,668	43.05
Age at first birth		
< 19 years	45,072	57.63
≥20 years	33,141	42.37
Mother working		
No	28,071	35.89
Yes	50,142	64.11
Number of under five children		
1–2	33,494	42.82
3–5	30,106	38.49
above 5	14,613	18.68
At least one ANC visit		
No	5,524	7.06
Yes	72,689	92.94
Place of delivery		
Home	18,111	23.16
Health facility	60,102	76.84
Twin		
No	76,885	98.3
Yes	1,327	1.7
Weight at birth		
Large	23,261	29.74

(Continued)

TABLE 3 (Continued)

Variables	Frequency (weighted)	Percentage (weighted)
Average	41,819	53.47
Small	13,133	16.79
Sex of the child		
Male	39,719	50.78
Female	38,494	49.22
Distance to health facility		
Not big problem	30,239	38.66
Big problem	47,974	61.34
Birth order		
1st	17,741	22.68
2nd or 3rd	28,682	36.67
4th and above	31,790	40.65
Residence		
Urban	18,088	23.13
Rural	60,125	76.87
Community ANC utilization		
Low	40,288	51.51
High	37,925	48.49
Community educational level		
low	39,903	51.02
High	38,310	48.98
Community distance to health facility		
Not long	71,405	91.3
Long	6,808	8.7
Community media exposure		
low	41,286	52.79
High	36,927	47.21
Community wealth level		
Low	39,516	50.52
High	38,697	49.48

models. Interpretations and reports were made based on this model. The random effect estimates have been determined by fitting four models (Model I (null model), Model II, Model III, and Model IV). The null model showed significant variability in the likelihood of early PNC uptake among East African countries ($\sigma^2 = 0.202$). The ICC of 0.06 in the null model implied that the difference between clusters contributed 6% of the total variation in the uptake of early PNC services. The MOR of 1.54 in the null model implied that if children were picked randomly from two different clusters (EAs), children within a cluster had a higher probability of receiving early PNC, with a 1.54 times higher chance of receiving early PNC services compared to children within a cluster with a lower chance of uptake of early PNC services. The proportional change in variance (PCV) in the full model was 55.7%, showing that both individual- and community-level factors explained 55.7% of the observed variation in uptake of early PNC (see Table 4).

Factor affecting early PNC uptake

In a multilevel multivariable Bayesian logistic regression analysis, variables, namely, maternal age, maternal education, marital status, mother's working status, wealth index, media exposure, age at first birth, parity, place of delivery, at least one ANC, birth size, birth order number, while residence, community media exposure, community wealth level, community ANC utilization and community distance to health facility were identified as significant individual and community-level factors of receiving early PNC service (Table 5).

The odds of early PNC service uptake among women in the age group of 25–34 years (AOR = 1.21; 95% CrI: 1.15, 1.27) and 35–49 years (AOR = 1.61; 95% CrI: 1.5, 1.72) were higher by 21 and 61%, respectively, compared to women aged 15–24 years old. Similarly, women who had achieved primary education (AOR = 1.96; 95% CrI: 1.88, 2.05) and secondary/higher education (AOR = 3.19;

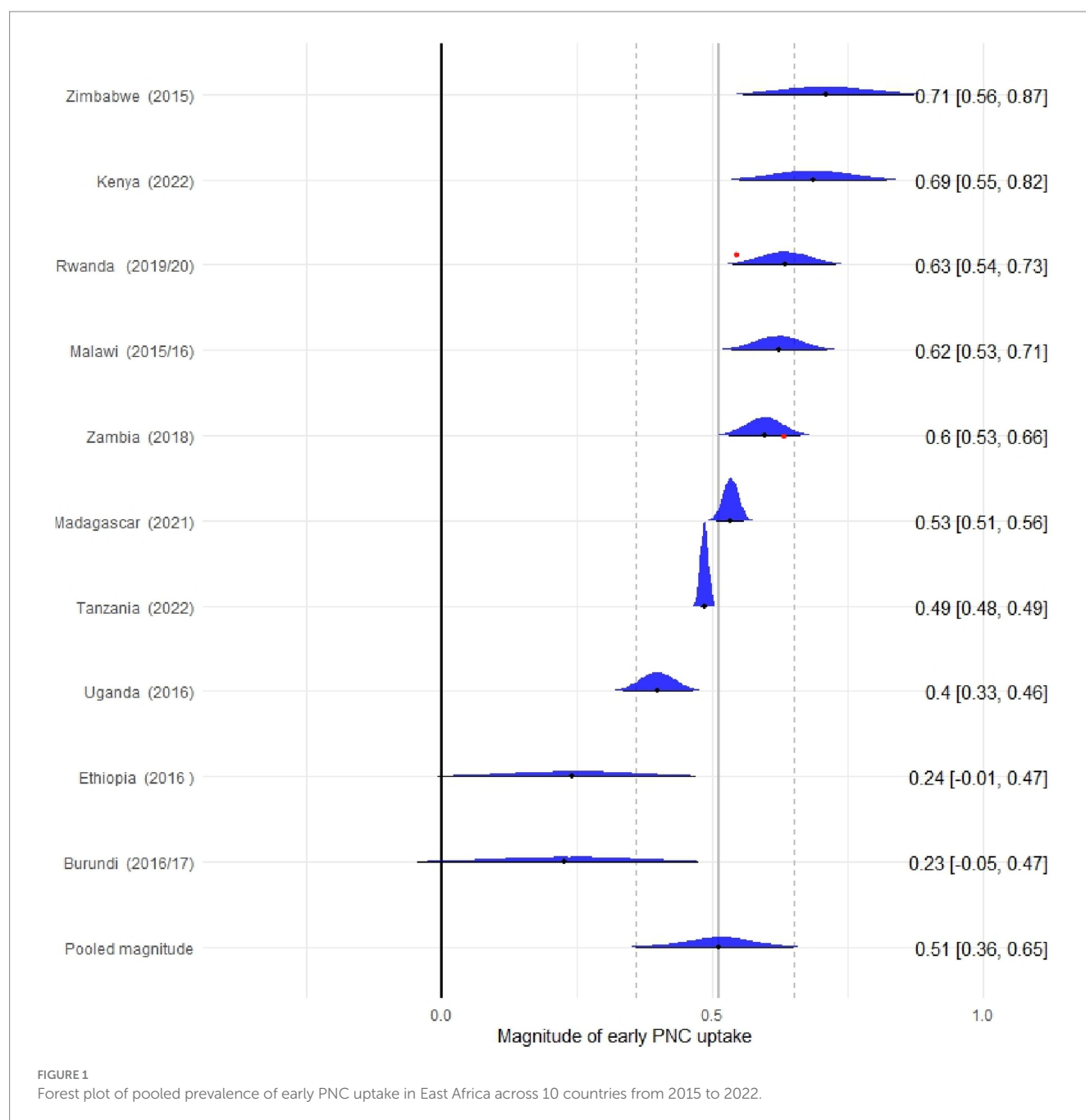


TABLE 4 Random effect analysis of PNC among women in East Africa.

Model comparisons parameters	Model I	Model II	Model III	Model IV
Cluster level variance	0.2	0.09	0.14	0.09
ICC	0.06	0.03	0.04	0.03
PCV	Ref	55.65%	31.18%	55.7%
MOR	1.54	1.33	1.43	1.34
WAIC	107,081.7	98,361.9	105,612	98,050.2

95% CrI: 3.03, 3.36) were 1.96 and 3.19 times more likely to receive early PNC services than formally uneducated women, respectively. Divorced or widowed women (AOR = 0.83; 95% CrI: 0.77, 0.89) had

17% lower odds of early PNC service uptake than unmarried women. Currently working women (AOR = 0.9; 95% CrI: 0.87, 0.93) had 10% lower odds of early PNC service uptake than those not

TABLE 5 Individual and community level factors associated with early PNC uptake among women in East African countries using the recent DHS datasets, 2015–2022.

Early PNC uptake	Estimate	Est. Error	AOR (95% CrI)	Rhat	Bulk_ESS	Tail_ESS
Maternal age						
15–24	Ref					
25–34	0.19	0.02	1.21 (1.15, 1.27)*	1	3,200	3,353
35–49	0.47	0.03	1.61 (1.5, 1.72) *	1	3,003	2,886
Maternal education						
Not primary education	Ref					
Primary education	0.67	0.02	1.96 (1.88, 2.05) *	1	4,248	3,453
secondary and Higher	1.16	0.03	3.19 (3.03, 3.36) *	1	4,343	3,082
Marital status						
Unmarried	Ref					
Married	−0.04	0.03	0.97 (0.9, 1.03)	1	3,783	3,041
Others **	−0.19	0.03	0.83 (0.77, 0.89)*	1	3,727	3,206
Mother working status						
Not working	Ref					
Working	−0.1	0.02	0.9 (0.87, 0.93)*	1	7,903	2,810
Wealth index						
Poorest	Ref					
Poorer	−0.13	0.02	0.88 (0.84, 0.92)*	1	7,039	2,722
Middle	−0.19	0.02	0.83 (0.79, 0.87)*	1	3,686	2,948
Richer	−0.26	0.03	0.77 (0.73, 0.81)*	1	3,211	3,289
Richest	−0.53	0.03	0.59 (0.55, 0.63)*	1	3,195	2,669
Media exposure						
No	Ref					
Yes	0.28	0.02	1.32 (1.27, 1.36)*	1	7,039	2,722
Parity						
1–2	Ref					
3–5	−0.12	0.03	0.89 (0.84, 0.94) *	1	2,910	2,761
Above 5	−0.36	0.04	0.69 (0.64, 0.75) *	1	3,143	3,209
Age at first birth						
< 19 years	−0.2	0.02	0.82 (0.79, 0.84) *	1	3,784	3,217
≥20 years	Ref					
ANC visit						
No	Ref					
Yes	0.66	0.04	1.93 (1.8, 2.08) *	1	6,705	3,115
Place of delivery						
Home	Ref					
Health facility	0.94	0.02	2.57 (2.46, 2.68) *	1	6,673	3,155
Child sex						
Male	Ref					
Female	0.01	0.02	1.01 (0.98, 1.04)	1	7,187	2,774

(Continued)

TABLE 5 (Continued)

Early PNC uptake	Estimate	Est. Error	AOR (95% CrI)	Rhat	Bulk_ESS	Tail_ESS
Weight at birth						
Large	Ref					
Average	−0.06	0.02	0.94 (0.91, 0.98) *	1	6,339	3,212
Small	−0.13	0.02	0.88 (0.84, 0.92) *	1	5,814	3,394
Twin						
No	Ref					
Yes	0.14	0.06	1.15 (1.02, 1.3) *	1	8,324	2,810
Birth order						
1st	Ref					
2nd or 3rd	−0.01	0.03	0.99 (0.95, 1.05)	1	3,622	2,894
4th and above	−0.12	0.04	0.88 (0.82, 0.95) *	1	2,959	2,791
Residence						
Urban	Ref					
Rural	−0.28	0.02	0.76 (0.72, 0.79)*	1	5,292	3,014
Community educational level						
low	Ref					
High	0.01	0.03	1.01 (0.95, 1.08)	1	2023	2,697
Community media exposure						
low	Ref					
High	0.1	0.03	1.1 (1.04, 1.18) *	1	1924	2,644
Community ANC utilization						
Low	Ref					
High	0.12	0.03	1.13 (1.07, 1.19) *	1	2,297	3,018
Community wealth						
Low	Ref					
High	−0.13	0.03	0.88 (0.83, 0.94) *	1	2039	2,801
Community distance to health facility						
Big problem	Ref					
Not big problem	0.41	0.04	1.5 (1.38, 1.63) *	1	2,524	2,699

NB: AOR, Adjusted odds ratio; CrI, Credible interval; ESS, Effective sample size, *statistically significant variable, and **divorced/widowed.

working. Regarding household wealth indexes, taking the poorest households as a reference, poorer women (AOR=0.88; 95% CrI: 0.84, 0.92), middle-class women (AOR=0.83; 95% CrI: 0.79, 0.87), richer (AOR=0.77; 95% CrI: 0.73, 0.81), and richest women (AOR=0.59; 95% CrI: 0.55, 0.63) all had decreased odds of early PNC service uptake as wealth increased. Women with media exposure (AOR=1.32; 95% CrI: 1.27, 1.36) had 32% higher odds of early PNC service uptake than those without media exposure. Women with 3–5 children (AOR=0.89; 95% CrI: 0.84, 0.94) and those with more than 5 children (AOR=0.69; 95% CrI: 0.64, 0.75) had lower odds of early PNC service uptake compared to those with one to two children. Women with an age at first birth <20 years (AOR=0.82; 95% CrI: 0.79, 0.84) had slightly lower odds of early PNC service uptake compared to those with an age at first birth ≥20 years. Women with at least one ANC visit (AOR=1.93, 95%

CrI: 1.8, 2.08) had 93% higher odds of early PNC service uptake than those without an ANC visit. Women delivering in health facilities (AOR=2.57; 95% CrI: 2.46, 2.68) were 2.57 times more likely to receive early PNC service uptake than those at home. Women with a child who had an average birth size (AOR=0.94; 95% CrI: 0.91, 0.98) and small birth size (AOR=0.88; 95% CrI: 0.84, 0.92) had slightly lower odds of early PNC service uptake compared to those with large birth size. Women with twins (AOR=1.15; 95% CrI: 1.02, 1.3) had 15% higher odds of early PNC service uptake than those without twins. Fourth- or above-born children (AOR=0.88; 95% CrI: 0.82, 0.95) had slightly lower odds of early PNC service uptake compared to first-born children. Regarding community-level variables, rural women (AOR=0.76; 95% CrI: 0.72, 0.79) had lower odds of early PNC service uptake by 24% compared to urban women. Communities with high media

exposure (AOR = 1.1; 95% CrI: 1.04, 1.18) had 10% higher odds of early PNC service uptake than their counterparts. Communities with high wealth levels (AOR = 0.88; 95% CrI: 0.83, 0.94) had 12% lower odds of early PNC service uptake. Communities with high ANC utilization (AOR = 1.13; 95% CrI: 1.07, 1.19) had 13% higher odds of early PNC service uptake than those with low ANC utilization. Communities in which the distance to a health facility is not a big problem (AOR = 1.5; 95% CrI: 1.38, 1.63) had 50% higher odds of early PNC service uptake than communities where it is a big problem (Table 5).

Discussion

Using the Bayesian multilevel modeling approach, the goal of this study was to pinpoint the underlying individual and community-level factors that contributed to the PNC uptake among mothers immediately following birth within 24–48 h. Based on our final model analysis, we found that the pooled prevalence of PNC following birth within 2 days of the delivery was about 52% (95% CrI: 39, 66). Although this pooled prevalence was still low, however, it has been shown to have approximately 20% increase as compared to the previous research subgroup analysis findings in SSA (44). In comparison to the prevalence recorded in Ethiopia (15.71%) (45), and Gambia (46), this prevalence was greater. Although the prevalence of PNC has increased over time in East Africa, this number is not very spectacular when compared to other countries such as Bangladesh (63%) (47), Benin (68%) (48), and Zambia (63%) (49). These differences may reflect the variety of country-specific factors, analysis model type, sampling, and other methodological changes, as well as the effectiveness of the health care system delivering mother and child care.

In this study, educated and older mothers have more PNC than their counterparts. According to a study conducted in SSA, Vietnam, and China, educated and older mothers have more PNC than their counterparts (44, 50, 51). Several previous studies have shown that a mother's education and age have a significant impact on a child's health (52). It is closely linked to her knowledge of health, which influences her use of maternal and child health services. Women with higher levels of education and age tend to have better knowledge about maternal health, enabling them to make informed decisions and seek appropriate medical care, including maternal health services. Higher education and being aged are associated with improved health-seeking behaviors, being more susceptible to maternal- and pregnancy-related complications, and are seen as a crucial way to empower women to access maternal healthcare services (53, 54). Therefore, the evidence suggests that educated and older women are more likely to have better knowledge and utilize maternal health services because they understand the importance of these services and can make informed choices.

When enabling factors are taken into account, mothers who had at least one ANC visit and gave birth in health facilities had a higher chance of getting a PNC checkup than their counterparts, which is supported by earlier research from India (55), Pakistan (56), Ethiopia (45, 57), Bangladesh (47) as well as Nigeria (58), and Uganda (59). This finding could be explained by the fact that pregnant women who receive counseling and information about the health risks of the

postpartum period during ANC visits are more likely to use adequate PNC services, which maintains their advantageous position regardless of their socioeconomic status. This finding might be explained by the fact that pregnant women who are exposed to counseling and information about the health risks of the postpartum period during ANC visits and during their delivery at medical facilities are more likely to use adequate PNC services, which maintain their advantageous position regardless of their socioeconomic status. Additionally, these women who gave birth in a hospital might be allowed to stay for an additional 2 days or advised to have a follow-up appointment 2 days after giving birth so that they can receive the proper medical attention for both themselves and their newborns. Mothers who give birth at home typically face cultural restrictions that prevent them from leaving their homes for a certain amount of time, exhibit negative attitudes, and use fewer postpartum services.

Although previous research did not provide specific explanations for why widowed mothers show less health-seeking behavior for themselves and their children, it can be inferred from the broader literature that the loss of a spouse has a significant impact on a woman's motivation and ability to seek healthcare. This impact includes increased levels of depression, anxiety, and psychological distress, which can affect a woman's willingness to access healthcare for herself and her children (60). Additionally, widowed mothers often lack social support, making it more difficult for them to seek healthcare (60). Moreover, the death of a spouse can lead to economic hardships, which further hinder a woman's ability to access healthcare for herself and her children. Furthermore, in some communities, widows may face stigmatization or discrimination, which can negatively influence their healthcare-seeking behavior (61). While the specific reasons for the lower health-seeking behavior among widowed mothers may vary depending on individual circumstances and cultural contexts, it is crucial to offer targeted support and interventions to address the unique challenges faced by this population.

The majority of the studies have investigated those urban women who had more PNC than rural women due to the unequal distribution of sources and various factors of women. Several factors could explain this difference. One reason is that rural areas often have limited transportation options and poor road infrastructure (62). This makes it difficult for women to travel to healthcare facilities for PNC visits. Additionally, rural women may have less information about PNC services and their importance, which can lead to lower utilization rates (62). Rural women may also face more socioeconomic challenges, such as poverty and a lack of resources, which can prevent them from seeking PNC services. Furthermore, rural areas typically have fewer healthcare facilities and resources, resulting in longer travel and wait times for PNC services, and women may face challenges in attending PNC visits due to the distance of the nearest health facility from their homes (63). Finally, in some rural communities, there may be cultural or social norms that discourage women from seeking PNC services (64). For example, there might be a preference for traditional birth attendants or a belief that PNC visits are unnecessary. All these could be caused by differences in the accessibility and availability of healthcare facilities, as well as the caliber of healthcare provided in the various regions.

This study showed that mothers who come from areas with high levels of media exposure and who frequently consume any form of media, including radio and television, are more likely to use PNC from any provider, regardless of qualification, than their counterparts who are not exposed to any media. This outcome is consistent with the research performed in Bangladesh (47), Uganda (59), Ethiopia (65), and Nigeria (66), where only qualified providers were considered. The fact that highly educated women who are already aware of the seeking behavior are more likely to be exposed to media can be used to explain this better occurrence. This demonstrates how the country can improve communication hurdles, PNC use, and other health services by leveraging the power of media.

Compared to those at parity 1, women at parity 4 and more had reduced probabilities of using PNC for their offspring. The most likely explanation is that women with higher parities may rely on the knowledge they gained from prior PNC visits. Studies from Uganda and Bangladesh have shown their agreement with this figure (47, 59). On the contrary, it is believed that a variety of obligations, such as raising younger and older children, frequently prevent women from seeking PNC, particularly in situations where access to a health facility is regarded to be difficult, mainly if they have more children and have not used contraception.

Compared to women who had single infants, twin mothers were more likely to seek PNC. Utilizing PNC services is crucial since they provide health professionals with a platform to identify and treat problems affecting expectant mothers and newborns. Women must use these services as a result, regardless of the manner of birth. Perhaps the stigma associated with twin pregnancies pushes women to seek PNC; however, more research on twin pregnancies and PNC uptake is required to fully understand the phenomena. Currently, studies from Bangladesh and Papua New Guinea have discovered a comparable number (47, 67). In the same way, if their babies are overweight or have obesity-like tendencies that are different from the babies they knew before and around them, they do not consider it as a good opportunity, so they are more likely to go to the health facility for a checkup.

This study found that wealthier and employed mother have a less likelihood chance of having PNC within 2 days following birth compared to their counterparts. According to a study conducted in Vietnam and SSA, women in wealthier households were significantly associated with postnatal health checks for their newborns. The proportion of postnatal health checks increased among households of near-poor, middle, rich, and richest as compared with the poorest households (44, 50). Although the author did not find earlier evidence, several factors could explain why wealthier and employed mothers may not return to health facilities within 2 days after giving birth, compared to poor and unemployed women. These factors include access to underreported private healthcare, self or relative postpartum support, dissatisfaction, and cultural or personal preferences. Wealthier women may have other options for postpartum care, such as home visits from healthcare providers. Cultural or personal preferences may also play a role in when women choose to visit health facilities after giving birth. Additionally, employed mothers may face challenges in taking time off work for these visits. These factors contribute to the disparities in postpartum

health facility visits among different socioeconomic groups. Further research and data analysis on this topic would provide a more comprehensive understanding of the underlying reasons.

Strengths and limitations of the study

Regarding the study's advantages, East African countries' nationally representative data, which is indicative of the entire nation, is used. To offer a more believable conclusion that considers the hierarchical nature of the survey data by incorporating prior information, this study also used a Bayesian multilevel modeling technique and sizable samples. This will improve the estimation of the results toward the reality of the country's current status. The study does have some flaws, though. Due to the self-reported nature of the interview, the survey is subject to social desirability, and the cross-sectional form of the study may not be able to account for the temporal connection of the independent and outcome variables. Furthermore, although there was a relatively short time variation among the countries in the dataset, time was not considered an independent factor in the regression. Therefore, readers should keep this in mind when interpreting and using the findings of this study.

Conclusion, recommendations, and implications of the study

Low utilization of immediate PNC uptake remains among the top public health importance agendas in East Africa. In the final model, the study at hand revealed several crucial individual and community-level factors, including older maternal age, higher education levels, being divorced/widowed women, better household wealth index, maternal working status, having mass media exposure, higher parity, having ANC follow up, institutional delivery, age at first birth, twin status, child weight at birth, and birth order were individual-level factors that have been independently associated with early PNC uptake. Similarly, regarding community-level factors, variables such as high community mass media exposure, being from a rural area, being from high ANC follow-up coverage communities, being from high-wealth communities and having a long distance to the health facilities were associated with the outcome variable, respectively, among women in East Africa.

Hence, targeted education and awareness campaigns are crucial. Given the positive correlation between higher education levels and early PNC uptake, it is important to implement campaigns that specifically target women with lower levels of education. These campaigns should emphasize the benefits of PNC and highlight the importance of seeking PNC services early in the postnatal period. Additionally, they should address any misconceptions or barriers that may exist. Similarly, it is important to strengthen ANC and institutional delivery services. The study has identified ANC follow-up and institutional delivery as factors that are positively associated with early PNC uptake. By improving access to quality ANC services, ensuring the presence of skilled birth attendants, and establishing adequate referral systems, the likelihood of women receiving timely PNC can be increased. Furthermore, community-based interventions are also crucial. The study has found that community-level factors, such as mass media exposure and ANC

follow-up coverage, can influence early PNC uptake. Therefore, implementing community health education programs and utilizing mass media platforms to disseminate PNC-related information can help improve awareness and promote early PNC-seeking behaviors. The future research should explore how the identified factors influence early PNC uptake and evaluate the effectiveness of interventions targeting these factors. Longitudinal studies could provide insights into the long-term impact of early PNC uptake on maternal and child health outcomes. Overall, the study underscores the importance of addressing both individual and community factors to enhance early PNC uptake in East Africa. By implementing targeted interventions and policies, healthcare systems can ensure that all women have equal access to timely and high-quality PNC services, improving maternal and child health 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

Ethical approval and a letter of permission were requested online at www.dhsprogram.com, and the DHS program was given permission through email to access the data for this study. This study made use of freely accessible data that was completely devoid of any personal information. The East African countries DHS provided the secondary data used in the study. Concerns about informed consent, confidentiality, anonymity, and privacy of the study sample were ethically addressed by the DHS authorities, and we did not alter or utilize the data in any other way. The study's data set was publicly accessible and devoid of any private information. Both patients and the general public were not involved in this investigation. The studies were conducted in accordance with the local legislation and institutional requirements.

Author contributions

BT: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Validation, Visualization, Writing – original draft. DA:

Investigation, Methodology, Resources, Software, Supervision, Validation, Writing – review & editing. FA: Data curation, Formal analysis, Funding acquisition, Investigation, Writing – review & editing. SA: Data curation, Formal analysis, Funding acquisition, Investigation, Supervision, Validation, Visualization, Writing – review & editing. TA: Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – review & editing.

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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.

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Supplementary material

The Supplementary material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fpubh.2024.1439280/full#supplementary-material>

References

1. Howden-Chapman P, Siri J, Chisholm E, Chapman R, Doll CN, Capon AJAgtsiftiP, France: ensure healthy lives and promote wellbeing for all at all ages. *Int Council Sci*. (2017):81–126.
2. WHO. Standards for improving quality of maternal and newborn care in health facilities. Geneva: WHO (2016).
3. UNICEF. The state of the world's children 2009: Maternal and newborn health. New York, NY: UNICEF (2008).
4. WHO. WHO recommendations on maternal and newborn care for a positive postnatal experience. Geneva: WHO (2022).
5. WHO. Pocket book of hospital care for children: Guidelines for the management of common childhood illnesses. Geneva: WHO (2013).
6. WHO Guidelines Approved by the Guidelines Review Committee. WHO recommendations on postnatal Care of the Mother and Newborn. Geneva: World Health Organization (2013).
7. WHO Guidelines Approved by the Guidelines Review Committee. Home visits for the newborn child: A strategy to improve survival. Geneva: World Health Organization (2009).
8. Nations U. (2020). The sustainable development goals report 2020. Available at: <https://unstats.un.org/sdgs/report/2020/The-Sustainable-Development-Goals-Report-2020.pdf>
9. Nations U. Progress towards the sustainable development goals report of the secretary-general 2019. Geneva: United Nations (2019).

10. Langlois EV, Miszkurka M, Ziegler D, Karp I, Zunzunegui MV. Protocol for a systematic review on inequalities in postnatal care services utilization in low- and middle-income countries. *Syst Rev*. (2013) 2:55. doi: 10.1186/2046-4053-2-55
11. Madaj B, Smith H, Mathai M, Roos N, van den Broek N. Developing global indicators for quality of maternal and newborn care: a feasibility assessment. *Bull World Health Organ*. (2017) 95:445–452. doi: 10.2471/BLT.16.179531
12. Organization WH. Trends in maternal mortality 2000 to 2017: estimates by WHO, UNICEF, UNFPA, World Bank Group and the United Nations population division: executive summary. Geneva: World Health Organization (2019).
13. McMahon SA, George AS, Chebet JJ, Mosha IH, Mpenbeni RN, Winch PJ. Experiences of and responses to disrespectful maternity care and abuse during childbirth: a qualitative study with women and men in Morogoro region. *Tanzania BMC Preg Childbirth*. (2014) 14:268. doi: 10.1186/1471-2393-14-268
14. World Bank. World Bank data. Mortality rate, under-5 (per 1,000 live births). Washington, DC: World Bank (2019).
15. WHO, UNFPA, the World Bank and the United Nations population division. Trends in maternal mortality: 1990 to 2013 estimates by WHO, UNICEF, UNFPA, the World Bank and the United Nations population division. Geneva: World Health Organization (2014).
16. Bhutta ZA, Das JK, Bahl R, Lawn JE, Salam RA, Paul VK, et al. Can available interventions end preventable deaths in mothers, newborn babies, and stillbirths, and at what cost? *Lancet*. (2014) 384:347–70. doi: 10.1016/S0140-6736(14)60792-3
17. Okawa S, Ansah EK, Nanishi K, Enameh Y, Shibanuma A, Kikuchi K, et al. High incidence of neonatal danger signs and its implications for postnatal Care in Ghana: a cross-sectional study. *PLoS One*. (2015) 10:e0130712. doi: 10.1371/journal.pone.0130712
18. Chalise B, Chalise M, Bista B, Pandey AR, Thapa S. Correlates of continuum of maternal health services among Nepalese women: evidence from Nepal multiple Indicator cluster survey. *PLoS One*. (2019) 14:e0215613. doi: 10.1371/journal.pone.0215613
19. Shibanuma A, Yeji F, Okawa S, Mahama E, Kikuchi K, Narh C, et al. The coverage of continuum of care in maternal, newborn and child health: a cross-sectional study of woman-child pairs in Ghana. *BMJ Glob Health*. (2018) 3:e000786. doi: 10.1136/bmjgh-2018-000786
20. Wang W, Hong R. Levels and determinants of continuum of care for maternal and newborn health in Cambodia-evidence from a population-based survey. *BMC Pregnancy Childbirth*. (2015) 15:62. doi: 10.1186/s12884-015-0497-0
21. Iqbal S, Maqsood S, Zakar R, Zakar MZ, Fischer F. Continuum of care in maternal, newborn and child health in Pakistan: analysis of trends and determinants from 2006 to 2012. *BMC Health Serv Res*. (2017) 17:189. doi: 10.1186/s12913-017-2111-9
22. Yeji F, Shibanuma A, Oduro A, Debpur K, Kikuchi K, Owusu-Agei S, et al. Continuum of Care in a Maternal, newborn and child health program in Ghana: low completion rate and multiple obstacle factors. *PLoS One*. (2015) 10:e0142849. doi: 10.1371/journal.pone.0142849
23. Sakuma S, Yasuoka J, Phongluxa K, Jimba M. Determinants of continuum of care for maternal, newborn, and child health services in rural Khammouane, Lao PDR. *PLoS One*. (2019) 14:e0215635. doi: 10.1371/journal.pone.0215635
24. Singh K, Story WT, Moran AC. Assessing the continuum of care pathway for maternal health in South Asia and sub-Saharan Africa. *Matern Child Health J*. (2016) 20:281–9. doi: 10.1007/s10995-015-1827-6
25. World Health Organization. Maternal mortality. Geneva: World Health Organization (2024).
26. Croft TN, Marshall AM, Allen CK, Arnold F, Assaf S, Balian S. Guide to DHS statistics. Rockville, MD: ICF (2018).
27. Union A. Report on sustainable development goals for the eastern Africa subregion. (2015) Addis Ababa, Ethiopia: United Nations Economic Commission for Africa.
28. Gambia Bureau of Statistics – GBoS, ICF. The Gambia demographic and health survey 2019–20. Banjul: GBoS/ICF (2021).
29. WHO. WHO recommendations on postnatal care of the mother and newborn. Geneva: World Health Organization (2014).
30. Williams DR, Rast P, Bürkner P-C. Bayesian meta-analysis with weakly informative prior distributions. (2018).
31. Lesaffre E, Lawson A. Statistics in practice: Bayesian biostatistics. Somerset, NJ: Wiley (2012).
32. Correa-Álvarez CD, Salazar-Urbe JC, Pericchi-Guerra LR. Bayesian multilevel logistic regression models: a case study applied to the results of two questionnaires administered to university students. *Comput Stat*. (2023) 38:1791–810. doi: 10.1007/s00180-022-01287-4
33. Draper D. Bayesian multilevel analysis and MCMC. Handbook of multilevel analysis. Cham: Springer (2008), p. 77–139.
34. Gelman A, Carlin JB, Stern HS, Rubin DB. Bayesian data analysis. London: Chapman and Hall/CRC (1995).
35. Hoffman MD, Gelman A. The no-U-turn sampler: adaptively setting path lengths in Hamiltonian Monte Carlo. *J Mach Learn Res*. (2014) 15:1593–623.
36. Bürkner P-C. Advanced Bayesian multilevel modeling with the R package BRMS. (2018) New Zealand: University of Auckland.
37. Vehtari A, Gelman A, Gabry J. Practical Bayesian model evaluation using leave one-out cross-validation and WAIC. *Stat Comput*. (2017) 27:1413–32. doi: 10.1007/s11222-016-9696-4
38. Gelman A, Hwang J, Vehtari A. Understanding predictive information criteria for Bayesian models. Springer Nature (2014), 24.
39. Kruschke J. Doing Bayesian data analysis: a tutorial with R, JAGS, and Stan. Academic Press (2014).
40. Vehtari A, Gelman A, Simpson D, Carpenter B, Bürkner PC. Rank-normalization, folding, and localization: an improved Rhat for assessing convergence of MCMC. International Society for Bayesian Analysis (ISBA). Bayesian Analysis (2019) arXiv.
41. Hesketh SR, Skrondal A. Multilevel and longitudinal modeling using Stata: STATA press (2021).
42. Larsen K, Merlo J. Appropriate assessment of neighborhood effects on individual health: integrating random and fixed effects in multilevel logistic regression. *Am J Epidemiol*. (2005) 161:81–8. doi: 10.1093/aje/kwi017
43. Goldstein H. Multilevel statistical models. London: John Wiley & Sons (2011).
44. Benova L, Owolabi O, Radovich E, Wong KL, Macleod D, Langlois EV, et al. Provision of postpartum care to women giving birth in health facilities in sub-Saharan Africa: a cross-sectional study using demographic and health survey data from 33 countries. *PLoS Med*. (2019) 16:e1002943. doi: 10.1371/journal.pmed.1002943
45. Kassie DG, Assimamaw NT, Tamir TT, Alemu TG, Techane MA, Wubneh CA, et al. Spatial distribution and determinants of new borns not receiving postnatal check-up within two days after birth in Ethiopia: a spatial and multilevel analysis of EDHS 2016. *BMC Pediatr*. (2022) 22:495. doi: 10.1186/s12887-022-03506-9
46. Kinteh B, Barrow A, Nget M, Touray E, Touray J, Kinteh SL, et al. Maternal and child health Services in Rural Settings of the Gambia: contextual determinants of postnatal care from mothers' perspectives—a community-based analytical cross-sectional study. *Adv. Pub. Health*. (2022) 2022:1–7. doi: 10.1155/2022/3558676
47. Sheba IT, Sarker AR, Tasnim A. Factors associated with post-Natal Care utilization among the women of reproductive age group: evidence from Bangladesh demographic and health survey 2017–18. *Health Services Res. Manage. Epidemiol*. (2022) 9:23333928221136393. doi: 10.1177/23333928221136393
48. Dansou J, Adekunle AO, Arowojolu AO. Factors associated with antenatal care services utilisation patterns amongst reproductive age women in Benin Republic: an analysis of 2011/2012 Benin Republic's demographic and health survey data. *Nigerian Postgraduate Med. J*. (2017) 24:67–74. doi: 10.4103/npmj.npmj_16_17
49. Chungu C, Makasa M, Chola M, Jacobs CN. Place of delivery associated with postnatal care utilization among childbearing women in Zambia. *Front Public Health*. (2018) 6:94. doi: 10.3389/fpubh.2018.00094
50. Lam ND, Anh ND, Ha NTT, Vinh TQ, Anh VTM, Kien VD. Socioeconomic inequalities in post-natal health checks for the newborn in Vietnam. *Int J Equity Health*. (2019) 18:1–7. doi: 10.1186/s12939-019-1029-8
51. Yang Y, Yu M. Disparities and determinants of maternal health services utilization among women in poverty-stricken rural areas of China: a cross-sectional study. *BMC Pregnancy Childbirth*. (2023) 23:1–14. doi: 10.1186/s12884-023-05434-7
52. Paul S, Paul S, Gupta AK, James K. Maternal education, health care system and child health: evidence from India. *Soc Sci Med*. (2022) 296:114740. doi: 10.1016/j.socscimed.2022.114740
53. Wang H, Frasco E, Takesue R, Tang K. Maternal education level and maternal healthcare utilization in the Democratic Republic of the Congo: an analysis of the multiple indicator cluster survey 2017/18. *BMC Health Serv Res*. (2021) 21:1–13. doi: 10.1186/s12913-021-06854-x
54. Taye BT, Kebede AA, Wondie KY. Intention to use maternal health services and associated factors among women who gave birth at home in rural Sehal Seyemit district: a community-based cross-sectional study. *BMC Pregnancy Childbirth*. (2022) 22:213. doi: 10.1186/s12884-022-04447-y
55. Krishnamoorthy Y, Majella MG. Determinants of postnatal care coverage among mothers and new-borns in India: evidence from a nationally representative survey. *Int J Health Plann Manag*. (2021) 36:1276–86. doi: 10.1002/hpm.3179
56. Yunus A, Iqbal S, Munawar R, Zakar R, Mushtaq SK, Sadaf F, et al. Determinants of postnatal care services utilization in Pakistan-insights from Pakistan demographic and health survey (PDHS) 2006-07. *Middle-East J Sci Res*. (2013) 18:1440–7. doi: 10.5829/idosi.mejrs.2013.18.10.12418
57. Teshale AB, Tesema GA, Yeshaw Y, Tesema AK, Alem AZ, Liyew AM. Individual and community level factors associated with delayed first postnatal care attendance among reproductive age group women in Ethiopia. *BMC Pregn. Childbirth*. (2021) 21:1–8. doi: 10.1186/s12884-020-03523-5
58. Oluwaseyi SD. Determinants of postnatal care non-utilization among women in Nigeria. Johannesburg: University of the Witwatersrand, Faculty of Humanities (2014).
59. Ndugga P, Namiyonga NK, Sebuwufu D. Determinants of early postnatal care attendance: analysis of the 2016 Uganda demographic and health survey. *BMC Pregnancy Childbirth*. (2020) 20:163. doi: 10.1186/s12884-020-02866-3

60. Holm AL, Berland AK, Severinsson E. Factors that influence the health of older widows and widowers—a systematic review of quantitative research. *Nurs Open*. (2019) 6:591–611. doi: 10.1002/nop2.243
61. Akter S, Azad T, Rahman MH, Raihan MF. Morbidity patterns and determinants of healthcare-seeking behavior among older women in selected rural areas of Bangladesh. *Dr Sulaiman Al Habib Medical Journal*. (2023) 5:70–9. doi: 10.1007/s44229-023-00033-2
62. Amsalu G, Talie A, Gezimu W, Duguma A. Non-utilization of postnatal care and its associated factors among women who gave birth in rural districts of northern Ethiopia: a community-based mixed-method study. *Womens Health*. (2022) 18:17455057221125091. doi: 10.1177/17455057221125091
63. Kanté AM, Chung CE, Larsen AM, Exavery A, Tani K, Phillips JF. Factors associated with compliance with the recommended frequency of postnatal care services in three rural districts of Tanzania. *BMC Pregnancy Childbirth*. (2015) 15:1–10. doi: 10.1186/s12884-015-0769-8
64. Akhter S, Dasvarma GL, Saikia U. Reluctance of women of lower socio-economic status to use maternal healthcare services—does only cost matter? *PLoS One*. (2020) 15:e0239597. doi: 10.1371/journal.pone.0239597
65. Ayele BG, Woldu MA, Gebrehiwot HW, Gebre-Egziabher EG, Gebretnsae H, Hadgu T, et al. Magnitude and determinants for place of postnatal care utilization among mothers who delivered at home in Ethiopia: a multinomial analysis from the 2016 Ethiopian demographic health survey. *Reprod Health*. (2019) 16:1–10. doi: 10.1186/s12978-019-0818-2
66. Agho KE, Ezech OK, Issaka AI, Enoma AI, Baines S, Renzaho AM. Population attributable risk estimates for factors associated with non-use of postnatal care services among women in Nigeria. *BMJ Open*. (2016) 6:e010493. doi: 10.1136/bmjopen-2015-010493
67. Appiah F, Fenteng JOD, Dare F, Salihi T, Darteh AO, Takyi M, et al. Understanding the determinants of postnatal care uptake for babies: a mixed effects multilevel modelling of 2016–18 Papua New Guinea demographic and health survey. *BMC Pregnancy Childbirth*. (2021) 21:1–13. doi: 10.1186/s12884-021-04318-y
68. R Core Team. (2023a). *R: A Language and Environment for Statistical Computing*. R Foundation for Statistical Computing. Available at: <https://www.r-project.org>
69. R Core Team. (2023b). R 4.3.2 Release Notes. Available at: <https://cran.r-project.org/doc/manuals/r-release/NEWS.html#R-4-3-2>
70. Bürkner, PC. brms: An R Package for Bayesian Multilevel Models using Stan. *J Stat Softw*. (2017) 80:1–28. doi: 10.18637/jss.v080.i01
71. Bürkner PC. *brms: An R Package for Bayesian Multilevel Models using Stan*. GitHub repository. (2023b). Available at: <https://github.com/paul-buerkner/brms>
72. Bürkner, PC. *brms: An R Package for Bayesian Multilevel Models using Stan*. CRAN Repository. (2023a). Available at: <https://cran.r-project.org/web/packages/brms/index.html>
73. Gelman A., Rubin DB. Inference from Iterative Simulation Using Multiple Sequences. *Stat. Sci.* (1992) 7:457–472. doi: 10.1214/ss/1177011136
74. Gelman A, Hill J. *Data Analysis Using Regression and Multilevel/Hierarchical Models*. Cambridge University Press. (2006).



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Automated approach for fetal and maternal health management using light gradient boosting model with SHAP explainable AI

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Fetal health holds paramount importance in prenatal care and obstetrics, as it directly impacts the wellbeing of mother and fetus. Monitoring fetal health through pregnancy is crucial for identifying and addressing potential risks and complications that may arise. Early detection of abnormalities and deviations in fetal health can facilitate timely interventions to mitigate risks and improve outcomes for the mother and fetus. Monitoring fetal health also provides valuable insights into the effectiveness of prenatal interventions and treatments. For fetal health classification, this research work makes use of cardiotocography (CTG) data containing 21 features including fetal growth, development, and physiological parameters such as heart rate and movement patterns with three target classes "normal," "suspect," and "pathological." The proposed methodology makes use of data upsampled using the synthetic minority oversampling technique (SMOTE) to handle the class imbalance problem that is very crucial in medical diagnosing with a light gradient boosting machine. The results show that the proposed model gives 0.9989 accuracy, 0.9988 area under the curve, 0.9832 recall, 0.9834 precision, 0.9832 F1 score, 0.9748 Kappa score, and 0.9749 Matthews correlation coefficient value on the test dataset. The performance of the proposed model is compared with other machine learning models to show the dominance of the proposed model. The proposed model's significance is further evaluated using 10-fold cross-validation and comparing the proposed model with other state-of-the-art models.

KEYWORDS

public health, risk perceptions, healthcare, mother and child care, machine learning

1 Introduction

The perinatal mortality rate refers to the total number of stillbirths and deaths occurring within the first seven days of life per 1,000 live births. The United Nations International Children's Emergency Fund (UNICEF) data from 2018 indicates that in third-world countries, the perinatal mortality rate is 19, while in developed countries this rate is between 3 and 7 for every 1,000 births, respectively. Sub-Saharan Africa and South Asia are amongst the regions with the highest perinatal mortality reaching 28 and 26 respectively, as per UNICEF (1). At the start of the 20th century, perinatal mortality rates were alarmingly high in the first-world countries of that era, but significant reductions were achieved through improved antenatal care, comprehensive C-section indicators, and perinatal screening technologies like amniocentesis, fetal echocardiography (ECG), amnioscopy, cardiotocograph (CTG), and ultrasound (2). Preterm births, maternal hypertension, birth asphyxia, and septicemia are the main contributors to perinatal deaths and complications related to childbirths (3). Asphyxia is caused by an extended period of oxygen deprivation brought about by interrupted placental blood flow resulting from umbilical cord prolapse, placental abruption, or maternal pre-eclampsia. Asphyxia signs are oversights lead by delivery mismanagement. Irretrievable organ damage or even death can be prevented by prompt detection of asphyxia signs by fetal heart rate monitoring during the antenatal and antepartum periods.

Fetal distress presents as an irregularity in fetal heart rate (FHR), either low or high, measured in beats per minute (BPM). Fetal status can primarily be detected through CTG, commonly utilized in clinical examinations (4). Uterine contractions (UC) and FHR are the vital physiological parameters monitored during CTG prenatal checks. Distress can manifest as abnormal FHR, aiding in the early identification of pathological conditions. CTG data enables the classification of fetal health relative to normal parameters. This diagnostic method, conducted during the third trimester of labor, involves continuous monitoring of UC and FHR via pressure transducers and ultrasound probes placed on the maternal abdomen. Real-time readings allow for immediate observation. Clinicians interpret CTG results based on predefined criteria, classifying them as Suspect, Normal, or Pathologic. In first-world countries, CTG stands as a prevalent method for evaluating fetal wellbeing (5). However, some experts oppose excessive CTG utilization in low-risk cases. CTG readings, morbidity, and perinatal mortality are correlated. Neonatal ICUs and low APGAR scores are related to pathological CTG results (6). Fetal distress can also be observed through CTG, and its outcomes vary depending on factors like causative factors, severity, and timeliness of medical interventions. Temporary fetal distress is addressed by changing the position of the mother, injecting IV fluids, administering oxygen supply, or undergoing cesarean sections if necessary, typically toward the end of the third trimester. These interventions aim to enhance the baby's condition and achieve favorable outcomes. However, prolonged fetal distress may result in enduring negative consequences such as intellectual deficiencies, motor impairments, learning disabilities, and disorders like cerebral palsy, albeit rarely (7). Prolonged distress, typically due to oxygen deprivation, may

even lead to birth asphyxia, contributing to roughly around 0.9 million neonatal casualties per annum (8).

Fetal death rates are notably higher in low-income countries compared to high-income nations, reflecting disparities in healthcare accessibility and resources between these regions. Despite a global decline in neonatal mortality rates from 36.7 per 1,000 live births in 1990 to 17 in 2020 over the past three decades, the rates remain disproportionately elevated in low-income areas (9). Even in high-income regions, complications of the placenta, often associated with fetal distress, stand as the leading cause of fetal death. Therefore, accurate assessment of fetal health is critical. CTG is an effective source to evaluate and find fetal distress at an early stage. CTG tests offer resource-efficient and timely evaluations, helping ease patient anxiety, particularly in high-volume settings. Certain CTG finding arrangements, such as loss of FHR variability, fixed FHR baselines, and absence of accelerations, signal a non-encouraging fetal status (10, 11). While CTG interpretation traditionally relies on expert visual analysis, automated mechanisms are being explored to augment this process.

Artificial intelligence (AI) has emerged as a valuable tool for assessing the status of the fetus (12). Within healthcare, machine learning is revolutionizing numerous facets, from tailoring treatments to enhancing diagnostic capabilities (13). Progress in health informatics and machine learning algorithms, a subset of AI, facilitates modeling processes, leading to more informed and optimized health decisions (14, 15). Ongoing advancements in machine learning continuously explore practical applications within real-world clinical settings. These algorithms find utility in decision-support systems across various biomedical domains, including fetal classification, aiming to identify compromised fetal statuses and prevent hypoxic injuries and pregnancy-related complications (16). This study proposes a fetal health arrangement framework utilizing a CTG dataset and machine learning. The primary contributions of this research are outlined as follows:

- The study introduces a comprehensive framework for fetal health classification using a light gradient boosting machine (LGBM) and cardiotocogram data.
- The proposed approach uses synthetic minority oversampling technique (SMOTE) as preprocessing for data resampling with the LGBM model for obtaining high accuracy, the area under the curve (AUC), recall, precision, F1, Kappa, and Matthew's correlation coefficient (MCC). In addition, computational complexity is greatly improved.
- The proposed framework is compared with several other machine learning models: catboost classifier (CB), extra trees classifier (ET), extreme gradient boosting (CGB), random forest classifier (RF), gradient boosting classifier (XGBoost), decision tree classifier (DT), K neighbors classifier (KNN), AdaBoost classifier (Ada), logistic regression (LR), linear kernel support vector machine (SVM), and Naive Bayes (NB) to show the efficacy of the proposed model. Furthermore, k-fold cross-validation is applied to validate its performance, in addition to, comparing its performance with state-of-the-art models.

The paper is structured as follows: Section 2 presents a comprehensive literature review concerning fetal health classification. Section 3 outlines the proposed framework, including details of the dataset, preprocessing, and the architecture of the proposed classification model, including hyperparameters. Section 4 covers the results obtained and discussions. The discussion is related to the findings and implications of the work. Finally, Section 5 concludes the paper.

2 Related works

Multiple research works investigated the application of machine learning in detecting fetal health status. This section delves into the theories and relevant concepts present in current literature, along with their findings, to pinpoint gaps. However, few studies have specifically addressed CTG data-based fetal health classification. Yin and Bingi (17) introduced a machine learning-based system employing XGB, LGBM, and SVM models. The study demonstrated SVM achieving an accuracy of 99.59% for classification. They also compared their system's results with local interpretable model agnostic explanations (LIME) and Shapley additive explanations (SHAP). Abiyev et al. (18) proposed a type 2 Fuzzy neural network (T2-FNN) for discovering the health status of the fetus. They conducted performance comparisons using various machine learning and deep learning models. Implementing T2-FNN with different rule sets, such as 21, 42, and 63 rules, they found that T2-FNN with 63 rules achieved an accuracy of 96.66%.

For early prognosis and classification of fetal health, Kuzu and Santur (19) introduced an ensemble learning model. They utilized ensemble learning techniques including LR, RF, GB, and XGB. The study results indicate that the XGB ensemble learning model surpassed others, achieving CTG dataset-based 99% accuracy. Hussain et al. (20) proposed an improved deep neural algorithm for classifying suspicious CTG recordings and untapped pathological with preferred time complexity. Their system integrates AlexNet architecture with SVM to reduce time complexity at fully connected layers. When a deep transfer learning process is employed, pre-learned topographies are relocated to their prototype. A strategy was implemented by them to further shrink time complexity where other layers were kept in the frozen state while partially training convolutional base layers. The proposed algorithm demonstrated superior performance compared to leading architectures, with instantaneous sensitivities, accuracy, and specificity reaching 96.67%, 99.72%, and 99.6%, respectively.

Piri and Mohapatra (21) proposed a rule-based approach for cardiotocographic fetal evaluation. The work involved utilizing an associative classifier in conjunction with traditional machine learning models. The study highlights that 83% accuracy was achieved by associative classifier prototype before feature selection and 84% after feature selection for classifying fetal health status. Duhayyim et al. (22) introduced an ensemble learning model for automatic fetal health classification. The authors conducted experiments in two scenarios. Initially, they employed five classifiers CatBoost, RF, LGBM, XGBoost, and Ada without oversampling, to categorize CTG readings into pathological, suspected, and healthy. Subsequently, they utilized oversampling deployed ensemble classifiers. They employed

random oversampling to balance CTG records for training the ensemble models. Results indicate that XGBoost, LGBM, and CatBoost classifiers achieved 99% accuracy.

Islam et al. (23) conducted research on classifying fetal states using machine learning algorithms. The study employed algorithms such as Ada, KNN, RF, SVM, GBC, DT, and LR. To ensure an unbiased dataset, scaling techniques were employed. Results indicate that GBC outperformed other models, achieving an accuracy of 95%. The study (24) focused on the application of classification techniques in gynecology and obstetrics for CTG data classification to predict normal, suspect, and pathologic cases. Six well-known classification algorithms were evaluated for fetal state classification in CTG datasets. The study revealed that NB achieved a classification accuracy of 83.06%.

Salini et al. (25) conducted a machine learning-based study, addressing the prominence of radical fetal health classification. They deployed various models such as RF, LR, DT, SVC, VC, and KNN on the dataset. The effectiveness of the model was evaluated in classifying fetal health by strenuous training and testing of these models. An outstanding accuracy of 93% was exhibited by the RF model as a promising outcome of this study. Sudharson et al. (26) utilized multiple classification algorithms on the CTG dataset and compared the results of individual algorithms. The comparison involved four different classification algorithms KNN, NB, DT, and SVM. Based on the overall comparison using these classification reports, DT exhibited the highest score among the four algorithms and achieved an accuracy of 90.8%.

Various machine learning techniques, classifiers, and ensemble learning methods have shown promising results in classifying fetal status accurately using the CTG dataset, as evidenced by early research. However, there remains a gap in evaluating these approaches comprehensively, as previous studies have primarily focused on recall, accuracy, F1 score, and precision-like metrics. Additional evaluation parameters such as MCC, Kappa, and training time are necessary to provide a comprehensive understanding of the performance of these methods. A summary of the literature discussed above is presented in Table 1.

3 Materials and methods

Fetal wellbeing serves as a crucial indicator for confirming fetal health. Inadequate fetal movement stands as a significant contributor to fetal mortality, underscoring the importance of early diagnosis to promote fetal health. This segment of the research encompasses the following components: dataset description, data visualization, data preprocessing techniques, study deployed ML models, evaluation parameters, and the proposed system for fetal health assessment.

3.1 Dataset

We used the Fetal Health classification dataset extracted from the Kaggle repository. This dataset is based on CTG readings of expecting mothers with gestational ages between 29 and 42 weeks comprising 2126 records (27). The author programmed an automated analysis of CTG readings. Signals

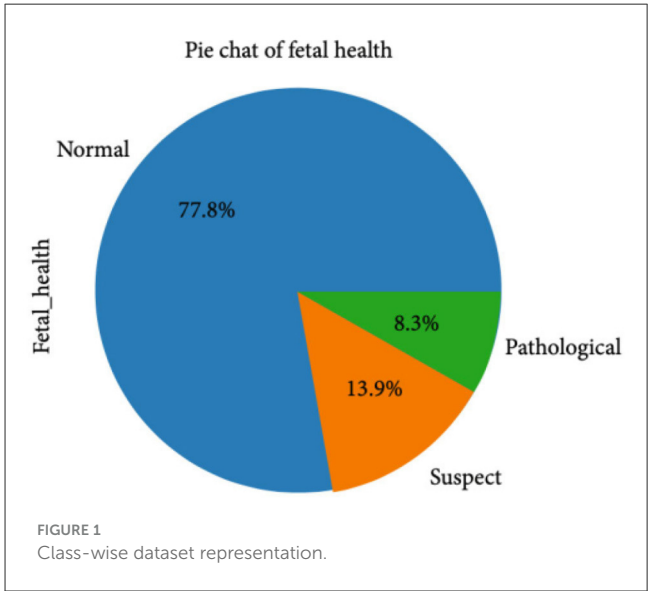
TABLE 1 Related work summary.

References	Classifier	Performance	Limitations
Yin and Bingi (17)	XGB, SVM	99.59% SVM	No cross-validation
Abiyev et al. (18)	LR, GNB, SVC, RBF SVC, ANN, CART, RF, RNN, CatBoost, T2-FNN (21 rules,42 rules, 63 rules)	96.66% T2-FNN (63 rules)	No cross-validation, Utilization of imbalanced dataset, and no Explainable AI
Kuzu and Santur (19)	LR, RF, GB, XGB	99% XGB	No cross-validation, Utilization of imbalanced dataset, and no Explainable AI
Muhammad Hussain et al. (20)	RNN, RF, GoogleNet, DesnseNet, NiftyNet, AlexNet, AlexNet-SVM	99.72% AlexNet-SVM,	No cross-validation, Utilization of imbalanced dataset, and no Explainable AI
Piri and Mohapatra (21)	SVM, CBA, DT, KNN, LR, RF, XGBoost, GNB	94% XGBoost and RF	No cross-validation, Utilization of imbalanced dataset, just accuracy is evaluated, and no Explainable AI
Al Duhayyim et al. (22)	RF, XGB, ADA, CatBoost, LGBM, VC	99% XGB, CatBoost, LGBM, VC	No cross-validation, Utilization of less number of features, and no Explainable AI
Islam et al. (23)	ADA, KNN, RF, SVM, GBC, DT, and LR	95% GBC	No cross-validation, Utilization of imbalanced dataset, and no Explainable AI
Afridi et al. (24)	J48, IBK, LR, NB, SMO and RF	83.06% NB	No cross-validation, and no Explainable AI
Salini et al. (25)	RF, LR, DT, SVC, VC, kNN	93% RF	No cross-validation, Utilization of imbalanced dataset, and no Explainable AI
Sudharson et al. (26)	KNN, Naive Bayes, DT, SVM	90.8% DT	No cross-validation, Utilization of imbalanced dataset, and no Explainable AI

from Hewlett-Packard fetal monitors and Sonicaid were collected using the SisPorto 2.0 system, comprising 6,000 tested pregnancy records.¹ Baseline acceleration, fetal heart, contraction, deceleration, and variability readings were established through the input of monitor readings from three experts. Therefore, the obtained dataset forms part of a study to validate the SisPorto 2.0 system. It consists of the individual record-corresponding label with 21 decimal value features, classifying the record into “Healthy,” “Suspected,” or “Pathological” fetal health status.

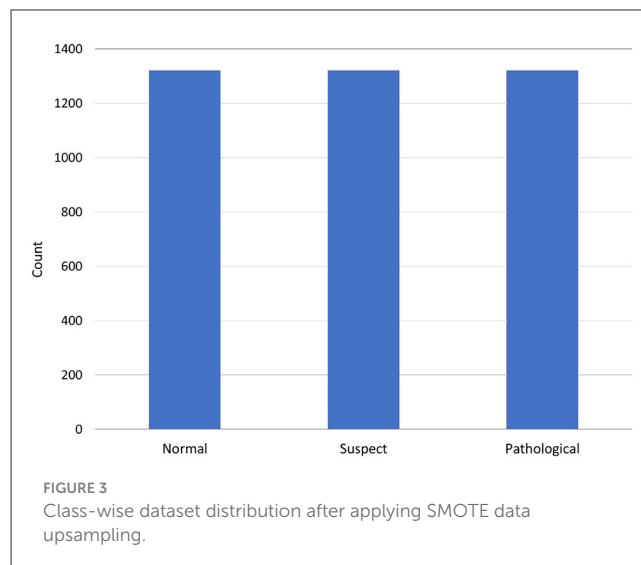
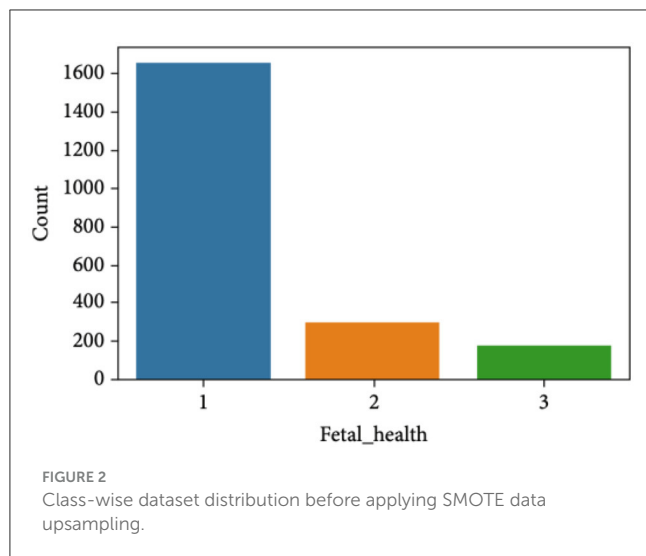
3.2 Data visualization

The CTG dataset contains a total of 2,126 records concerning fetal health conditions. Further analysis indicates that the dataset has a class imbalance problem and the distribution of the class samples is not balanced, as illustrated in Figure 1. The dataset has three classes: “pathological,” “normal,” and “suspect,” and has 176, 1,655, and 295 samples, respectively.



1 [https://onlinelibrary.wiley.com/doi/10.1002/1520-6661\(200009/10\)9:5%3C311::AID-MFM12%3E3.0.CO;2-9](https://onlinelibrary.wiley.com/doi/10.1002/1520-6661(200009/10)9:5%3C311::AID-MFM12%3E3.0.CO;2-9)

Figure 2 clearly indicates the necessity for balancing the dataset due to its inherent imbalance. To address this issue, various techniques were employed to balance the dataset, resulting in 295 suspicious attributes, 1,655 normal attributes, and 176 pathological attributes.



3.3 Data resampling

The CTG dataset encompasses readings from labor and random gestation cases. Critical undeniable findings from CTG readings were established despite the low probability of abnormality in these readings. However, the utilized Fetal Health Assessment dataset has class imbalance with a higher ratio of healthy fetuses 1,655 as compared to 176 pathological and 295 suspected occurrences (28). Results can be misleading based on such imbalanced data when used for training a prototype because there is a high probability of the model's learning from a very high ratio of healthy instances in contrast to suspected or pathological cases. Therefore, it's imperative to balance the dataset before constructing a prediction model. Various techniques have been proposed by researchers to address imbalanced datasets, including random under-sampling, random over-sampling, SMOTE, and imbalanced resampling, among others.

In this study, we opted for the SMOTE technique to balance our dataset. SMOTE augments the number of data instances by creating synthetic data points for the minority class using Euclidean distance based on their nearest neighbors (29). These fresh instances being based on the original features look like the original data. While SMOTE may introduce additional noise, it remains a suitable choice for our dataset. Over-sampling with replacement, in particular, serves as a straightforward technique for balancing the dataset, and it aligns well with our dataset characteristics since the CTG records exhibit relatively low variation within a class. Additionally, data integrity is preserved by over-sampling, and the large dataset is facilitated in the process, thereby enhancing model simplification.

Before applying the SMOTE oversample technique, we made a dataset division of 80%–20% which means 20% of the entire dataset is used for testing and 80% for training. From the 20% testing dataset (426 records), healthy fetuses records are 333, suspected 64, and pathological 29. After this training division of 80% (1,700 records), healthy fetus records are 1,322 as compared to 147 pathological and 231 suspected. Then we applied SMOTE data oversampling on this training dataset division and upsampled all classes to 1,322 samples. In this way, our transformed dataset

shape becomes $(1,322 \times 3 = 3,966)$ samples with 22 features in total. Then on this transformed dataset we trained our models and tested on 426 (20% of testing data) that we split before applying SMOTE oversampling. Figure 3 shows data balancing after applying SMOTE.

3.4 Machine learning models for fetal health classification

In this section, we provide a brief description of the classification methods utilized in the study, along with details on the calibration process of the classifier. The following machine learning techniques were employed in the current study, chosen for their widespread use in fetal health classification and other tasks. All models were implemented using scikit-learn. The section includes a concise overview of each model and its corresponding hyperparameters.

3.4.1 Light gradient boosting machine

LightGBM is a swift, efficient, and distributed gradient-boosting structure DT-embedded algorithm. LightGBM is extensively employed in boosting algorithms across multiple ML tasks like classification, ranking, and regression (30). Boosting methods yield a powerful learning model by combining multiple weak ML algorithms. Through successive iterations, the importance of misclassified data points is enhanced while that of correctly classified diminishes by such boosting algorithms. A greater intention is ensured by this iterative process to the misclassified classifier in the subsequent training sessions. Eventually, all individual ML models are linearly united, with adjustments made to the combined model weights based on the classifiers' error rates. LightGBM core concept is symbolized

in Equation 1.

$$f(x) = \sum_{q=1}^Q \alpha_q T(x, \theta_q) \quad (1)$$

where $f(x)$ represents the training sample x corresponding target value, Q denotes base learners' numbers, α_q signifies the weighted coefficient of the q -th base learner, x denotes the drilling example, θ_q represents the learner's classification parameters, $T(x, \theta_q)$ stands for the q -th base learner involved in the preparing process.

3.4.2 Random forest classifier

Being an ensemble learning procedure, RF is very proficient at both regression and classification tasks (31). It harnesses the collective strength of numerous decision trees alongside a technique called Bootstrap and Aggregation, or bagging. This approach involves randomly selecting rows and features from the dataset to generate sample datasets for each tree a process known as Bootstrap. Subsequently, the Aggregation step consolidates the predictions of all individual trees to yield the ultimate results. While RF constructs multiple decision trees and averages their predictions, methods like gradient boosting (GB) and XGBoost build models sequentially to rectify the errors of preceding models. RF demonstrates proficiency with unseen data, exhibits reduced susceptibility to overfitting, and maintains computational efficiency. The ultimate forecast is presented as follows.

$$\gamma(\text{predicted}) = \frac{1}{N} \sum_{f=1}^N M_i \quad (2)$$

In the provided equation, M_i represents the prediction of the i -th decision tree, and N denotes the total number of decision trees in the Random Forest ensemble.

3.4.3 Logistic regression

LR is a performance-enhancing combined multiple RF and AdaBoost-like classifiers type of ensemble learning using an iterative ensemble approach. Consequently, a strong classifier is constructed by it (32). LR identifies the correlation between the categorical independent and dependent variables. Additionally, it computes the posterior probability p by fitting the data into the logistic function of an event. The classifier's weights and sample training are fixed in each successive iteration aimed at boosting the basic underlying concept to correctly ascertain the target class of the provided data. LR's classification y^* is illustrated as follows:

$$y^* = \ln\left(\frac{p}{1-p}\right) \quad (3)$$

3.4.4 Decision tree classifier

DT represents a non-parametric supervised ML approach utilized to establish classification systems based on multiple covariates or to develop prediction algorithms for a target variable (33). This method involves constructing a model capable of predicting the value of a target variable through the learning of

simple decision rules derived from data features. An inverted tree structure is formed after the dataset is organized into branched segments, consisting of internal, root, and leaf nodes. Being a non-parametric algorithm, complex and big datasets are easily handled by it without the need for a complex parametric structure. In the case of the enormous data samples, the data is organized as test and training samples. The training data is then used to build a DT prototype while the test sample determines the appropriate tree size for optimal final model attainment.

3.4.5 Extra trees classifier

Extremely randomized trees or extra trees, are part of the ensemble learning procedures category, similar to RF, where multiple individual DT results are aggregated (34). ETs are superior in performance in comparison to RF algorithms. The baseline difference between ET Regressor and RF is the utilization of bootstrap aggression, which is used by RF while ET doesn't. Instead, it uses the entire training dataset to construct its DTs. ET Regressor, instead of determining the best-split point after all features are taken into consideration, selects features' subset randomly, and eventually a random split point is selected. Overfitting in the model is mitigated by reducing the variance aided by this added randomness. The benefits of ET regressor are proven when datasets are high-dimensional and computational efficiency is a priority.

3.4.6 Extreme gradient boosting

XGBoost employs an objective function comprising a regularization term and a loss function. The discrepancy between expected and actual values of a model is measured using the loss function while overfitting and complexity of the model are managed by the regularization term (35). Notably, XGBoost incorporates parallel processing methods, facilitating quicker computation. In contrast, traditional Gradient Boosting trains each new model sequentially, correcting errors from the preceding model. XGBoost represents a refined version of Gradient Boosting, integrating sophisticated regularization methods and streamlined tree construction processes.

3.4.7 Ada boost classifier

AdaBoost leverages the boosting principle to generate a strong classifier from weaker ones. By integrating subpar classifiers and extracting their predictive value, AdaBoost enhances the overall efficacy of machine learning classifiers, forming a superior ensemble classifier (36). This approach mitigates issues associated with overfitting and contributes to improved results. AdaBoost meticulously evaluates the optimal contributions of each individual classifier, thereby selecting the most effective values for inclusion in the ensemble.

3.4.8 Gradient boosting classifier

Gradient Boosting serves as an ensemble meta-estimator comprising weak prediction models, often decision trees, commonly employed for classification tasks (37). The algorithm predicts classes based on a weighted majority vote of the predictions

from the weak learners, with weights determined by their respective accuracy rates. Notably, Gradient Boosting is applicable even to small samples, ranging from as few as 100–1,000 data points.

3.4.9 Support vector machine—linear kernel

SVM is a prominent and preferred supervised algorithm dealing with both the classification and regression tasks, yet it stands out when it comes to classification circumstances (38). In the realm of N-dimensional spaces, SVM algorithms aim to identify a hyperplane that optimally segregates the two classes. In simpler terms, if there are only two input features, this hyperplane reduces to a line; if there are more features, it becomes a multidimensional plane. The ideal scenario occurs when the data are perfectly separable, resulting in maximum distance between the nearest class elements and the hyperplanes. SVM endeavors to approximate this scenario as closely as possible. Nonlinear SVM introduces different classes of manifolds as an alternative to hyperplanes, yet the underlying rule remains consistent.

While linear SVM kernels are commonly employed to delineate class labels using lines, not all datasets exhibit linear separability. Kernel functions address this challenge by projecting data points from the original space to a feature space, thereby enhancing separability. However, kernel functions have limitations; they may not be universally applicable across all datasets, and the transformation process itself can be computationally expensive, leading to heightened training and prediction costs.

3.4.10 K nearest neighbors classifier

The KNN algorithm is an extensively used procedure in ML for both the regression and the classification tasks (39). It derived its basis from the fact that similar values or labels are shared by the data points having related features. The entire training dataset is stored as a reference during the training stage. Distance between all training examples and input data points is computed while making predictions, characteristically Euclidean distance-like distance metric is selected. Afterward, the K nearest neighbors are identified by the algorithm based on their distances to the input data point. When it comes to classification tasks, the most common class label among the K neighbors is assigned by the KNN as the input data point's anticipated label. Furthermore, the value of the input data point is predicted by either calculating the weighted averages or the simple averages of K neighbors' target values for the regression tasks.

3.4.11 Naive Bayes

NB function operates on the principles of Bayes' theorem and adopts a conditional probability model. Its fundamental assumption is that every pair of features is independent (40). Employing a supervised learning approach, NB classifies outcomes. Notably, NB necessitates only a small amount of data to construct the model. In determining the probability of mode selection, it is assumed that mode choice adheres to a Gaussian distribution.

3.4.12 CatBoost classifier

CatBoost or Categorical Boosting, Yandex developed an open-source library, specifically tailored to address regression and classification challenges involving numerous independent features (41). A distinguishing feature of CatBoost is its capability to manage both categorical and numerical features seamlessly, eliminating the need for feature encoding techniques and thereby streamlining data preprocessing efforts. Moreover, CatBoost automatically scales all features internally to a suitable range, a feature absent in traditional boosting algorithms. The trained model's overall performance is augmented and faster convergence is facilitated by this.

3.5 Evaluation parameters

The proposed model's efficiency and reliability are ensured and demonstrated using various evaluation parameters like accuracy, recall, precision, F1 score, MCC, Kappa, and AUC are among the commonly utilized performance metrics to gauge the performance of similar models. These metrics are comprehensively used to evaluate the performance of the model across various aspects, allowing for a thorough assessment of its reliability and efficacy.

Accuracy is a metric linked to the model's ability to predict the results correctly (42). It is essential to first determine the true negatives (TN), false positives (FP), true positives (TP), and false negatives (FN) when computing accuracy. Using these elements, the following equation is used to calculate the accuracy.

$$Accuracy = \frac{No, of CPr}{CPr + FPr} \quad (4)$$

This formula expresses accuracy as the sum of true outcomes (either positives and/or negatives) divided by the total number of observations (the sum of true positives, false positives, true negatives, and false negatives).

Precision, in the context of classification models, can indeed be computed by determining the proportion of correctly predicted to the total predicted positive observations (43). The equation to calculate precision is as follows.

$$Precision = \frac{TP}{TP + FP} \quad (5)$$

Furthermore, in order to demonstrate the number of genuine positive cases our model can predict accurately, we will calculate recall (44). Recall is determined by the ratio of correctly predicted positive observations to all observations in the actual class, as indicated by the following equation.

$$Recall = \frac{TP}{TP + FN} \quad (6)$$

Through the computation of precision and recall, we derive the F1 score, another valuable metric used for evaluating model performance (45). The F-score is obtained by taking the weighted

average of precision and recall, as described by the following equation:

$$F1Score = 2 \times \frac{Precision \times Recall}{Precision + Recall} \quad (7)$$

The AUC assesses the quality of the model predictions, ranging from zero to one, where a score of 1 indicates the best performance and 0 indicates the worst (46). Furthermore, AUC reflects the degree of separability, elucidating the model's ability to differentiate between classes.

The Kappa is a statistics-based prominent evaluation metric denoted by k , which measures the reliability in relation to other evaluators or parameters (47). The following equation computes the value of k .

$$k = \frac{prob(O) - prob(C)}{1 - prob(C)} \quad (8)$$

In this context, O represents the likelihood of observed agreements among the evaluators, while C signifies the prospect of agreements anticipated by chance. If $k = 1$, it indicates complete agreement among the evaluators, conversely, if $k = 0$, it suggests no agreement among the evaluators.

MCC is an unaffected and substitute measure for uneven datasets and employs a likelihood matrix method to calculate the Pearson product-moment correlation coefficient between predicted and actual values (48). Expressed in terms of the entries of the contingency matrix M , MCC is formulated as follows:

$$MCC = \frac{TP.TN - FP.FN}{(TP + FP).(TP + FN).(TN + FP).(TN + FN)} \quad (9)$$

The MCC is unique among binary classification metrics in that it yields a high score only when the binary predictor successfully predicts the majority of positive and negative data instances.

4 Experiments and analysis

The experiments were performed using Python 3.8, and TensorFlow and Scikit-learn libraries. The experimental setup operated with 8GB of available RAM, on Windows 10 (64-bit) operating system. The CPU utilized was 7th Gen, Intel Core i7 having a clock speed of 2.8 GHz, and an 8 GB, GTX 1060 GPU from Nvidia. Technical specifications of the computational resources deployed in research are crucial for the in-depth understanding of the model. Table 2 summarizes the experimental setup.

4.1 Results of machine learning models on CTG dataset for fetal health

Extensive experiments were conducted for fetal health detection, wherein various machine learning models were applied under different scenarios. These models were optimized concerning various hyperparameters for better performance. Furthermore, the results were examined by employing individual machine-learning

TABLE 2 Framework specifications.

Element	Details
Programming environment	Python 3.8
Software libraries	Scikit-learn, TensorFlow
OS	Windows 10 (64-bit)
RAM	8GB
Processor	7th Gen, Intel Core i7, 2.8 GHz processor
Graphics card	8 GB- GTX 1060 Powered GPU from Nvidia

models across all feature sets in the experiments. The results of all learning models are shared in Table 3.

The provided information outlines the performance metrics of various machine learning models across multiple evaluation criteria. Each model undergoes assessment based on AUC, MCC, recall, precision, F1 score, accuracy, kappa score, and training time in seconds. These metrics collectively offer insights into how effectively each model performs in a classification task.

Beginning with the top-performing models, LightGBM achieves notable results with an accuracy of 99.89% and an AUC of 99.88%, showcasing its proficiency in correctly classifying instances and distinguishing between classes. Additionally, its recall, precision, and F1 score of 97.91% indicate its ability to identify positive instances accurately while minimizing false positives. Moreover, the kappa score and MCC of ~96.80% further validate the model's reliability. Similarly, the CatBoost classifier and ETC demonstrate strong performance with high accuracy of 97.66% and 97.62%, respectively, and AUC values of 99.84% and 99.87%, respectively. These models maintain recall, precision, and F1 scores above 97%, reflecting their effectiveness across various evaluation metrics. Despite slight variations in training times of 8.465 s for CatBoost and 0.938 s for ETC, both models exhibit robust performance in classification tasks.

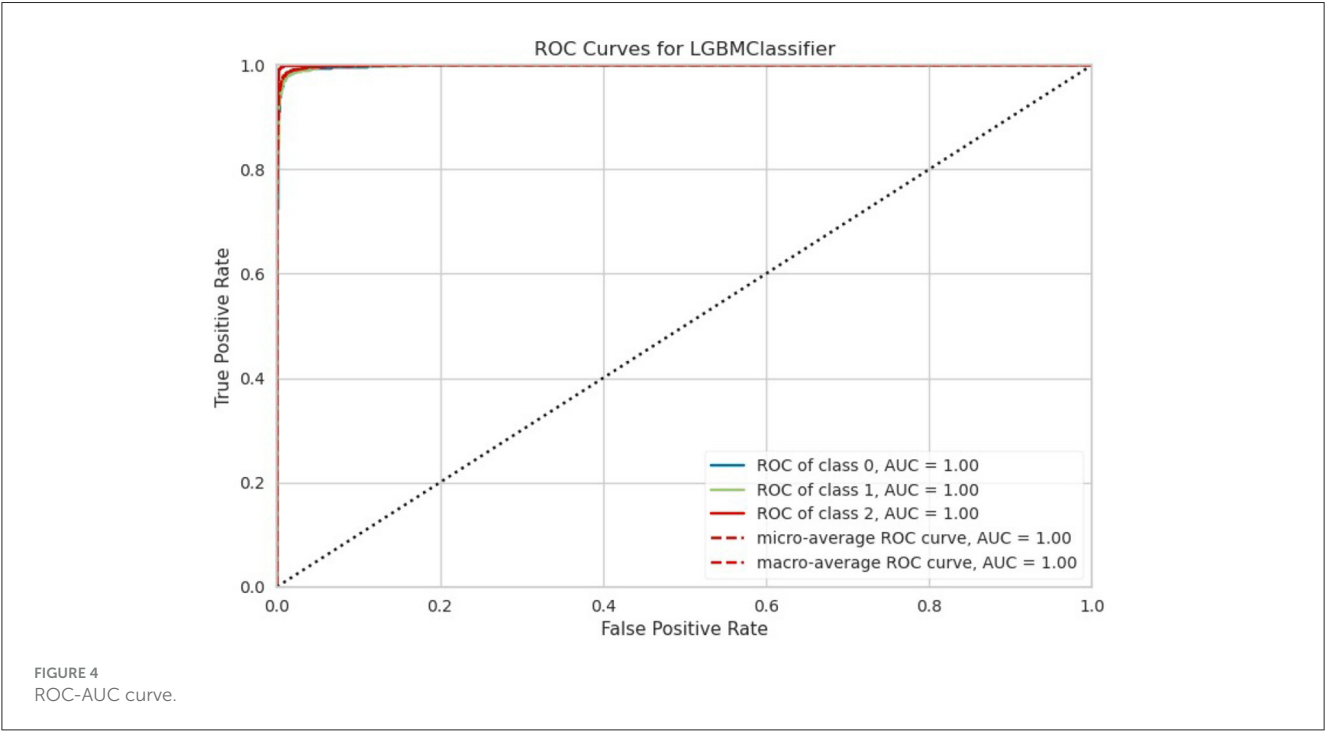
The XGBoost and RF classifier also deliver commendable results with accuracy and AUC values exceeding 97% and 99%, respectively. Leveraging ensemble methods, these models harness multiple decision trees to achieve strong performance, as evidenced by their high recall, precision, and F1 scores. Furthermore, they boast reasonable training times, making them efficient choices for practical applications.

Descending through the list, the GBC, DT classifier, and KNN classifier demonstrate good performance with accuracy scores ranging from 96.47% to 95.10%. Although their AUC values are slightly lower compared to the top performers, they still exhibit respectable recall, precision, and F1 scores, underscoring their efficacy in classification tasks.

Further down the spectrum, the LR, SVM with a linear kernel, AdaBoost classifier, and NB show diminishing performance in terms of accuracy, AUC, and other evaluation metrics. While these models offer reasonable results, they may not be as suitable for tasks requiring high precision or discrimination between classes. Notably, the SVM with a Linear Kernel exhibits an AUC of 0.00%, indicating potential issues with its discriminative ability in the given dataset, highlighting the importance of meticulous model selection and parameter tuning to ensure optimal performance.

TABLE 3 Classification report of all learning models.

Model	Accuracy	AUC	Recall	Prec.	F1	Kappa	MCC	TT (s)
LightGBM	0.9989	0.9988	0.9832	0.9834	0.9832	0.9748	0.9749	2.8470
CB	0.9766	0.9984	0.9766	0.9770	0.9766	0.9649	0.9651	8.4650
ETC	0.9762	0.9987	0.9762	0.9769	0.9762	0.9643	0.9647	0.9380
XGBoost	0.9748	0.9984	0.9748	0.9752	0.9747	0.9622	0.9624	2.0540
RF	0.9708	0.9982	0.9708	0.9713	0.9708	0.9562	0.9565	1.2220
GBC	0.9647	0.9969	0.9647	0.9656	0.9648	0.9470	0.9474	4.1070
DT	0.9510	0.9633	0.9510	0.9516	0.9510	0.9265	0.9268	0.2000
KNN	0.9416	0.9893	0.9416	0.9455	0.9416	0.9125	0.9143	0.4690
Ada	0.9121	0.9673	0.9121	0.9140	0.9123	0.8682	0.8689	0.7400
LR	0.8897	0.9735	0.8897	0.8935	0.8904	0.8346	0.8358	0.3100
SVM	0.8768	0.0000	0.8768	0.8815	0.8775	0.8152	0.8167	0.1710
NB	0.7677	0.8925	0.7677	0.8223	0.7708	0.6515	0.6757	0.1700



In summary, the data provides a comprehensive overview of the performance of different machine learning models in a classification task. Ensemble methods like LightGBM, CatBoost, ETC, XGBoost, and RF classifier excel in terms of accuracy, AUC, and overall robustness, as shown in Figure 4. However, the selection of a model should consider not only performance metrics but also dynamics like computational efficiency, interpretability, and explicit task specifications to ensure the most suitable model is chosen for deployment.

Figure 5 shows the class-wide prediction error rate from the proposed LightGBM model indicating that the model shows a similar performance for all the classes used for experiments. In addition, the number of wrong predictions is very few. The same

can be confirmed by the confusion matrix shown in Figure 6 which shows the number of wrong predictions. The model makes a total of 15 wrong predictions indicating better performance of the proposed LightGBM compared to other models used in this study.

4.2 Interpretation and explainable analysis of results using SHAP

In this subsection, we will discuss the LGBM model feature importance results and Explainable AI SHAP summary and dependency results of each class and analyze what each feature

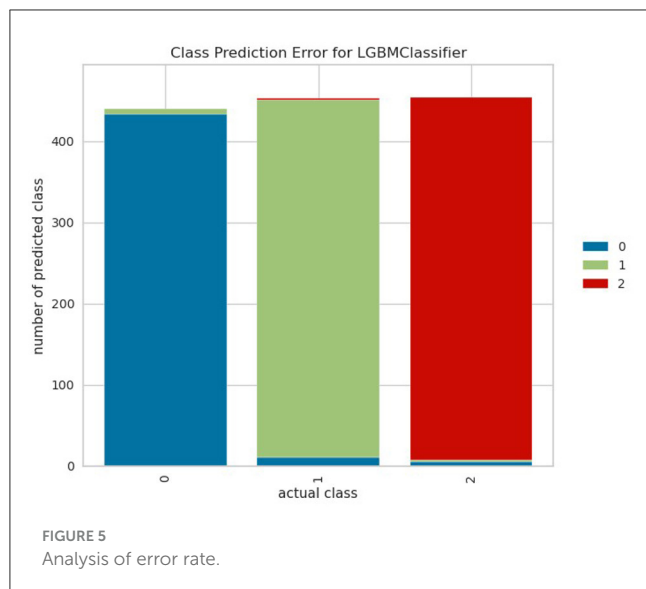


FIGURE 5
Analysis of error rate.

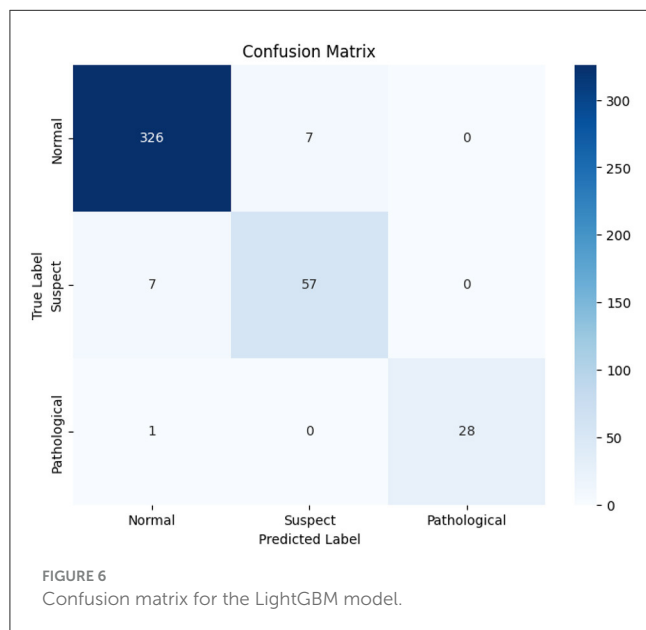


FIGURE 6
Confusion matrix for the LightGBM model.

describes (49). The feature importance of the LGBM model is shown in Figure 7. The feature importance plot gives us an indication of which features have the most significant impact on the model's predictions. The interpretation of feature importance shown in Figure 7 is "abnormal_short_term_variability" feature has the highest importance score, meaning it has the most significant impact on predicting fetal health. Short-term variability in fetal heart rate is known to be a strong indicator of fetal distress or abnormal conditions. The "percentage_of_time_with_abnormal_long_term_variability" is another key feature, which likely tracks the percentage of time during which the fetal heart rate exhibits abnormal long-term patterns. Long-term variability is crucial for assessing the fetus's health. Other features like "histogram_mean,"

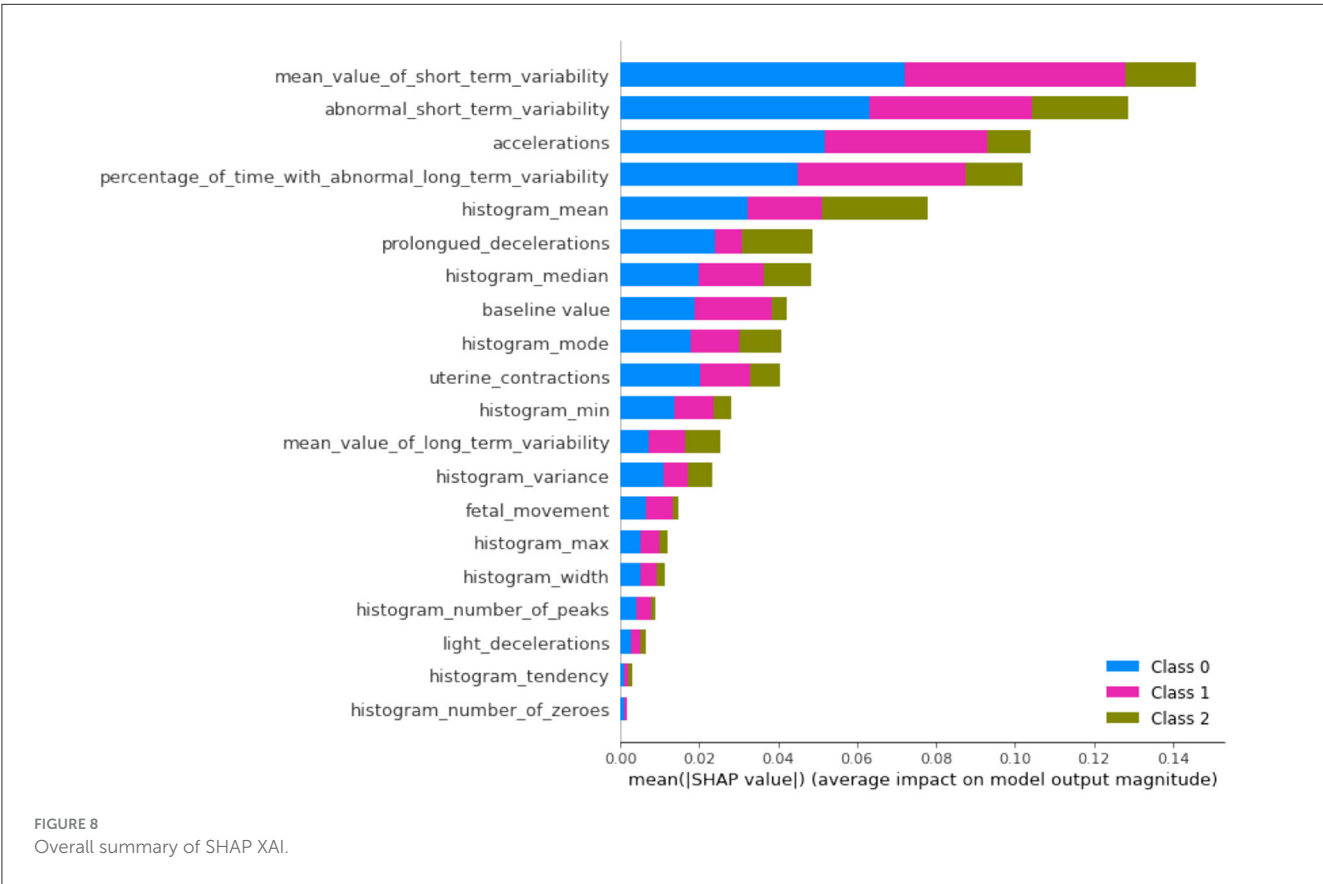
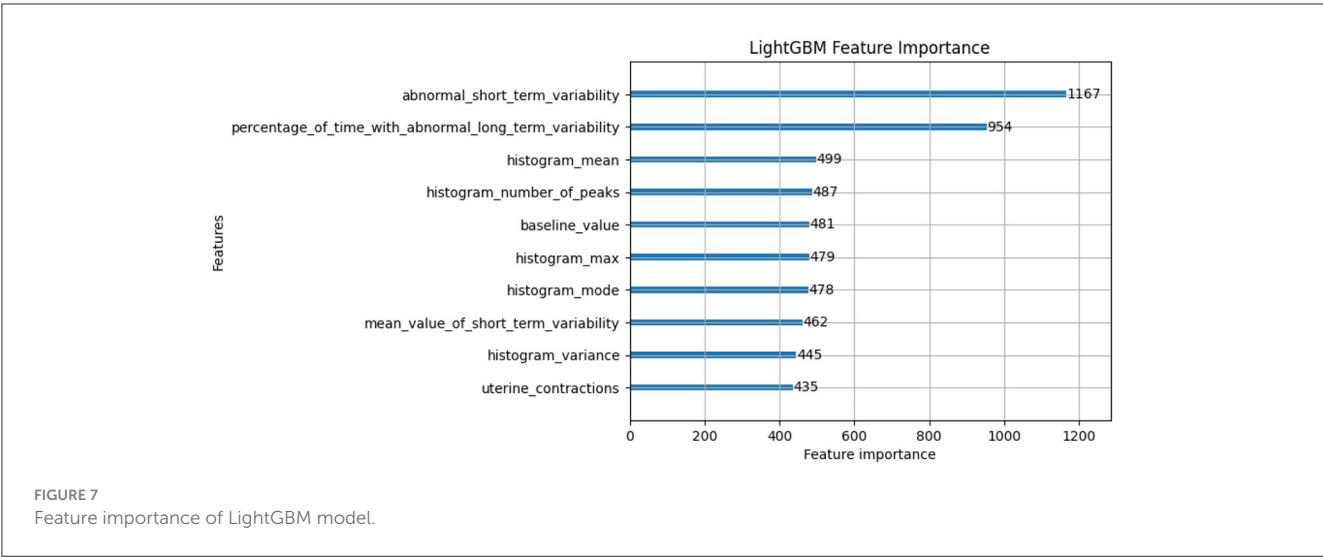
"histogram_number_of_peaks," and "baseline_value" are related to heart rate statistics and also play a significant role in classification. They likely capture the overall distribution and trends in fetal heart rates, which are critical for monitoring fetal wellbeing. Other notable features include "histogram_max," "mean_value_of_short_term_variability," and "uterine_contractions." All of these are highly relevant to assessing the fetus's response to external stimuli or stress during pregnancy.

The SHAP plots allow us to interpret how each feature impacts individual predictions. Positive SHAP values push the model toward predicting a certain class (e.g., a good fetal condition), while negative values push toward the opposite class. The color gradient (red to blue) represents the feature value, with red indicating high feature values and blue indicating low feature values. Again the importance feature "abnormal_short_term_variability" high values (in red) tend to increase the SHAP value, pushing the model toward predicting abnormal fetal health. This aligns with clinical knowledge, as greater variability is often indicative of fetal distress. The second-ranked feature "percentage_of_time_with_abnormal_long_term_variability" high values of long-term variability push the model toward predicting abnormal conditions. The features "prolongued_decelerations" and "accelerations" in fetal heart rate are critical markers for predicting fetal health. In this case, abnormal values increase the likelihood of predicting fetal issues. It can also be observed from Figure 8, where overall SHAP summary is explained that the lower impact features are "histogram_mean," "baseline_value," and "histogram_median" have more nuanced impacts. Their effects are smaller but still crucial for the model. For example, a low "baseline_value" (blue dots) typically pushes the model toward predicting normal fetal health, while higher baseline values (red dots) lean toward predicting abnormality.

If we compare SHAP pathological (Figure 9) vs. SHAP suspect (Figure 10), comparing the two SHAP plots, we see similar features driving predictions, with slight differences in order. This likely reflects different aspects of the model's behavior under various conditions (e.g., distinguishing between normal and abnormal health states). The interaction between features (such as short-term variability with other heart rate metrics) also becomes evident in these plots. The SHAP explanation of the normal target class is shown in Figure 11.

4.3 K-fold cross-validation results

The proposed model's performance is validated using ten-fold validation. Its purpose is to validate and ascertain the robustness of the generated results by the recommended model. The cross-validation process ensures the performance consistency of the model across all data subsets. In this study, 10-fold cross-validated results are summarized in Table 4. The suggested LGBM model exhibits a 97.91% average accuracy score in cross-validation results. Additionally, the average recall, precision, and F1 scores are found to be 97.91%, 97.93%, and 97.91%, respectively. In 10-fold cross-validation, LGBM also attains an AUC value of 99.88%, Kappa score of 96.86, and MCC of 96.88. The standard deviation of accuracy for LGBM across the 10 folds is calculated to be 0.0088.



4.4 Comparison of performance with existing studies

The recommended prototype's performance is evaluated against previous advanced models by conducting a performance comparison in-between them. To demonstrate the performance of the projected model in comparison to previous advanced

models, a comparison with existing models is conducted. This research selects the nine most relevant previous studies for this purpose. For instance, Yin and Bingi (17) utilized the SVM ML model for fetal health classification, and a 99.59% impressive accuracy score was obtained. In another study (23), the GBC was employed, achieving the highest accuracy score of 95%. T2-FNN was utilized by Abiyev et al. (18), resulting in an accuracy

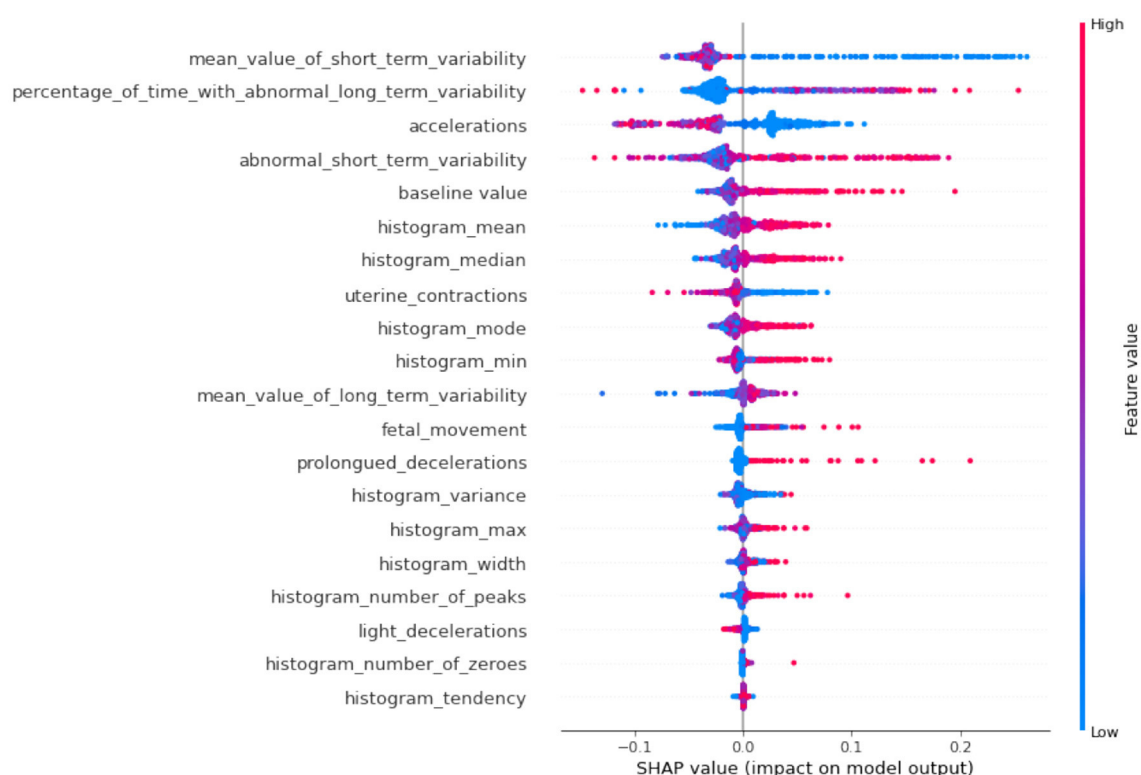


FIGURE 9
SHAP summary of pathological class.

score of 96.66%. Additionally, Sudharson et al. (26) utilized DT resulting in 90.8% accuracy. Likewise, Afridi et al. (24) and Salini et al. (25) utilized the RF model and NB models, with 93% and 83.06% accuracy, respectively. Table 5 illustrates the performance comparison between the proposed model and existing studies, revealing the superiority of the proposed model.

When we compare the proposed LightGBM model with the traditional approaches and potential models used for fetal health monitoring, several benefits of the proposed model can be observed. In terms of real-time performance and computation, LightGBM has proved to be faster than other models such as SVM, AlexNet, RF, FNN, and XGBoost utilized in previous research works. This also gives it an advantage in dealing with diverse numerical feature datasets which is a crucial area of consideration given the ever-increasing nature of medical data. LightGBM's built-in regularization mechanisms help prevent overfitting, ensuring strong generalization to unseen data. The model also provides a detailed feature importance analysis itself and through techniques such as SHAP thereby helping clinicians understand the model's decisions. In this research work, we utilized and shared both information (obtained through the feature importance of LGBM and by SHAP dependency graphs). As opposed to most of the other frameworks, LightGBM can identify rather intricate interactions between specific fetal health characteristics and other factors and has good generality. Furthermore, it reduces human error in prognosis analysis by detecting subtle variations that may be missed during manual assessments, leading to more accurate diagnoses.

This combination of efficiency, accuracy, and interpretability makes the proposed model superior to existing clinical standards and machine learning models.

4.5 Ethical implications, deployment, biases, and data privacy

AI models like LightGBM can introduce biases if the training data is not representative of diverse populations, potentially leading to misdiagnoses or unequal healthcare outcomes. Ensuring diversity in datasets, conducting bias audits, and employing fairness metrics are essential steps to mitigate these risks. Additionally, privacy concerns must be addressed by anonymizing patient data, adhering to regulations like HIPAA or GDPR, and implementing secure data handling practices.

Ethical deployment of AI models requires transparency, explainability, and human oversight. Clinicians should understand how the model makes decisions through tools like SHAP plots, and AI should support (like we have added SHAP plots and feature importance) rather than replace human judgment. Regular monitoring and validation of the model's performance in real-world settings ensure safety and accuracy over time. By incorporating these measures, any research can demonstrate a responsible and ethical approach to AI in fetal and maternal health monitoring.

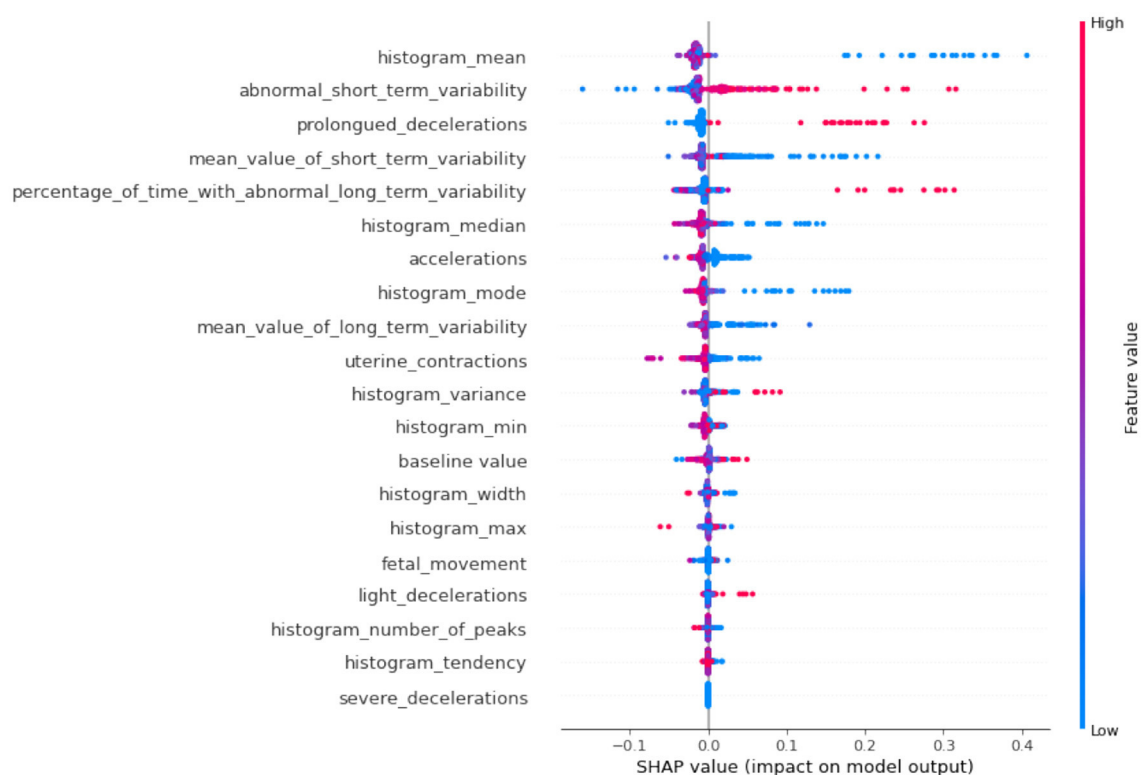


FIGURE 10
SHAP summary of suspect class.

4.6 Implications of proposed approach concerning traditional clinical methods

Traditional clinical methods emphasize diagnosis, prognosis, and treatment (50). Diagnosis has been regarded as the primary element in clinical methods providing classification of subjects into sick and healthy subjects. It is the basis for treatment and prognosis where prognosis determines the future happenings of individuals being classified (51). While all components are important, this study focuses on the diagnosis part of traditional clinical methods due to its importance.

It is important to emphasize that the proposed LightGBM model has been developed with input from a medical professional, a consultant gynecologist who guided the research design. According to her insights, traditional clinical standards such as differential diagnosis methods and prognosis analysis are commonly used by obstetricians and gynecologists. However, these methods are often labor-intensive and prone to human error, particularly when it comes to analyzing complex data over extended periods. The proposed AI-driven model aims to reduce such errors by providing more precise and automated decision support, which can help in the earlier detection of potential complications.

Another doctor highlighted that cardiotocography and ultrasound analysis, despite being widely adopted in fetal monitoring, can sometimes miss critical diagnostic points. Both the patient and doctor might overlook subtle but important signs, leading to potential complications. The integration of

LightGBM and data mining techniques offers an opportunity to enhance these traditional methods by identifying patterns that might go unnoticed during manual assessments. This model can therefore supplement traditional approaches, making fetal health monitoring more accurate and less prone to human oversight.

5 Conclusions and future work

Fetal health monitoring has substantial importance in saving the lives of pregnant women and fetuses. This research underscores the paramount importance of fetal health in prenatal care and obstetrics, emphasizing its direct impact on both the fetus and the mother. Through continuous monitoring throughout pregnancy, potential risks or complications can be identified and addressed promptly, leading to improved outcomes for both parties. Leveraging cardiotocography data, which encompasses crucial fetal physiological parameters, this study employs a robust methodology for fetal health classification. The utilization of the SMOTE data upsampling technique addresses the class imbalance issue inherent in medical diagnostics, enhancing the model's performance. By employing the LightGBM model, remarkable results are achieved, with high accuracy, AUC, recall, precision, F1 score, Kappa, and MCC values obtained on the test dataset. Comparative analysis against eleven other machine learning models highlights the superiority of the proposed approach

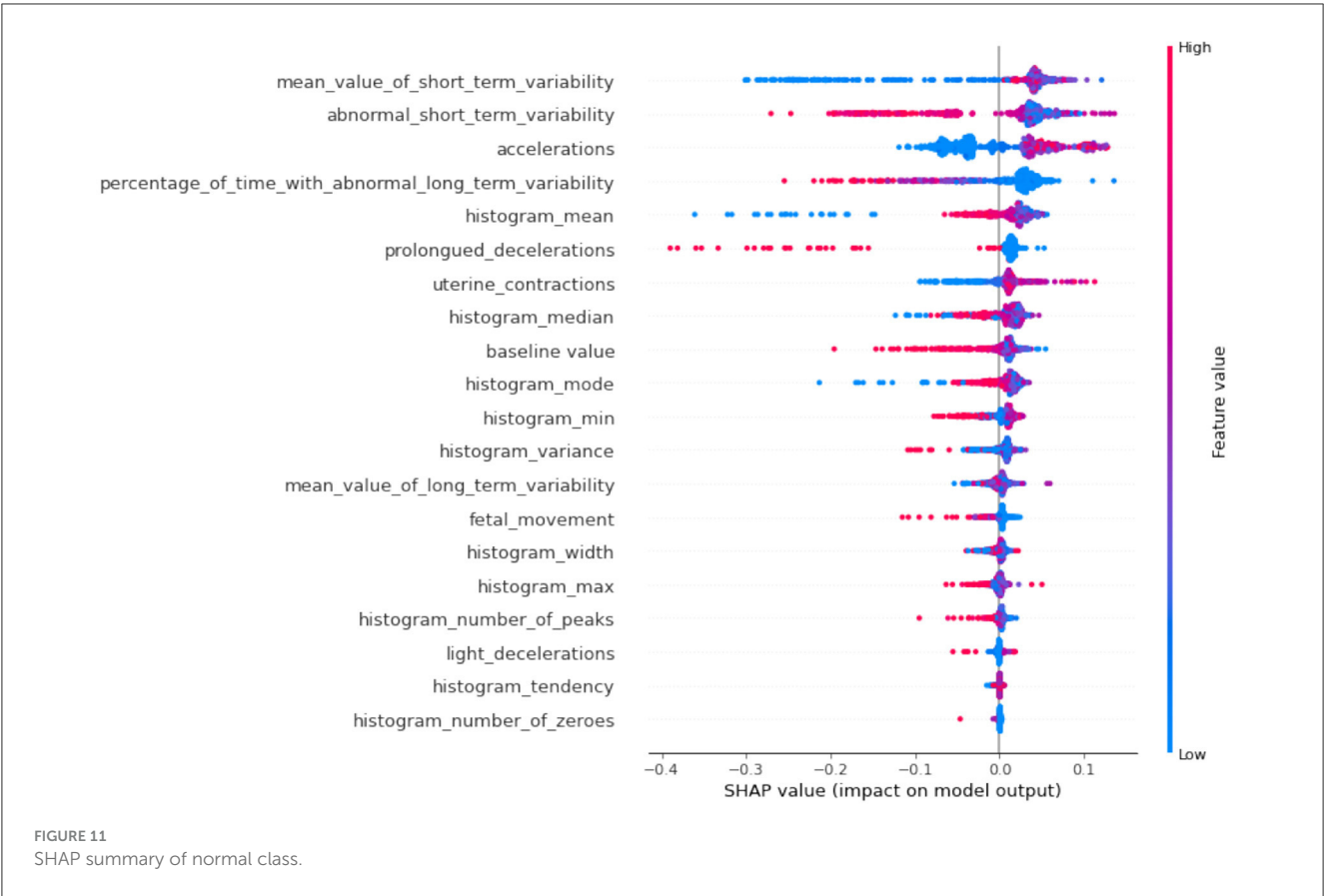


TABLE 4 10-fold cross-validation results concerning various metrics.

Fold	Accuracy	AUC	Recall	Precision	F1	Kappa	MCC
0	0.9928	0.9995	0.9928	0.993	0.9928	0.9892	0.9893
1	0.9712	0.9982	0.9712	0.972	0.9714	0.9568	0.9571
2	0.982	0.9985	0.982	0.982	0.982	0.973	0.973
3	0.9784	0.9988	0.9784	0.9787	0.9785	0.9676	0.9678
4	0.9892	0.9999	0.9892	0.9892	0.9892	0.9838	0.9838
5	0.9784	0.9973	0.9784	0.9786	0.9784	0.9676	0.9677
6	0.9856	0.9997	0.9856	0.9858	0.9855	0.9783	0.9785
7	0.9603	0.9983	0.9603	0.9608	0.96	0.9404	0.9409
8	0.9747	0.9992	0.9747	0.9747	0.9747	0.9621	0.9621
9	0.9783	0.9985	0.9783	0.9786	0.9784	0.9675	0.9676
Mean	0.9791	0.9988	0.9791	0.9793	0.9791	0.9686	0.9688
Std	0.0088	0.0008	0.0088	0.0087	0.0089	0.0132	0.0131

in fetal health classification. Furthermore, the significance of the proposed model is investigated through rigorous evaluation using a 10-fold cross-validation and previous research works comparison. Overall, this research contributes to advancing prenatal care by providing an effective and reliable framework for fetal health assessment and classification. The future work direction of this research is to incorporate additional data sources such as ultrasound images, maternal health records, and genetic information as it could provide a more comprehensive understanding of fetal health and improve classification accuracy. In addition, enhancing the interpretability and explainability of the classification model could improve its acceptance and

TABLE 5 Performance comparison with existing studies.

References	Classifier	Accuracy
Yin and Bingi (17)	SVM	99.59%
Abiyev et al. (18)	T2-FNN (63 rules)	96.66%
Kuzu and Santur (19)	XGB	99.10%
Muhammad Hussain et al. (20)	AlexNet-SVM,	99.72%
Piri and Mohapatra (21)	XGBoost and RF	94.32%
Al Duhayyim et al. (22)	XGB, CatBoost, VC	99.05%
Islam et al. (23)	GBC	95.19%
Afridi et al. (24)	NB	83.06%
Salini et al. (25)	RF	93.15%
Sudharson et al. (26)	DT	90.80%
Proposed	LGBM	99.89%

Bold values indicating the results of proposed model which is better than all SOTA models.

adoption by healthcare providers, facilitating better-informed clinical decisions.

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.

Author contributions

NI: Investigation, Software, Supervision, Validation, Visualization, Writing – original draft. SA: Data curation, Methodology, Resources, Validation, Visualization, Writing –

original draft. EA: Conceptualization, Investigation, Software, Writing – original draft, Writing – review & editing. AA: Conceptualization, Funding acquisition, Resources, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. MU: Conceptualization, Methodology, Software, Visualization, Writing – original draft. ST: Formal analysis, Funding acquisition, Investigation, Project administration, Supervision, Validation, Writing – review & editing. IA: Conceptualization, Funding acquisition, Methodology, Software, Visualization, Writing – review & editing.

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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.

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References

1. UNICEF. *UNICEF, World Health Organization, the World Bank Group, and the United Nations 2019 Levels and trends in child mortality Report 2019*. (2019). Available at: <https://data.unicef.org/resources/levels-and-trends-in-child-mortality/> (accessed April 12, 2022).
2. Goldenberg RL, Saleem S, Pasha O, Harrison MS, McClure EM. Reducing stillbirths in low-income countries. *Acta Obstet Et Gynecol Scand*. (2016) 95:135–43. doi: 10.1111/aogs.12817
3. Mahdizadeh J, Bouraghi H, Panahi SSGS, Mohammadpour A, Shargh AK, Mojarad MR, et al. A theory map of the causes of perinatal death in a developing country. *Crescent J Med Biol*. (2019) 6:237–41.
4. Ayres-de Campos D, Spong CY, Chandrachan E. FIGO consensus guidelines on intrapartum fetal monitoring: cardiotocography. *Int J Gynecol Obstet*. (2015) 131:13–24. doi: 10.1016/j.ijgo.2015.06.020
5. Jepsen I, Blix E, Cooke H, Adrian SW, Maude R. The overuse of intrapartum cardiotocography (CTG) for low-risk women: an actor-network theory analysis of data from focus groups. *Women Birth*. (2022) 35:593–601. doi: 10.1016/j.wombi.2022.01.003
6. Nazir L, Lakhta G, Anees K, Khan FR, Safdar S, Nazir GR, et al. Admission cardiotocography as a predictor of low Apgar score: an observational, cross-sectional study. *Cureus*. (2021) 13:e14530. doi: 10.7759/cureus.14530
7. Nadeem G, Rehman A, Bashir H. Risk factors associated with birth asphyxia in term newborns at a tertiary care hospital of Multan, Pakistan. *Cureus*. (2021) 13:e18759. doi: 10.7759/cureus.18759
8. World Health Organization. *Perinatal asphyxia*. (2022). Available at: <https://www.who.int/teams/maternal-newborn-child-adolescent-health-and-ageing/newborn-health/perinatal-asphyxia> (accessed January 22, 2024).
9. World Health Organization. *Health Statistics 2022: Monitoring Health for the SDGs, Sustainable Development Goals*. (2022). Available at: <https://www.who.int/publications/i/item/9789240051157> (accessed January 22, 2024).
10. Eleftheriades M, Pervanidou P, Chrousos G. Fetal stress. In: Fink G, editor. *Encyclopedia of Stress*, 2nd Edn. New York, NY: Academic Press (2007), p. 46–51. doi: 10.1016/B978-012373947-6/00492-X

11. K H Yu C, Bower S. Chapter 10–Fetal growth. In: AM Coady, S Bower, editors. *Twining's Textbook of Fetal Abnormalities*, 3rd Edn. New York, NY: Churchill Livingstone (2015), p. 211–22. doi: 10.1016/B978-0-7020-4591-2.00010-3
12. Manikandan M, Vijayakumar P. Improving the performance of classifiers by ensemble techniques for the premature finding of unusual birth outcomes from cardiotocography. *IETE J Res.* (2021) 69:1734–44. doi: 10.1080/03772063.2021.1910579
13. Davidson L, Boland MR. Enabling pregnant women and their physicians to make informed medication decisions using artificial intelligence. *J Pharmacokinet Pharmacodyn.* (2020) 47:305–18. doi: 10.1007/s10928-020-09685-1
14. Sadiq MT, Yu X, Yuan Z, Rehman AU, Ullah I, Li G, et al. Motor imagery EEG signals decoding by multivariate empirical wavelet transform-based framework for robust brain-computer interfaces. *IEEE Access.* (2019) 7:171431–51. doi: 10.1109/ACCESS.2019.2956018
15. Ahmad I, Ullah I, Khan WU, Rehman AU, Adrees MS, Saleem MQ, et al. Efficient algorithms for E-healthcare to solve multiobject fuse detection problem. *J Health Eng.* (2021) 2021:9500304. doi: 10.1155/2021/9500304
16. Moreira MWL, Rodrigues JJPC, Carvalho FHC, Chilamkurti N, Al-Muhtadi J, Denisov V. Biomedical data analytics in mobile-health environments for high-risk pregnancy outcome prediction. *J Ambient Intell Humaniz Comput.* (2019) 10:4121–34. doi: 10.1007/s12652-019-01230-4
17. Yin Y, Bingi Y. Using machine learning to classify human fetal health and analyze feature importance. *BioMedInformatics.* (2023) 3:280–98. doi: 10.3390/biomedinformatics3020019
18. Abiyev R, Idoko JB, Altiparmak H, Tüzünkan M. Fetal health state detection using interval type-2 fuzzy neural networks. *Diagnostics.* (2023) 13:1690. doi: 10.3390/diagnostics13101690
19. Kuzu A, Santur Y. Early diagnosis and classification of fetal health status from a fetal cardiotocography dataset using ensemble learning. *Diagnostics.* (2023) 13:2471. doi: 10.3390/diagnostics13152471
20. Muhammad Hussain N, Rehman AU, Othman MTB, Zafar J, Zafar H, Hamam H. Accessing artificial intelligence for fetus health status using hybrid deep learning algorithm (AlexNet-SVM) on cardiotocographic data. *Sensors.* (2022) 22:5103. doi: 10.3390/s22145103
21. Piri J, Mohapatra P. Exploring fetal health status using an association based classification approach. In: *2019 International Conference on Information Technology (ICIT)*. Bhubaneswar: IEEE (2019), p. 166–71. doi: 10.1109/ICIT48102.2019.00036
22. Al Duhayyim M, Abbas S, Al Hejaili A, Kryvinska N, Almadhor A, Mughal H. Ensemble learning for fetal health classification. *Comput Syst Sci Eng.* (2023) 47:823–42. doi: 10.32604/csse.2023.037488
23. Islam MM, Rokunojjaman M, Amin A, Akhtar MN, Sarker IH. Diagnosis and classification of fetal health based on CTG data using machine learning techniques. In: *International Conference on Machine Intelligence and Emerging Technologies*. Cham: Springer Nature Switzerland (2022), p. 3–16. doi: 10.1007/978-3-031-34622-4_1
24. Afridi R, Iqbal Z, Khan M, Ahmad A, Naseem R. Fetal heart rate classification and comparative analysis using cardiotocography data and KNOWN classifiers. *Int. J. Grid Distrib. Comput.* (2019) 12:31–42. doi: 10.33832/ijgcd.2019.12.1.03
25. Salini Y, Mohanty SN, Ramesh JVN, Yang M, Chalapathi MMV. Cardiotocography data analysis for fetal health classification using machine learning models. *IEEE Access.* (2024) 12:26005–22. doi: 10.1109/ACCESS.2024.3364755
26. Sudharson D, Vignesh K, Dubey AK, Mukilan K, Kizore MN, Ram SA. Impact of classification algorithms on cardiotocography dataset for fetal state prediction. *Asian J Comput Sci Eng.* (2022) 7:71–6.
27. LARXEL. *Fetal Health Classification*. (2020). Available at: <https://www.kaggle.com/datasets/andrewmvd/fetal-health-classification> (accessed January 5, 2024).
28. Han H, Wang WY, Mao BH. Borderline-SMOTE: a new over-sampling method in imbalanced data sets learning. *Adv Intell Comput.* (2005) 3644:878–87. doi: 10.1007/11538059_91
29. Chawla NV, Bowyer KW, Hall LO, Kegelmeyer WP, SMOTE. Synthetic minority over-sampling technique. *J Artif Intell Res.* (2002) 16:321–57. doi: 10.1613/jair.953
30. Ke G, Meng Q, Finley T, Wang T, Chen W, Ma W, et al. LightGBM: a highly efficient gradient boosting decision tree. *Adv Neural Inf Process Syst.* (2017) 30:3149–57. doi: 10.5555/3294996.3295074
31. Breiman L. Random forests. *Mach Learn.* (2001) 45:5–32. doi: 10.1023/A:1010933404324
32. Hosmer Jr DW, Lemeshow S, Sturdivant RX. *Applied Logistic Regression*, Vol. 398. Hoboken, NJ: John Wiley & Sons (2013). doi: 10.1002/9781118548387
33. Breiman L, Friedman JH, Olshen RA, Stone CJ. *Classification and Regression Trees*. Boca Raton, FL: CRC Press (1984).
34. Geurts P, Ernst D, Wehenkel L. Extremely randomized trees. *Mach Learn.* (2006) 63:3–42. doi: 10.1007/s10994-006-6226-1
35. Chen T, Guestrin C. Xgboost: a scalable tree boosting system. In: *Proceedings of the 22nd ACM SIGKDD international conference on knowledge discovery and data mining*. New York, NY: ACM (2016), p. 785–94. doi: 10.1145/2939672.2939785
36. Freund Y, Schapire RE. A decision-theoretic generalization of on-line learning and an application to boosting. *J Comput Syst Sci.* (1997) 55:119–39. doi: 10.1006/jcss.1997.1504
37. Friedman JH. Greedy function approximation: a gradient boosting machine. *Ann Stat.* (2001) 29:1189–232. doi: 10.1214/aos/1013203451
38. Cortes C, Vapnik V. Support-vector networks. *Mach Learn.* (1995) 20:273–97. doi: 10.1007/BF00994018
39. Cover T, Hart P. Nearest neighbor pattern classification. *IEEE Trans Inf Theory.* (1967) 13:21–7. doi: 10.1109/TIT.1967.1053964
40. Rish I. An empirical study of the naive Bayes classifier. In: *IJCAI 2001 workshop on empirical methods in artificial intelligence*, Vol. 3. Atlanta, GA (2001). p. 41–6.
41. Dorogush AV, Ershov V, Gulin A. CatBoost: gradient boosting with categorical features support. *arXiv.* [Preprint]. arXiv:1706.09516. (2017). doi: 10.48550/arXiv.1706.09516
42. Sokolova M, Lapalme G. A systematic analysis of performance measures for classification tasks. *Inf Process Manag.* (2009) 45:427–37. doi: 10.1016/j.ipm.2009.03.002
43. Powers DMW. Evaluation: from precision, recall and F-measure to ROC, informedness, markedness & correlation. *arXiv.* [Preprint]. arXiv:2010.16061. (2020). doi: 10.48550/arXiv.2010.16061
44. Davis J, Goadrich M. The relationship between precision-recall and ROC curves. In: *Proceedings of the 23rd international conference on Machine learning*. New York, NY: ACM (2006), p. 233–40. doi: 10.1145/1143844.1143874
45. Van Rijsbergen CJ. *Information Retrieval*. Oxford: Butterworth-Heinemann (1979).
46. Fawcett T. An introduction to ROC analysis. *Pattern Recognit Lett.* (2006) 27:861–74. doi: 10.1016/j.patrec.2005.10.010
47. Cohen J. A coefficient of agreement for nominal scales. *Educ Psychol Meas.* (1960) 20:37–46. doi: 10.1177/001316446002000104
48. Chicco D, Jurman G. The advantages of the Matthews correlation coefficient (MCC) over F1 score and accuracy in binary classification evaluation. *BMC Genomics.* (2020) 21:6. doi: 10.1186/s12864-019-6413-7
49. Lombardi A, Diacono D, Amoroso N, Monaco A, Tavares JMR, Bellotti R, et al. Explainable deep learning for personalized age prediction with brain morphology. *Front Neurosci.* (2021) 15:674055. doi: 10.3389/fnins.2021.674055
50. Lucas PJ, Abu-Hanna A. Prognostic methods in medicine. *CiteSeer.* (1999). doi: 10.1016/S0933-3657(98)00047-5
51. Croft P, Altman DG, Deeks JJ, Dunn KM, Hay AD, Hemingway H, et al. The science of clinical practice: disease diagnosis or patient prognosis? Evidence about “what is likely to happen” should shape clinical practice. *BMC Med.* (2015) 13:1–8. doi: 10.1186/s12916-014-0265-4



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Sources of polycyclic aromatic hydrocarbons exposure and their effects on glycolipid metabolism in pregnant women and their newborn in Haikou City, China

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Background: Polycyclic aromatic hydrocarbons (PAHs) are a class of large organic compounds that persist in the environment and are classified as an important subset of persistent organic pollutants (POPs). This study aimed to assess PAH exposure in pregnant women and newborns in Haikou City, China, and evaluate their impact on glycolipid metabolism.

Methods: A total of 300 pregnant women and their newborns were selected for the study between May 2022 and December 2023. Data on lifestyle and dietary habits were collected, and PAH levels in venous blood and umbilical cord blood were measured using gas chromatography-mass spectrometry. Glycolipid metabolism indicators, including fasting plasma glucose (FPG), triglycerides (TG), total cholesterol (TC), high-density lipoprotein (HDL), and low-density lipoprotein (LDL), were also measured. Correlation and regression analyses were conducted to explore the relationships between PAH exposure and metabolic indicators.

Results: Thirteen PAHs were detected in both maternal and cord blood. The median concentrations of Σ PAHs (the total concentration of the 16 detected PAHs) were 11.211 $\mu\text{g/L}$ in maternal blood and 10.921 $\mu\text{g/L}$ in newborns. Significant correlations were observed between PAH exposure and glycolipid metabolism, with PAH exposure linked to reduced levels of TC and TG. Factors such as proximity to roads, cooking fuel type, and dietary habits influenced PAH levels. Higher education levels were associated with lower PAH concentrations, whereas living near roads and using gas as cooking fuel increased exposure.

Conclusion: There is a notable risk of PAH exposure in pregnant women and newborns in Haikou, influenced by environmental and lifestyle factors. PAH exposure during pregnancy may affect glycolipid metabolism in both mothers and newborns, highlighting the need for interventions to reduce exposure.

KEYWORDS

glycolipid metabolism, Hainan, new born, polycyclic aromatic hydrocarbon, pregnancy

Introduction

Polycyclic aromatic hydrocarbons (PAHs) are a class of large organic compounds composed of 2–7 fused aromatic rings. They are primarily formed through the incomplete combustion of fossil fuels, biomass, and other organic materials. PAHs have garnered significant attention due to their persistence in the environment and their classification as a critical subset of persistent organic pollutants [POPs; (1, 2)]: the compounds are highly stable in the environment, and their hydrophobic nature enables them to persist in soils, sediments, and water bodies. They can also bind to atmospheric particulate matter, facilitating their long-range atmospheric transport (LRAT) across national borders. This phenomenon has been observed in remote regions such as the Arctic and Antarctic (3), where PAHs have accumulated, serving as “cold reservoirs” for POPs (4, 5). The U.S. Environmental Protection Agency (EPA) has identified 16 PAHs as priority pollutants, highlighting their potential health risks and the need for regulatory control (6). Their widespread distribution, combined with their tendency to bioaccumulate, makes PAHs a significant global public health concern.

Human exposure to PAHs occurs through various routes, including inhalation of polluted air, ingestion of contaminated food or water, and dermal contact with PAH-containing materials. As a result, PAHs are ubiquitous in human organs and have been detected in the urine, blood, and hair of the general population (7, 8). This widespread exposure is primarily attributed to the presence of PAHs in traffic-related air pollution, industrial emissions, and the combustion of biomass and fossil fuels. For individuals living in urban environments or near industrial zones, exposure is often unavoidable, resulting in both chronic and acute health risks, including respiratory disorders, cardiovascular diseases, and immunosuppression (9). Moreover, certain PAHs, such as benzo[a]pyrene, are recognized carcinogens, and long-term exposure is associated with an increased risk of developing cancers, particularly lung, skin, and bladder cancer.

The endocrine-disrupting potential of PAHs is also a critical concern for public health systems. As members of a class of chemicals known as endocrine-disrupting chemicals (EDCs), PAHs can interfere with the body's hormonal system by binding to hormone receptors or altering hormone production and metabolism. This disruption can result in a wide range of health issues, including reproductive harm, developmental disorders, metabolic diseases, and cancer (10). Moreover, PAH exposure may indirectly affect blood lipid levels through intermediate mechanisms such as inflammation and oxidative stress (11). For example, environmental PAHs have been shown to exert toxic effects on nuclear receptor signaling, disrupt endogenous metabolism, and induce cellular stress (12). PAHs are particularly concerning because they can cross the placental barrier, exposing fetuses to these chemicals during critical windows of development. Prenatal exposure to PAHs has been linked to various developmental issues, including lower birth weight, reduced head circumference, and impaired neurological function (13, 14). These findings underscore the importance of studying PAH exposure during pregnancy and its potential long-term effects on both maternal and fetal health.

Pregnant women are particularly susceptible to environmental pollutants due to the physiological changes that occur during pregnancy (13, 14). Increased metabolic activity and blood flow during gestation can enhance the absorption and distribution of PAHs within the body. Additionally, hormonal fluctuations during pregnancy may influence the metabolism of PAHs, potentially increasing their bioactivation and toxicity. Consequently, pregnant women exposed to PAHs may experience disruptions in metabolic processes, particularly glycolipid metabolism, which regulates blood sugar and lipids—processes essential for maintaining energy balance and overall health. Disruptions in glycolipid metabolism during pregnancy can lead to complications such as gestational diabetes and dyslipidemia, which, in turn, elevate the risk of adverse pregnancy outcomes (13, 14).

Hainan Island, located at the southernmost tip of China, offers a unique environment for studying the effects of PAHs on human health. With its tropical climate and rapid urbanization, the island faces significant environmental pollution challenges, particularly in its capital city, Haikou—a major shipping hub and economic center—which has led to increased emissions from industrial activities and traffic. Despite being surrounded by the sea and generally having excellent air quality, PAHs were detected in atmospheric PM_{2.5} samples collected in Haikou, with the exception of fluorene (Flu). Among the detected compounds, four-ring PAHs accounted for the highest proportion (15). PAHs are commonly found in marine environments. High molecular weight PAHs (also known as high-ring PAHs, containing 4–7 benzene rings) tend to adhere to particle surfaces and settle into sediments, whereas low molecular weight PAHs (low-ring PAHs, containing 2–3 benzene rings) are absorbed by aquatic organisms through various exposure pathways, including inhalation, skin contact, and ingestion. These compounds can cause both acute and chronic toxic effects (16). In Hainan's Yangpu Bay and Haikou Bay, low molecular weight PAHs, such as naphthalene, fluorene, phenanthrene (Phe), and acenaphthene, primarily derived from petroleum hydrocarbon contamination, dominate in seawater and sediments (17, 18). PAHs have been detected in various marine products from Hainan, including fish, shrimp, crabs, and shellfish. Among these, three-ring PAHs are the most prevalent, accounting for 41.58% to 83.35% (19, 20). Among the 16 PAHs detected, phenanthrene and naphthalene are the most abundant in coral tissue. PAHs in aquatic organisms can enter the human body through the food chain. Additionally, remote transfer via atmospheric currents and sea-air transport contributes to the widespread exposure to PAHs in Hainan. Studies have demonstrated that PAH levels in pregnant women and newborns are primarily influenced by factors such as the distance between their residences and roads, indoor ventilation conditions, and cooking methods during pregnancy. Similar findings have been observed in other inland cities in China, such as Urumqi in Xinjiang, further confirming that traffic emissions are a significant source of human exposure to PAHs. Haikou, the capital of Hainan Province and a key water and land transportation hub, has been found to contain PAHs in nearby water bodies and aquatic organisms. However, whether the PAHs detected in humans are directly related to those in the aquatic environment and organisms remains to be further investigated.

In this study, we aimed to provide valuable insights into the exposure of pregnant women and newborns in Haikou to PAHs, focusing on their internal PAH burden and the effects of PAHs on glycolipid metabolism. By assessing PAH levels in maternal and neonatal blood samples, the study seeks to identify sources of PAH exposure in subtropical island climates and evaluate their potential impact on maternal and fetal health. Understanding these relationships is essential for developing strategies to reduce PAH exposure and mitigate its harmful effects on vulnerable populations, particularly pregnant women and their offspring.

Methods

Study subjects

A total of 300 pairs of pregnant women and their newborns, admitted to Haikou Hospital affiliated with the Xiangya School of Medicine at Central South University between May 2022 and December 2023, were included in this study. According to the 2018 statistical yearbook, there were 134,700 newborns in Hainan Province. Haikou City, with a permanent resident population of 2.3023 million (accounting for 24.6% of Hainan Province's total population of 9.3432 million), was estimated to have ~33,000 newborns that year. In a preliminary study of non-occupationally exposed women, the concentration of 1-hydroxypyrene was $0.042 \pm 0.4 \mu\text{g}/\text{mmol Cr}$. Using this data, the sample size for the current study was determined based on the formula for cross-sectional surveys, calculated with PASS software, to be 300.

The inclusion criteria was as followings: (1) Pregnant women aged 18 years or older. (2) Permanent residents of Haikou (residing for more than 1 year). (3) No history of smoking or alcohol consumption. (4) Consent to provide relevant biological samples for the study and willingness to cooperate with researchers, including providing personal contact information. (5) Singleton full-term delivery. Participants were excluded if they met any of the following criteria: (1) History of acute or chronic illnesses such as hypertension, diabetes, or coronary heart disease. (2) Diagnosis of gestational diabetes or gestational hypertension during pregnancy. (3) History of hereditary or infectious diseases. (4) History of stillbirth, miscarriage, or medication use.

Data collected from all participants included age, ethnicity, health status, family history, reproductive history, household fuel use, heating methods, and dietary habits. Biological samples were obtained, including peripheral venous blood from the mothers and umbilical cord blood from the newborns. The study was conducted with the approval of the Ethics Committee of Hainan Academy of Medical Sciences (HYLL-2021-108). All participants provided written informed consent, and all procedures adhered to the principles outlined in the Declaration of Helsinki.

Blood sample collection and processing

Peripheral venous blood (10 mL) from pregnant women and umbilical cord blood (10 mL) from newborns were collected by a professional nurse using EDTA anticoagulation tubes. The samples were centrifuged within 30 min of collection at 3,500 rpm for 5 min,

and the supernatant (plasma) was transferred to cryovials using a micropipette and stored at -80°C .

Detection of PAH levels

A mixed standard solution of 16 PAHs (ultra-pure, provided by Aladdin, Tianjin, China) and a gas chromatography-tandem triple quadrupole mass spectrometer (TSQ9000, Thermo Fisher Scientific, USA) were used to detect PAH levels in maternal venous blood and newborn umbilical cord blood through gas chromatography-mass spectrometry (GC-MS). Serum samples were thawed at room temperature before analysis, and 4 mL of a 0.4 mol/L sodium hydroxide ethanol-water solution was prepared for the procedure. In brief, 500 μL of serum was mixed with 4 mL of sodium hydroxide ethanol-water solution and incubated in a water bath at 60°C for 30 min. Next, 3 mL of n-hexane was added for liquid-liquid extraction, and the organic layer was concentrated to 0.5 mL using a nitrogen blow-down apparatus. The residue was then reconstituted to 1 mL with n-hexane and transferred to sample vials for GC-MS analysis. If the concentration of a detected compound was below the minimum detection limit, it was recorded as 0. Detailed GC-MS parameters for the 16 PAHs are provided in [Supplementary Table 1](#).

The quality control of the detection was performed as followings: before each GC-MS analysis, automatic tuning of the mass spectrometer (MS) was performed. The GC and MS were then set to the operating conditions specified by the analytical method and placed in standby mode. A 1.0 μL sample of n-hexane was injected directly into the GC injection port, and the analytical method was run until the n-hexane peak appeared. The ion abundance of its mass fragments was required to meet specified criteria, with a stable baseline and no extraneous peaks. If these conditions were not met, the ion source of the mass spectrometer was cleaned. For each batch of samples (up to 20), a blank experiment was conducted. The concentration of target compounds in the blank results was required to be below the method detection limit. If it exceeded the limit, the reagent blank, instrument system, and pretreatment process were inspected. Each batch of samples (up to 20) included one pair of parallel samples. The relative deviation between the parallel sample measurements was required to be $<30\%$.

Measurement of 8-OHdG levels

An enzyme-linked immunosorbent assay (ELISA) was used to measure the levels of 8-OHdG in maternal plasma and newborn umbilical cord blood serum. The process followed the manufacturer's instructions for the ELISA kit: briefly, the samples were thawed at 4°C for 30 min and centrifuged at 3,000 rpm and 4°C for 5 min, retaining the supernatant. For standard wells, 50 μL of standards at different concentrations were used, while 40 μL of sample diluent and 10 μL of the sample were added to the sample wells. The plate was incubated at 37°C for 60 min. A 20-fold diluted washing solution was used to wash the wells five times, with 350 μL added per

TABLE 1 General demographic characteristics and assignments of pregnant women in Haikou (*n* = 300).

Characteristic	Classification	Assignment	Number of cases	Proportion (%)
Age (years)	18	Continuous variable	55	18.3
	27	–	84	28.0
	31	–	84	28.0
	35–44	–	77	25.7
Education ^a	Junior high school or below	1	88	30.4
	High school	2	179	61.7
	College/Undergraduate	3	18	6.2
	Graduate school	4	5	1.7
Ethnicity	Han	1	282	94.0
	Others	2	18	6.0

^aMissing 10 cases.

TABLE 2 Living and environmental conditions during pregnancy in Haikou pregnant women (*n* = 300).

Characteristic	Classification	Assignment	Number of cases	Proportion (%)
Cooking method during pregnancy ^a	Induction cooker	1	39	14.2
	Gas	2	128	46.5
	Natural gas	3	108	39.3
Home renovation during pregnancy ^b	No	0	263	94.6
	Yes	1	15	5.4
Distance from home to road ^c	Far (≥800 m)	1	60	20.6
	Close (400–800 m)	2	169	58.1
	Beside the road (≤400 m)	3	62	21.3
Daily time spent on the road ^d	Less than 1 h	1	191	69.2
	1–2 h	2	70	25.4
	More than 2 h	3	15	5.4
Presence of large waste processing facility near residence ^e	No	0	275	98.9
	Yes	1	3	1.1
Presence of chemical plants, refineries, etc. near residence ^f	No	0	268	97.1
	Yes	1	8	2.9
Ventilation condition of residence during pregnancy ^g	Very good	1	183	66.3
	Good	2	92	33.3
	Poor	3	1	0.4
Presence of carpet or rug in the residence ^h	No	0	249	90.2
	Yes	1	27	9.8

^aMissing 25 cases; ^bMissing 10 cases; ^cMissing 9 cases; ^dMissing 24 cases; ^eMissing 22 cases; ^fMissing 24 cases; ^gMissing 24 cases; ^hMissing 24 cases.

wash and a 30-s standing period before discarding. Afterward, 50 μL each of Color Reagents A and B were added, incubated at 37°C for 15 min, and the reaction was stopped with 50 μL of Stop Solution. A standard curve was plotted using OD values and standard concentrations, and sample concentrations were calculated by substituting measured OD values into the regression equation, with final concentrations adjusted by the dilution factor.

Measurement of glucose and lipid metabolism

Fasting blood glucose (FBG) concentrations were measured using a glucose oxidase ELISA kit, while triglycerides (TG), total cholesterol (TC), high-density lipoprotein (HDL), and low-density lipoprotein (LDL) levels in maternal plasma were analyzed with a biochemical analyzer (Mindray BS-380, China).

TABLE 3 Dietary conditions during pregnancy in Haikou pregnant women (n = 300).

Characteristic	Classification	Assignment	Number of cases	Proportion (%)
Seafood consumption during pregnancy ^a	Every day	3	14	5.1
	Frequently	2	87	31.8
	Rarely	1	155	56.6
	None	0	18	6.6
Meat consumption during pregnancy ^b	Every day	3	121	44.0
	Frequently	2	117	42.5
	Rarely	1	36	13.1
	None	0	1	0.4
Bean and dairy products consumption ^c	Every day	3	57	20.8
	Frequently	2	138	50.4
	Rarely	1	75	27.4
	None	0	4	1.4
Vegetable and fruit consumption ^d	Every day	3	186	67.9
	Frequently	2	77	28.1
	Rarely	1	10	3.6
	None	0	1	0.4
Egg consumption ^e	Every day	3	136	51.1
	Frequently	2	5	1.9
	Rarely	1	17	6.4
	None	0	108	40.6
Fried or grilled food consumption ^f	Every day	3	2	0.7
	Frequently	2	17	6.2
	Rarely	1	6	2.2
	None	0	250	90.9
Water source during pregnancy	Well water	1	7	2.3
	Tap water	2	276	92.0
	Mineral water	3	17	5.7
Tea drinking habit during pregnancy ^g	No	0	235	84.5
	Yes	1	43	15.5

^aMissing 26 cases; ^bMissing 25 cases; ^cMissing 26 cases; ^dMissing 26 cases; ^eMissing 34 cases; ^fMissing 25 cases; ^gMissing 22 cases.

Gestational diabetes was diagnosed based on the International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria, with FBG levels ≥ 5.1 mmol/L (21). Dyslipidemia was defined according to the 2016 Chinese guidelines for the prevention and treatment of adult dyslipidemia, with normal ranges as follows: TG < 2.26 mmol/L, TC < 6.22 mmol/L, LDL < 4.14 mmol/L, and HDL ≥ 1.04 mmol/L.

Statistical analysis

Data entry was conducted using Epidata 3.1 with double-entry verification, and statistical analysis was performed with SPSS 25.0. Quantitative data were expressed as mean $\pm$ standard deviation and compared using *t*-tests, while categorical data were

analyzed using chi-square tests. Spearman correlation analysis examined associations between variables such as PAH and 8-OHdG levels, and multiple linear regression identified influencing factors. Statistical significance was defined as $\alpha = 0.05$.

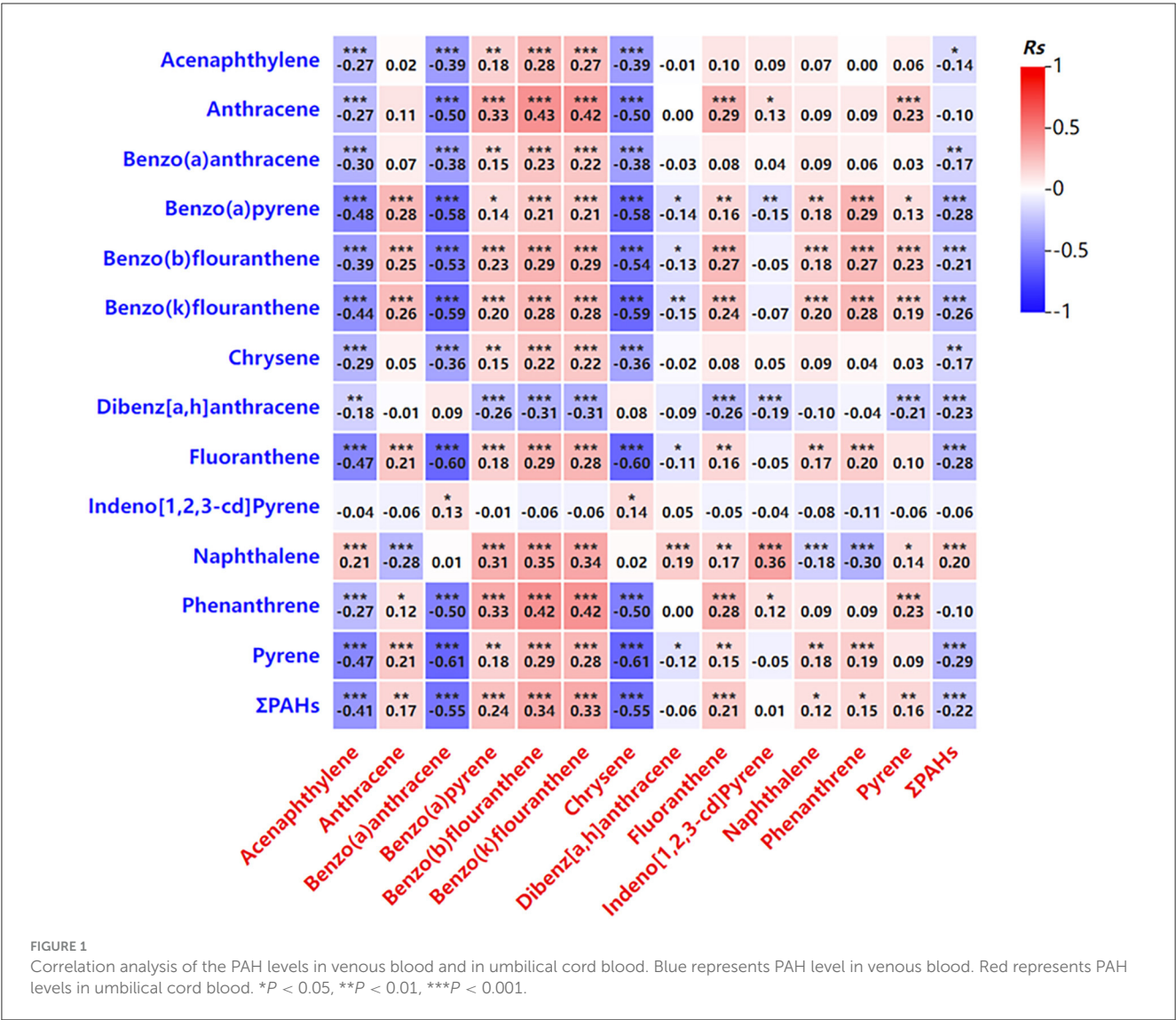
Results

General conditions and pregnancy lifestyle of pregnant women in Haikou city

The study included 300 pairs of pregnant women and their newborns. The age of the pregnant women ranged from 18 to 44 years, with a mean age of 31 years. Most participants (94.0%) were of Han ethnicity, while 6.0% belonged to minority groups. Regarding education, 7.9% had attained a college degree or higher

TABLE 4 PAH levels in venous blood of pregnant women and umbilical cord blood of newborns in Haikou and related correlation coefficients (r_s ; $n = 300$).

PAHs	Venous blood			Umbilical cord blood		
	Detection rate [n (%)]	Concentration M (P25, P75; $\mu\text{g/L}$)	Extreme value ($\mu\text{g/L}$)	Detection rate (%)	Concentration M (P25, P75; $\mu\text{g/L}$)	Extreme value ($\mu\text{g/L}$)
Acenaphthylene (Ace)	Not detected	–	–	Not detected	–	–
Acenaphthene (Acy)	284 (94.7%)	0.523 (0.460, 0.677)	0.000–0.088	298 (99.3%)	0.634 (0.474, 0.659)	0.000–0.855
Anthracene (Ant)	300 (100.0%)	1.812 (1.760, 1.910)	1.521–2.516	300 (100.0%)	1.751 (1.717, 1.801)	1.522–2.654
Benzo[a]anthracene (BaA)	281 (93.7%)	0.541 (0.529, 0.661)	0.000–0.733	297 (99.0%)	0.672 (0.533, 0.680)	0.000–0.816
Benzo[a]pyrene (BaP)	280 (93.3%)	0.687 (0.677, 0.701)	0.000–0.835	297 (99.0%)	0.701 (0.679, 0.722)	0.000–0.849
Benzo[b]fluoranthene (BbFA)	289 (96.3%)	0.618 (0.611, 0.631)	0.000–0.766	299 (99.7%)	0.632 (0.611, 0.654)	0.000–0.778
Benzo[ghi]perylene (BgHiP)	Not detected	–	–	Not detected	–	–
Benzo[k]fluoranthene (BkFA)	293 (97.7%)	0.617 (0.611, 0.630)	0.000–0.766	299 (99.7%)	0.631 (0.611, 0.654)	0.000–0.778
Chrysene (Chr)	279 (93.0%)	0.550 (0.539, 0.667)	0.000–0.741	297 (99.0%)	0.679 (0.543, 0.688)	0.000–0.823
Dibenzo[ah]anthracene (DahA)	93 (31.0%)	0.000 (0.000, 2.432)	0.000–2.593	59 (19.7%)	0 (0, 0)	0.000–2.544
Fluoranthene (FLa)	298 (99.3%)	1.520 (1.500, 1.549)	0.000–2.048	299 (99.7%)	1.530 (1.504, 1.552)	0.000–2.187
Fluorene (FLu)	Not detected	–	–	Not detected	–	–
Indeno[123-cd]pyrene (InP)	100 (33.3%)	0.000 (0.000, 1.695)	0.000–1.991	92 (30.7%)	0.000 (0.000, 1.690)	0.000–1.792
Naphthalene (Nap)	240 (80.0%)	0.463 (0.214, 0.700)	0.000–4.077	289 (96.3%)	0.412 (0.279, 0.467)	0.000–2.503
Phenanthrene (Phe)	300 (100.0%)	1.837 (1.779, 1.926)	1.538–2.539	300 (100.0%)	1.768 (1.733, 1.819)	1.538–2.046
Pyrene (Pyr)	298 (99.3%)	1.592 (1.571, 1.625)	0.000–2.119	299 (99.7%)	1.606 (1.580, 1.628)	0.000–2.258
Σ PAHs	–	11.211 (10.700, 14.619)	3.822–17.954	–	10.921 (10.698, 12.734)	3.261–16.717



(Table 1). The majority of women lived in homes that had not been recently renovated, used gas or natural gas for cooking, and reported good ventilation. A significant proportion resided near roads, though few lived close to industrial sites or waste treatment facilities. In terms of dietary habits, most consumed fruits and vegetables daily, while seafood and meat were consumed less frequently. Fried or grilled foods were largely avoided, and nearly all participants drank tap water. Detailed information on lifestyle factors is provided in Tables 2, 3.

PAH levels in pregnant women's venous blood and newborn cord blood

Among the 16 types of PAHs initially analyzed, 13 were detected in both maternal and newborn samples. Certain PAHs, including anthracene (Ant) and phenanthrene (Phe) were present in 100% of maternal blood samples (Table 4). In contrast, some PAHs, such

as dibenz[a,h]anthracene (DahA), had much lower detection rates, with only 31% of maternal samples testing positive (Table 4). A similar detection profile was observed in newborn cord blood, where PAHs like anthracene and phenanthrene were detected in all samples, whereas others, such as dibenz[a,h]anthracene, were found in only 19.7% of cases (Table 4). Phenanthrene exhibited the highest median concentration among the detected PAHs, with levels of 1.837 µg/L in maternal venous blood and 1.768 µg/L in newborn cord blood (Table 4). In contrast, dibenz[a,h]anthracene showed the lowest concentrations, often being undetectable or present only at trace levels (Table 4). Other PAHs, such as benzo[a]pyrene (BaP) and benzo[b]fluoranthene (BbFA), demonstrated high detection rates, approaching 99.0% in both maternal and cord blood samples, highlighting widespread exposure among the study population (Table 4).

The total concentration of PAHs (ΣPAHs, the total concentration of the 16 PAHs tested) in maternal blood was positively correlated with the concentrations of specific PAHs in newborn cord blood, including benzo[a]pyrene,

TABLE 5 Multiple linear regression analysis of PAH concentrations in venous blood of pregnant women in Haikou (*n* = 300).

PAHs Type	Variable	β	SD	t-Value	P-Value
ΣPAHs	Intercept	7.596	4.512	1.684	0.094
	(Daily time on the road during pregnancy)	1.404	0.607	2.313	0.022
Acenaphthylene (Acy)	Intercept	0.225	0.189	1.192	0.235
	(Carpet or rug in the house)	0.106	0.048	2.177	0.030
Benzo[a]pyrene (BaP)	Intercept	0.508	0.274	1.852	0.065
	(Carpet or rug in the house)	0.156	0.071	2.211	0.028
Benzo[b]fluoranthene (BbFA)	Intercept	0.576	0.246	2.343	0.020
	X2 (Education)	−0.070	0.031	−2.225	0.027
	(Carpet or rug in the house)	0.138	0.063	2.183	0.030
Benzo[k]fluoranthene (BkFA)	Intercept	0.534	0.246	2.169	0.031
	(Distance from home to road)	−0.063	0.030	−2.098	0.037
	(Carpet or rug in the house)	0.135	0.063	2.130	0.034
Dibenzo[ah]anthracene (DahA)	Intercept	0.075	0.589	0.128	0.899
	(Daily time on the road during pregnancy)	0.273	0.079	3.448	0.001
	(Ventilation condition of the house)	−0.230	0.093	−2.484	0.014
Indeno[123-cd]pyrene (InP)	Intercept	0.141	0.424	0.332	0.740
	(Daily time on the road during pregnancy)	0.165	0.057	2.902	0.004
	(Ventilation condition of the house)	−0.159	0.067	−2.391	0.018
Naphthalene (Nap)	Intercept	0.287	0.185	1.555	0.121
	(Cooking method during pregnancy)	0.046	0.021	2.175	0.031
	(Vegetable and fruit consumption)	−0.065	0.026	−2.541	0.013

benzo[b]fluoranthene, and benzo[k]fluoranthene (Table 4; Figure 1). Conversely, a negative correlation was observed between maternal PAH concentrations and certain PAHs in cord blood, such as chrysene (Chr) and benzo[a]anthracene (BaA; Table 4; Figure 1). These findings indicate a strong relationship between maternal PAH exposure during pregnancy and newborn exposure, likely due to the transplacental transfer of these compounds.

The analysis revealed that certain PAHs in maternal blood, such as acenaphthylene and benzo[a]anthracene, were negatively correlated with their concentrations in newborn cord blood, while others, including benzo[a]pyrene, exhibited a positive correlation (Table 4; Figure 1). These findings suggest a complex interaction between maternal PAH exposure and placental transfer mechanisms, which influence the distribution of these compounds in the fetus.

Factors influencing PAH concentration in pregnant women’s blood

Several factors were identified as influencing PAH concentrations in maternal blood, including time spent near roads, the presence of carpets in the home, and the mothers’ educational background (Table 5). Higher PAH concentrations were associated with more time spent near roads and the

presence of household carpets. In contrast, higher educational attainment was linked to lower PAH levels. Additionally, increased consumption of fruits and vegetables during pregnancy was correlated with reduced maternal PAH concentrations. Detailed information on these influencing factors is provided in Table 5.

8-OHdG metabolism levels and their correlation with PAH levels

The median 8-OHdG level in maternal blood was 56.5 ng/mL, while newborn cord blood had a median of 54.0 ng/mL, indicating oxidative stress in both groups. No significant correlation was found between PAH concentrations and 8-OHdG levels in maternal blood. However, in newborn umbilical cord blood, significant positive correlations were observed between several PAHs—including dibenz[a,h]anthracene (DahA), fluoranthene (FLa), indeno[1,2,3-cd]pyrene (InP), and pyrene (Pyr)—and 8-OHdG levels (Table 6). This suggests that PAH exposure during pregnancy contributes to oxidative stress in newborns. This heightened fetal vulnerability highlights the importance of minimizing PAH exposure during pregnancy to protect against oxidative damage and its potential long-term health consequences for the child.

TABLE 6 Correlation between PAHs exposure levels in venous blood of pregnant women and umbilical cord blood of newborns in Haikou and 8-OHdG levels (*n* = 300).

PAHs	8-OHdG ^a (Venous blood)		8-OHdG ^b (Umbilical cord blood)	
	rs	<i>P</i>	rs	<i>P</i>
Acenaphthylene (Ace)	–	–	–	–
Acenaphthene (Acy)	–0.106	0.198	0.082	0.320
Anthracene (Ant)	–0.024	0.771	–0.047	0.567
Benzo[a]anthracene (BaA)	0.012	0.888	0.126	0.124
Benzo[a]pyrene (BaP)	0.157	0.055	0.121	0.139
Benzo[b]fluoranthene (BbFA)	0.144	0.078	0.141	0.086
Benzo[ghi]perylene (BghiP)	–	–	–	–
Benzo[k]fluoranthene (BkFA)	0.097	0.236	0.134	0.102
Chrysene (Chr)	–0.001	0.992	0.128	0.118
Dibenzo[ah]anthracene (DahA)	0.018	0.825	0.223	0.006
Fluoranthene (FLa)	0.042	0.608	0.194	0.018
Fluorene (FLu)	–	–	–	–
Indeno[123-cd]pyrene (InP)	0.044	0.590	0.190	0.020
Naphthalene (Nap)	–0.148	0.071	–0.118	0.150
Phenanthrene (Phe)	–0.030	0.718	–0.120	0.145
Pyrene (Pyr)	0.016	0.850	0.187	0.022
ΣPAHs	–0.014	0.862	0.177	0.030

^aCorrelation with PAHs concentration in venous blood; ^bCorrelation with PAHs concentration in umbilical cord blood.

TABLE 7 Glucose and lipid metabolism levels in venous blood of pregnant women and umbilical cord blood of newborns in Haikou and related correlation coefficients (rs; *n* = 300).

	Venous blood	Umbilical cord blood	rs	<i>P</i>
FPG (mmol/L)	4.215 (3.383, 5.108)	3.700 (2.590, 5.055)	0.079	0.186
TC (mmol/L)	6.600 (5.245, 8.340)	1.665 (1.240, 2.243)	–0.085	0.154
TG (mmol/L)	3.530 (2.763, 4.488)	0.400 (0.320, 0.530)	–0.121	0.041
HDL (mmol/L)	1.825 (1.480, 2.258)	0.880 (0.670, 1.198)	–0.060	0.315
LDL (mmol/L)	2.980 (2.280, 3.790)	0.460 (0.330, 0.630)	–0.076	0.203

Blood glucose and lipid metabolism in pregnant women and newborns

As shown in Table 7, triglyceride (TG) levels in maternal blood were negatively correlated with those in newborn blood, suggesting a potential inverse relationship in metabolic function between mothers and their newborns. Other metabolic markers, including total cholesterol, fasting blood glucose, and HDL cholesterol, were also analyzed, further confirming the negative association between TG levels in maternal and newborn blood (Table 7).

Correlation between PAH and 8-OHdG levels and metabolic levels

Further analysis revealed that increased PAH exposure was associated with adverse effects on glucose and lipid metabolism in

pregnant women (Figure 2). Higher PAH concentrations showed negative correlations with key metabolic indicators, including total cholesterol, triglycerides, and HDL cholesterol (Figure 2). Similar trends were observed in newborns, where certain PAHs were weakly correlated with lower levels of metabolic markers such as fasting glucose and HDL cholesterol (Figure 3). However, no significant correlations were identified between glucose and lipid metabolism and 8-OHdG levels in either maternal or newborn blood samples (Table 8).

Discussion

The current study investigated PAH exposure among pregnant women and newborns in Haikou, China, with a particular focus on its potential effects on maternal and neonatal health, specifically glucose and lipid metabolism. Thirteen different PAHs were

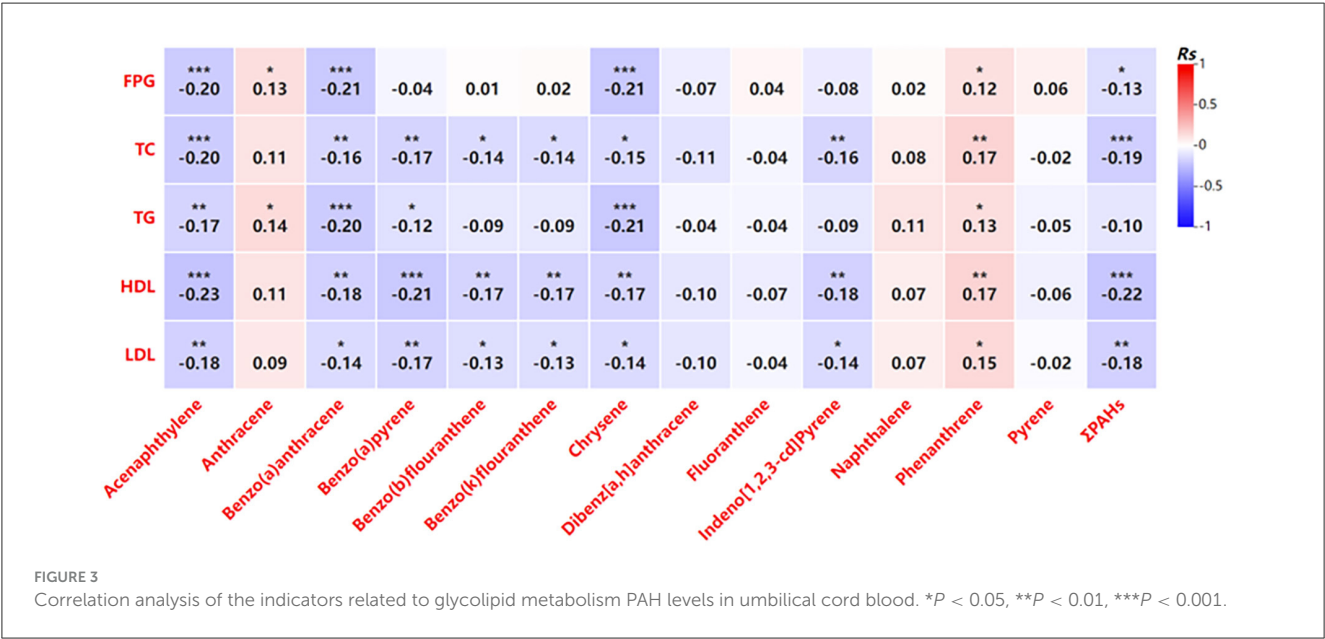
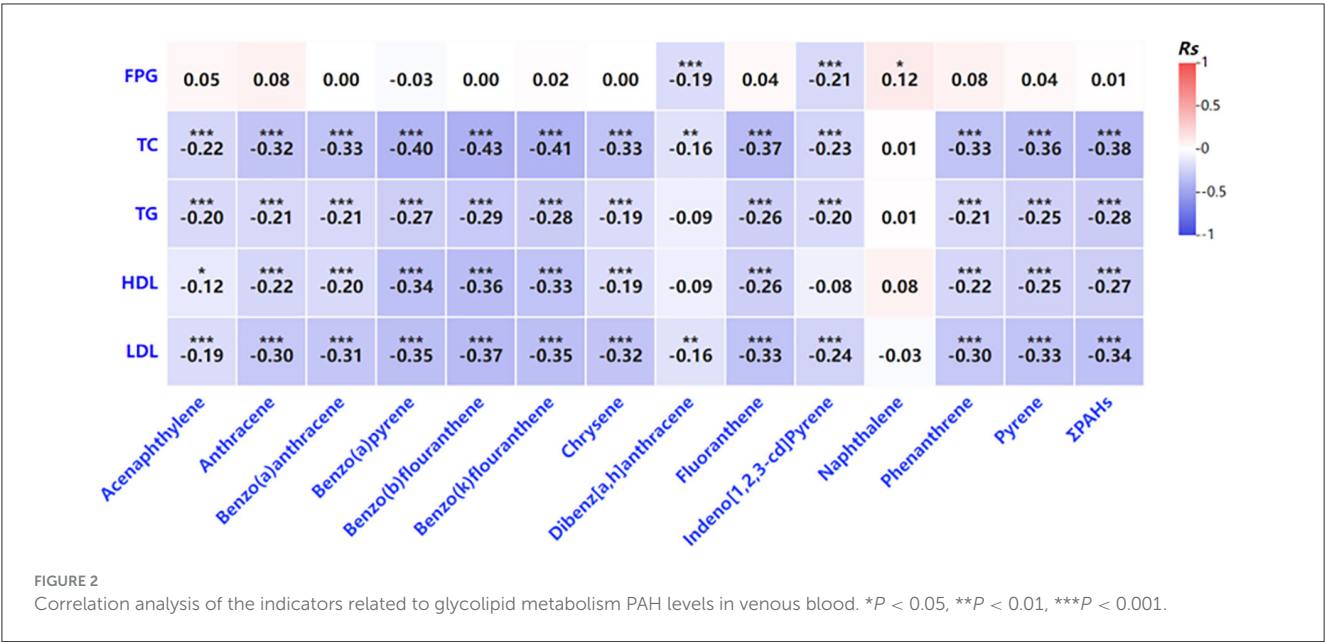


TABLE 8 Multiple linear regression analysis of 8-OHdG concentration in venous blood of pregnant women and umbilical cord blood of newborns in Haikou ($n = 300$).

Glucose and lipid metabolism indicators	Venous blood 8-OHdG ^a		Umbilical cord blood 8-OHdG ^b	
	rs	P	rs	P
FPG	0.005	0.948	−0.035	0.005
TC	−0.069	0.404	−0.059	−0.069
TG	−0.147	0.075	−0.091	−0.147
HDL	−0.025	0.767	−0.075	−0.025
LDL	−0.024	0.777	−0.092	−0.024

^aCorrelation with 8-OHdG levels in venous blood; ^bCorrelation with 8-OHdG levels in umbilical cord blood.

detected in both maternal venous blood and neonatal umbilical cord blood, with notable exceptions such as acenaphthene, benzo[a]pyrene, and fluorene, which were not detected in either sample. These findings underscore a significant exposure risk for pregnant women and their newborns in Haikou, driven primarily by various environmental and lifestyle factors.

Polycyclic aromatic hydrocarbons, known for their toxic properties, are introduced into the environment through various sources, including tobacco smoke, vehicle exhaust, grilled and charred foods, industrial emissions, and natural events such as forest fires and volcanic activity (22–24). The study highlighted that PAH concentrations in pregnant women's blood were influenced by factors such as proximity to major roads, cooking methods, and dietary habits during pregnancy, particularly the consumption of fruits and vegetables. High-temperature cooking methods, including grilling, roasting, and frying, were identified as significant contributors to increased PAH exposure. Traditional Chinese cooking, which often involves temperatures exceeding 200°C, can lead to the breakdown of unsaturated fatty acids in oils and foods, thereby generating PAHs (25). These findings underscore the critical role of lifestyle choices, especially dietary habits and cooking methods, in determining PAH exposure levels during pregnancy.

We also explored the relationship between PAH exposure and metabolic indicators. A weak negative correlation was observed between the concentration of certain PAHs, such as indeno[1,2,3-cd]pyrene, and fasting plasma glucose (FPG) levels in maternal blood. This finding suggests that PAHs may interact with metabolic processes in pregnant women, potentially influenced by the physiological insulin resistance characteristic of pregnancy. The study further hypothesized that elevated estrogen levels during pregnancy might play a protective role in regulating glucose metabolism. As estrogen levels increase, particularly after 20 weeks of gestation, they enhance the function of pancreatic beta cells, promoting glucose uptake and utilization, which could contribute to lower blood glucose levels (26, 27). PAHs, known for their estrogen-mimicking properties, may contribute to the observed effects, although the specific mechanisms remain unclear and warrant further investigation. While the study identified a correlation between PAHs and glucose metabolism, no significant relationship was found between glucose-lipid metabolism and oxidative stress markers such as 8-OHdG, a biomarker for oxidative DNA damage (28). Although similar levels of 8-OHdG were observed in both maternal and neonatal blood, this only indicates comparable quantities of oxidative damage markers. It does not imply that the oxidative stress or damage levels are identical in mothers and infants. Neonates, as a vulnerable group, have underdeveloped systems, including the nervous and immune systems, making them more susceptible to oxidative damage. The same level of oxidative damage that might be tolerable in adults could have more significant, prolonged, or even irreversible effects on fetuses or newborns, potentially leading to lifelong consequences. These findings suggest that while PAHs may influence glucose regulation during pregnancy, their impact on oxidative stress and lipid metabolism is more complex and may involve other factors not addressed in this study. The authors hypothesized that PAHs might act synergistically with estrogen during pregnancy, but further research is needed to clarify the mechanisms by which PAHs interact with metabolic pathways in pregnant women.

The long-term implications of PAH exposure are concerning. The study highlighted that chronic exposure to low levels of PAHs, even among non-pregnant individuals, could result in a range of health issues, including weakened immune function, respiratory disorders, cardiovascular diseases, and cancer. Being lipophilic, PAHs are transported throughout the body via lipoproteins in the bloodstream. Their ability to enter and accumulate in the human body through multiple pathways—such as inhalation, ingestion, and skin contact—underscores significant public health concerns (29, 30). PAHs can cross the placental barrier, and the study found a correlation between PAH concentrations in maternal blood and cord blood, suggesting that these toxic compounds may affect fetal development, particularly lipid metabolism. Notably, the detection rate of some PAHs in newborn umbilical cord blood was even higher than in maternal venous blood. Since newborns are not directly exposed to PAHs, the compounds detected in their blood are derived from the mother. However, some PAHs in the maternal body may be metabolized into different forms, and various types of PAHs have different abilities to cross the placenta. If a metabolized PAH has a particularly strong ability to penetrate the placental barrier, it could result in higher concentrations of that specific PAH in the umbilical cord blood compared to maternal venous blood.

The research also highlighted elevated levels of total cholesterol (TC) and triglycerides (TG) in maternal blood samples, which is typical during pregnancy as the body prepares for increased energy demands and supports fetal growth (31). These elevated lipid levels, combined with PAH exposure, may have long-term effects on both maternal and fetal cardiovascular health (32, 33). However, the study acknowledges several limitations. It was conducted solely in Haikou, limiting the generalizability of the findings to other regions of China or globally. Additionally, the sample size was relatively small, and the study lacked air quality monitoring data, which could have provided more comprehensive insights into environmental PAH exposure levels. Future studies with larger, more diverse populations, and better environmental monitoring are needed to further explore the connections between PAH exposure and health outcomes during pregnancy.

In conclusion, this study underscores the importance of addressing PAH exposure among pregnant women, given its potential impact on both maternal and fetal health. Reducing PAH exposure through lifestyle modifications, improved air quality, and public health interventions could help mitigate the risks associated with these toxic compounds. Further research is necessary to deepen the understanding of PAHs' role in metabolic regulation during pregnancy and to develop effective strategies for protecting maternal and neonatal 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 humans were approved by the Ethics Committee of Hainan Academy of Medical Sciences

(HYLL-2021-108). 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.

Author contributions

XC: Data curation, Formal analysis, Writing – original draft. HG: Data curation, Formal analysis, Writing – original draft. QL: Data curation, Formal analysis, Writing – original draft. NZ: Data curation, Formal analysis, Writing – original draft. YL: Conceptualization, Data curation, Formal analysis, Writing – review & editing.

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References

- Kim KH, Jahan SA, Kabir E, Brown RJ. A review of airborne polycyclic aromatic hydrocarbons (PAHs) and their human health effects. *Environ Int.* (2013) 60:71–80. doi: 10.1016/j.envint.2013.07.019
- Patel AB, Shaikh S, Jain KR, Desai C, Madamwar D. Polycyclic aromatic hydrocarbons: sources, toxicity, and remediation approaches. *Front Microbiol.* (2020) 11:562813. doi: 10.3389/fmicb.2020.562813
- Sheng Y, Yan C, Nie M, Ju M, Ding M, Huang X, et al. The partitioning behavior of PAHs between settled dust and its extracted water phase: coefficients and effects of the fluorescent organic matter. *Ecotoxicol Environ Saf.* (2021) 223:112573. doi: 10.1016/j.ecoenv.2021.112573
- Vecchiato M, Barbaro E, Spolaor A, Burgay F, Barbante C, Piazza R, et al. Fragrances and PAHs in snow and seawater of Ny-Ålesund (Svalbard): local and long-range contamination. *Environ Pollut.* (2018) 242(Pt. B):1740–7. doi: 10.1016/j.envpol.2018.07.095
- Mai B, Qi S, Zeng EY, Yang Q, Zhang G, Fu J, et al. Distribution of polycyclic aromatic hydrocarbons in the coastal region off Macao, China: assessment of input sources and transport pathways using compositional analysis. *Environ Sci Technol.* (2003) 37:4855–63. doi: 10.1021/es034514k
- Humel S, Schmidt SN, Sumetzberger-Hasinger M, Mayer P, Loibner AP. Enhanced accessibility of polycyclic aromatic hydrocarbons (PAHs) and heterocyclic PAHs in industrially contaminated soil after passive dosing of a competitive sorbate. *Environ Sci Technol.* (2017) 51:8017–26. doi: 10.1021/acs.est.7b01198
- Chen M, Huang P, Chen L. Polycyclic aromatic hydrocarbons in soils from Urumqi, China: distribution, source contributions, and potential health risks. *Environ Monit Assess.* (2013) 185:5639–51. doi: 10.1007/s10661-012-2973-6
- Choi J, Knudsen LE, Mizrak S, Joas A. Identification of exposure to environmental chemicals in children and older adults using human biomonitoring data sorted by age: results from a literature review. *Int J Hyg Environ Health.* (2017) 220(Pt. A):282–98. doi: 10.1016/j.ijheh.2016.12.006
- Boström CE, Gerde P, Hanberg A, Jernström B, Johansson C, Kyrklund T, et al. Cancer risk assessment, indicators, and guidelines for polycyclic aromatic

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.

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Supplementary material

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hydrocarbons in the ambient air. *Environ Health Perspect.* (2002) 110(Suppl. 3):451–88. doi: 10.1289/ehp.110-1241197

10. Maqbool F, Mostafalou S, Bahadar H, Abdollahi M. Review of endocrine disorders associated with environmental toxicants and possible involved mechanisms. *Life Sci.* (2016) 145:265–73. doi: 10.1016/j.lfs.2015.10.022

11. Zhou S, Li X, Dai Y, Guo C, Peng R, Qin P, et al. Association between polycyclic aromatic hydrocarbon exposure and blood lipid levels: the indirect effects of inflammation and oxidative stress. *Environ Sci Pollut Res Int.* (2023) 30:123148–63. doi: 10.1007/s11356-023-31020-7

12. Šimečková P, Pěncíková K, Kováč O, Slavík J, Parenicová M, Vondráček J, et al. *In vitro* profiling of toxic effects of environmental polycyclic aromatic hydrocarbons on nuclear receptor signaling, disruption of endogenous metabolism and induction of cellular stress. *Sci Tot Environ.* (2022) 815:151967. doi: 10.1016/j.scitotenv.2021.151967

13. Crowell SR, Sharma AK, Amin S, Soelberg JJ, Sadler NC, Wright AT, et al. Impact of pregnancy on the pharmacokinetics of dibenzo[def,p]chrysene in mice. *Toxicol Sci.* (2013) 135:48–62. doi: 10.1093/toxsci/kft124

14. Dehghani S, Fararouei M, Rafiee A, Hoepner L, Oskoei V, Hoseini M. Prenatal exposure to polycyclic aromatic hydrocarbons and effects on neonatal anthropometric indices and thyroid-stimulating hormone in a Middle Eastern population. *Chemosphere.* (2022) 286(Pt. 1):131605. doi: 10.1016/j.chemosphere.2021.131605

15. Liu J, Qian L, Li HJ, Zhang J. Distribution characteristics of PAHs in PM_{2.5} during Autumn and Winter in Haikou. *Environ Sci Technol.* (2016) 39:86–90.

16. Lee K, Raverty S, Cottrell P, Zoveidadianpour Z, Cottrell B, Price D, et al. Polycyclic aromatic hydrocarbon (PAH) source identification and a maternal transfer case study in threatened killer whales (*Orcinus orca*) of British Columbia, Canada. *Sci Rep.* (2023) 13:22580. doi: 10.1038/s41598-023-45306-w

17. Yang B. *Distribution Characteristics of Polycyclic Aromatic Hydrocarbons (PAHs) in Seawater in Typical Waters of Yangpu Bay and Their Ecotoxicological Effects on Shellfish*. Hainan University (2012).

18. Zhang XY, Wang Y, Yang B, Diao XP. Distribution and sources of PAHs in Haikou Bay. *Environ Sci Technol.* (2012) 35:102–5.

19. Zhang JC. *Bioaccumulation of Antibiotics and Polycyclic Aromatic Hydrocarbons in the Yellow River Estuary and Transport in the Marine Food Chain*. Shandong University (2022).
20. Chen GQ, Li YC, Huang JM, Nan Y, Lin MH. PAHs Concentrations in aquatic products and food safety evaluation in the coupled mangrove planting-aquaculture ecological system. *Environ Sci*. (2012) 33:1846–51. doi: 10.13227/j.hjxx.2012.06.024
21. Chu RJ, Gao RL, Zhao SP, Lu GP, Zhao D, Li JJ. Guidelines for the prevention and treatment of dyslipidemia in chinese adults. *Chin Circ J*. (2016) 31:937–53.
22. Srogi K. Monitoring of environmental exposure to polycyclic aromatic hydrocarbons: a review. *Environ Chem Lett*. (2007) 5:169–95. doi: 10.1007/s10311-007-0095-0
23. Ma X, Han X, Jiang Q, Huang C, Huang T, Yang H, et al. Historical records and source apportionment of polycyclic aromatic hydrocarbons over the past 100 years in Dianchi lake, a Plateau Lake in Southwest China. *Arch Environ Contam Toxicol*. (2018) 75:187–98. doi: 10.1007/s00244-018-0525-y
24. Tobiszewski M, Namieśnik J. PAH diagnostic ratios for the identification of pollution emission sources. *Environ Pollut*. (2012) 162:110–9. doi: 10.1016/j.envpol.2011.10.025
25. Moret S, Conte LS. Polycyclic aromatic hydrocarbons in edible fats and oils: occurrence and analytical methods. *J Chromatogr*. (2000) 882:245–53. doi: 10.1016/S0021-9673(00)00079-0
26. Alshaarawy O, Zhu M, Ducatman AM, Conway B, Andrew ME. Urinary polycyclic aromatic hydrocarbon biomarkers and diabetes mellitus. *Occup Environ Med*. (2014) 71:437–41. doi: 10.1136/oemed-2013-101987
27. Wang L, Hou J, Hu C, Zhou Y, Sun H, Zhang J, et al. Mediating factors explaining the associations between polycyclic aromatic hydrocarbons exposure, low socioeconomic status and diabetes: a structural equation modeling approach. *Sci Tot Environ*. (2019) 648:1476–83. doi: 10.1016/j.scitotenv.2018.08.255
28. Jung E, Romero R, Yeo L, Gomez-Lopez N, Chaemsaitong P, Jaovisidha A, et al. The etiology of preeclampsia. *Am J Obstetr Gynecol*. (2022) 226:S844–66. doi: 10.1016/j.ajog.2021.11.1356
29. Loftus CT, Szpiro AA, Workman T, Wallace ER, Hazlehurst MF, Day DB, et al. Maternal exposure to urinary polycyclic aromatic hydrocarbons (PAH) in pregnancy and childhood asthma in a pooled multi-cohort study. *Environ Int*. (2022) 170:107494. doi: 10.1016/j.envint.2022.107494
30. Singh A, Kamal R, Tiwari R, Gaur VK, Bihari V, Satyanarayana GNV, et al. Association between PAHs biomarkers and kidney injury biomarkers among kitchen workers with microalbuminuria: a cross-sectional pilot study. *Clin Chim Acta*. (2018) 487:349–56. doi: 10.1016/j.cca.2018.10.021
31. Waage CW, Mdala I, Stigum H, Jenum AK, Birkeland KI, Shakeel N, et al. Lipid and lipoprotein concentrations during pregnancy and associations with ethnicity. *BMC Pregn Childb*. (2022) 22:246. doi: 10.1186/s12884-022-04524-2
32. Alexander DL, Ganem LG, Fernandez-Salguero P, Gonzalez F, Jefcoate CR. Aryl-hydrocarbon receptor is an inhibitory regulator of lipid synthesis and of commitment to adipogenesis. *J Cell Sci*. (1998) 111(Pt. 22):3311–22. doi: 10.1242/jcs.111.22.3311
33. Kwack SJ, Lee BM. Correlation between DNA or protein adducts and benzo[a]pyrene diol epoxide I-triglyceride adduct detected *in vitro* and *in vivo*. *Carcinogenesis*. (2000) 21:629–32. doi: 10.1093/carcin/21.4.629



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Level of non-adherence and associated factors among children on antiretroviral therapy in public hospitals of South Wollo Zone, Northeast Ethiopia

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Background: Poor adherence to antiretroviral therapy (ART) occurs when an individual with Human Immune deficiency Virus does not follow the prescribed treatment regimen correctly. This includes missing doses, not taking medication as scheduled, taking medication inconsistently or irregularly, and failing to adhere to specific instructions. The lack of adherence to antiretroviral therapy (ART) among children is a noteworthy issue that necessitates attention. The study aims to determine the level of non-adherence to antiretroviral therapy (ART) and its associated factors in children receiving ART in public hospitals in the South Wollo Zone.

Methods: A multi-center cross-sectional study was conducted among children receiving antiretroviral therapy at South Wollo Zone public hospitals. A single population proportion formula was used to determine the required sample size. A computer-generated simple random sampling method was employed to select the participants. The tools used to assess adherence for all participants were viral load monitoring, Self-reporting, Pill counts, and Pharmacy refill records. Data were collected through face-to-face interviews, and reviewing patients' documents using a structured checklist. The data were entered into Epi Data version 4.1 and analyzed using STATA 17. Binary logistic regression was employed to evaluate the relationship between the factors and the outcome variable. Variables were considered significant if the *p*-value was less than 0.05.

Result: Of 291 participants, 286 were involved in the study, making the response rate 98.3%. The mean age of the participants was 7.8 years old (± 3.64 SD), and half of the 146 children (51%) were male. The overall proportion of ART non-adherence was 24.1% (95% CI: 19.2–29.0%). Positive TB status (Adjusted odd ratio (AOR) = 4.10, 95% CI: 1.90–8.88), diagnostic status not disclosed (AOR = 2.69, 95% CI: 1.43–5.00), and poor caregiver knowledge (AOR = 2.18, 95% CI: 1.04–4.56) were significantly associated with poor adherence.

Conclusion: According to the current study, the level of non-adherence to antiretroviral therapy remains high compared to the targets set by the United Nations Joint Program on HIV/AIDS (UNAIDS) Project 95-95-95. TB co-infection, undisclosed diagnostic status, and poor caregiver knowledge were found to be significantly associated with non-adherence. Before and throughout ART, healthcare providers should provide intense and ongoing counseling to children and their caregivers.

KEYWORDS

non-adherence, antiretroviral therapy (ART), children, South Wollo Zone, Ethiopia

Background

In 2023, approximately 630,000 individuals died from HIV-related causes, and around 1.3 million people acquired HIV (1). By the end of the year, approximately 1.4 million children aged 0–14 were living with HIV, with 120,000 newly infected. Around 76,000 children succumbed to AIDS-related illnesses. Early testing and treatment are critical to decreasing HIV-related deaths and diseases in this vulnerable group (1). Without timely intervention, half of the children with HIV will die by age 2, and 80% will not survive past their fifth birthday (1–3).

According to an Ethiopian Public Health Institute report published in 2021, around 42,000 Ethiopian children were infected with HIV during the same year. The report also indicates that in 2013 the country's ART coverage for children was only 12%. Additionally, it highlights that the HIV epidemic among Ethiopian youth has received minimal attention from government initiatives (4, 5).

ART is a combination of antiretroviral medications that can extend and enhance the quality of life of HIV patients by reducing viral loads and raising CD4 cell counts. ART is an HIV medication that should be taken constantly (6). Adherence to appropriate and prolonged treatment is critical to ART success (7).

Poor adherence (non-adherence) to ART occurs when an individual with HIV does not follow the prescribed treatment regimen correctly. This includes missing doses, not taking medication as scheduled, taking medication inconsistently or irregularly, failing to adhere to specific instructions such as taking the drug with food or at designated times, completely discontinuing medication, or not refilling prescriptions as required. Such poor adherence can result in less effective treatment, including treatment failure, higher viral loads, development of drug resistance, and disease progression. Contributing factors may include side effects, the complexity of the regimen, lack of support, or various personal and systemic issues (1, 8, 9).

The study shows that non-adherence levels in Ethiopia ranged from 4.5% at Tikur Anbessa Hospital (10) to 65.5% at Debre Birhan Hospital (11).

Some studies state factors that contribute to poor adherence among children. These factors include socio-economic, socio-demographic, and socio-cultural aspects, as well as problems with service delivery, which can have an impact on adherence to pediatric ART (12, 13). High pill burden, poor palatability, long-term toxicity, ART side effects, ART regimens, and medication dosing are additional factors that can affect adherence. Pediatric ART adherence has also been linked to children's health, length of time on antiretroviral therapy (ART), knowledge of their HIV status, and psychological variables (10–18).

Routine assessment of medication adherence in clinical care should include increasing the frequency of viral load monitoring after starting

or changing medications. Additionally, healthcare providers should ask the child/adolescent and caregiver about the number of missed doses over specific periods (e.g., 1, 3, or 7 days) and request details about the medication, such as its name, appearance, dosage, and frequency of intake. Engaging in conversations with the child and caregiver about potential adherence barriers and strategies to overcome them is essential. Pharmacy-based or clinic-based methods can be used to assess on-time medication refills. Both remote and in-person visits should be utilized to support families, observe ART preparation, handling, and administration, and conduct directly observed therapy (DOT) at home. Finally, announced and unannounced pill counts can be performed by asking individuals to bring medications to the clinic, conducting home visits, or referring them to community health nursing (19, 20).

Non-adherence to ART poses a major challenge to achieving optimal health outcomes for children living with HIV, leading to virologic failure, drug resistance, and increased morbidity and mortality. Understanding the extent of non-adherence is essential for improving pediatric HIV treatment. Ethiopia's sociocultural, economic, and healthcare contexts significantly influence adherence, and identifying these factors can guide the development of targeted locally relevant interventions.

This study aligns with Ethiopia's national HIV/AIDS strategic plan and global UNAIDS 95–95–95 goals, contributing to viral suppression and the effort to end the pediatric HIV epidemic. By quantifying non-adherence and its associated factors, the research provides critical data to inform policymakers and healthcare providers, enabling better resource allocation, caregiver training, and implementation of evidence-based strategies.

Non-adherence not only leads to treatment failure but also increases healthcare costs due to the need for second-line therapies and hospitalizations. Addressing adherence early can reduce this burden on the healthcare system. Limited data exist on pediatric ART adherence in Ethiopia, particularly in the study area. This research employs innovative methods, including adherence assessment through viral load measurement, which has not been extensively studied before. The findings will fill critical knowledge gaps, advance pediatric HIV care, and support Ethiopia's fight against HIV/AIDS. This study aimed to determine the level of non-adherence to ART and its associated factors in children receiving ART in public hospitals in the South Wollo Zone.

Methods

Study setting, design, and period

An institution-based cross-sectional study was conducted from June 1 to June 30, 2023, among children receiving antiretroviral

therapy at South Wollo Zone public hospitals. It was far from Addis Ababa, a distance of 401 km, and from Bahir Dar, a distance of 471 km. It has a total population of 2,518,862 and 499 health posts, 126 health centers, and 14 hospitals.

Population

All HIV-infected children <15 years of age who started ART at South Wollo Zone Public Hospitals and their primary caregivers served as our source population for this study. Our study population includes all HIV-infected children <15 years of age who started ART at South Wollo Zone Public Hospitals from September 1, 2019, to June 30, 2023, and their primary caregivers.

Inclusion criteria

The study included children under 15 who had been on ART for at least 1 month and their primary caregivers.

Exclusion criteria

Participants with incomplete data (charts lacking significant explanatory and outcome variables) were excluded from this study.

Sample size determination

A single population proportion formula was used to determine the required sample size with the following statistical assumptions: 22% proportion (p) of the level of non-adherence was taken from a study conducted in northwest Ethiopia (16); 5% margin of error; 10% incomplete or inconsistent data; and 95% confidence intervals (CI).

$$n = \frac{(Z_{\alpha/2})^2 P(1-P)}{(d)^2} \quad n = \frac{(1.96)^2 0.22(1-0.22)}{(0.05)^2} = 264$$

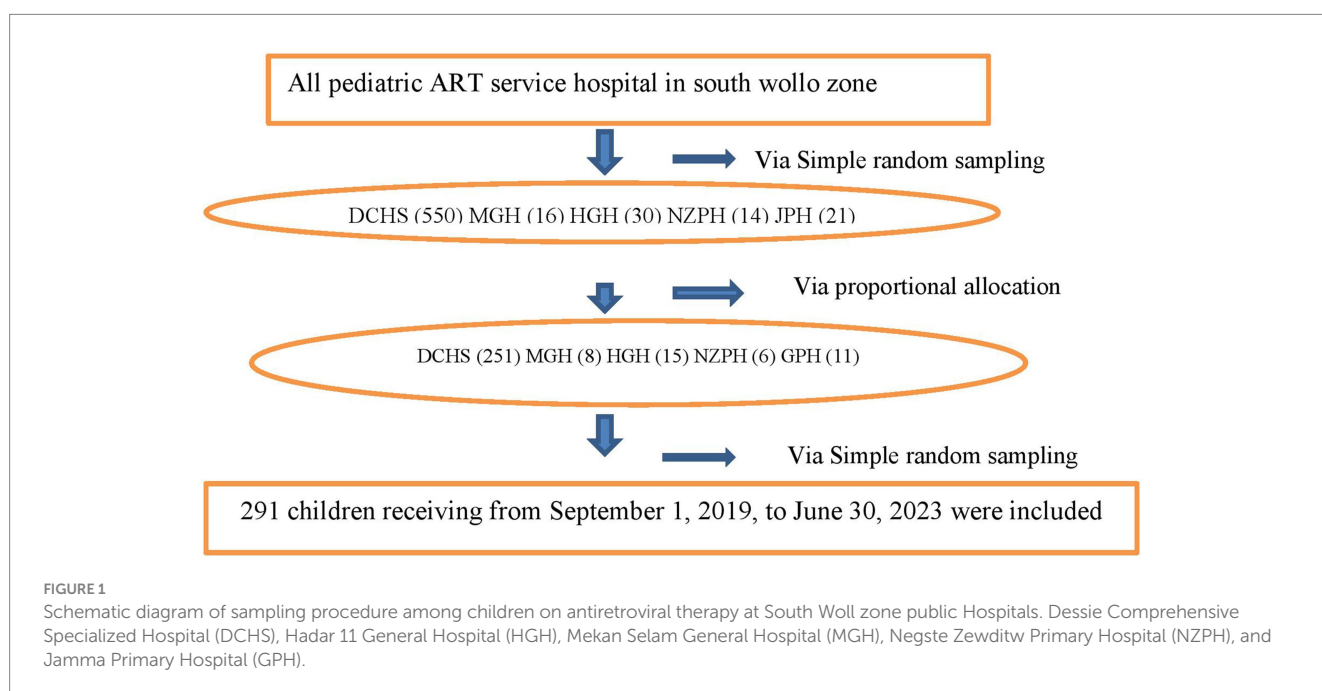
Where: n = the required sample size, $Z_{\alpha/2}$ = the standard normal variation, p = proportion (0.22) of the level of non-adherence, and d = margin of sampling error (0.05). By considering 10% of the incomplete or inconsistent data, the final sample size of our study was 291.

Sampling technique and procedure

From the South Wollo zone hospitals, Dessie Comprehensive Specialized Hospital, Akasta (Hadar 11) General Hospital, Mekan Selam General Hospital, Negste Zewditu Primary Hospital, and Jamma Primary Hospital were selected through a simple random sampling method. In each hospital, the sample size was allocated proportionally. Using the ART registration logbook as the sampling frame, a simple random sampling technique was applied. From September 1, 2019, to June 30, 2023, children on ART were enrolled in the following hospitals: Dessie Comprehensive Specialized Hospital (550 children), Akasta Hadar 11 General Hospital (30 children), Mekan Selam General Hospital (16 children), Negste Zewditu Primary Hospital (14 children), and Jamma Primary Hospital (21 children) (Figure 1).

Data collection procedure

The data collection checklist was developed using the Federal Ministry of Health's HIV/ART follow-up and intake records. Data were collected through face-to-face interviews and reviewing patients' documents using a structured checklist. The data extraction form



includes information on socio-demographic variables, treatment and additional drugs, clinical and laboratory data, etc. Under the direction of one MSc nursing practitioner, three BSc nurses with ART service experience and training collected data for 4 weeks in July 2023. Pre-testing was performed on 13 newborns (5% of the sample population) at Dessie Compressive Specialized Hospital before the real data-gathering process.

Study variables

Dependent variable: Adherence to first-line ART, which was classified as “non-adherent” or “adherent.”

Independent variables: age of the child, sex, residence, Caregiver knowledge, Caregiver marital status, Educational status, HIV disclosure Status, Weight for age, height for age, Hemoglobin (Hgb) level, CD4 counts or %, WHO clinical stages, Duration on ART, CPT (Co-trimoxazole Preventive Therapy), IPT (Isoniazid Preventive Therapy), Treatment failure, and TB status.

Operational definition

Level of ART adherence: the tools used to assess adherence for all participants were viral load monitoring, Self-reporting, Pill counts, and Pharmacy refill records.

To assess adherence using viral load, first measure the viral load before initiating ART to establish a baseline. This baseline helps in evaluating the treatment's effectiveness over time. Regular viral load tests, typically conducted every 3–6 months, should be scheduled to track the amount of HIV in the blood. Consistently low viral loads suggest good adherence and effective viral suppression. An undetectable viral load usually indicates that the treatment is working well. However, if the viral load remains low but detectable, it may imply some level of adherence but might also require further evaluation or adjustment of the treatment regimen. Conversely, a high viral load often indicates poor adherence (non-adherence), possible treatment failure, or drug resistance, necessitating a review of adherence strategies and potentially a change in therapy (1, 19, 20).

A 1-Month Self-Recall Report (Visual Analogue Scale): Caregivers were asked to mark on a calibrated line scale from 1 to 10, reflecting how they administered medications to the child over the past month. The marks were converted into percentages to estimate their drug administration adherence for the entire month. Adherence was classified as follows: a mark below 8.5 (<85%) indicated poor adherence, 8.5–9.4 (85–94%) indicated fair adherence, and 9.5 or above ($\geq 95\%$) indicated good adherence (21, 22).

Pill counts: counting the remaining pills in bottles during routine healthcare visits helps assess adherence (21). Adherence (%) = (Number of pills prescribed - Number of pills returned) $\times$ 100.

Pharmacy refill records: pharmacy refill records provide information on when individuals pick up their antiretroviral (ARV) drugs. Irregular pharmacy refill intervals may indicate non-adherence to antiretroviral therapy (ART). Calculation: Proportion of days covered (PDC) = (Number of days the patient

had medication) $\div$ (Number of days in the observation period) $\times$ 100.

Overall adherence measures combining these four adherence measures, an overall response rate of 95% or higher is considered good adherence, 85–94% is fair adherence, and below 85% is poor adherence (non-adherence) (19, 21–23).

Knowledge of caregiver on children ART adherent: caregivers who scored at or above the overall mean on the adherence knowledge assessment were categorized as having good knowledge, while those who scored below the mean were categorized as having poor knowledge (24, 25).

A CD4 count: CD4 below the threshold level was classified based on the age of the child (i.e. infants CD4 < 1,500/mm³, 12–35 months <750/mm³, 36–59 months <350/mm³ and ≥ 5 years <200/mm³) (26).

Underweight or stunting was defined as weight for age Z-score < -2 SD for under-five children and BMI for age Z-score < -2 SD for older children (26).

Tuberculosis: Cases were detected using sputum or stomach aspirate microscopy, chest X-ray examination, and/or histology, following the Ethiopian Ministry of Health's TB diagnosis guidelines (27).

ART treatment failure: when an antiretroviral regimen is unable to control HIV infection (21).

The World Health Organization (WHO) clinical staging system: categorizes HIV patients into four stages based on their immune deficiency and clinical symptoms (28).

Data processing and analysis

The data were entered into Epi Data version 4.1, and STATA 17 was used for the analysis. The table and figures provide an exploration of the descriptive and summary statistics. The outcome level of ART adherence was divided into two categories: “non-adhered” and “adhered.” For each predictor variable, the bivariate logistic regression model was fitted. Furthermore, a multivariate logistic regression model was fitted for those variables with a *p*-value of less than 0.25 in a bivariate analysis. Adjusted odds ratios with 95% confidence intervals and *p*-values were employed to assess the strength of the relationship to determine statistically significant predictors. Variables with a *p*-value of less than 0.05 in multivariable analysis were regarded as significant predictors of poor levels of adherence. The multicollinearity assumption was assessed using a correlation matrix, confirming that all correlations were below 0.8. Hosmer-Lemeshow test data and the Omnibus assumption were also used to check the model fitness.

Ethical approval and consent to participate

Approval was obtained from the Research and Ethical Review Committee of Wollo University College of Medicine and Health Sciences, with reference number CMHS/RCPGC/03/14. All hospital administrations and the ART clinic's focal person provided permission letters. Written informed consent was obtained from caregivers willing to participate in the study. The names or identification numbers of the children were not permitted to be recorded in the data. Furthermore, the study was conducted by the ethical principles of the Declaration of Helsinki.

Result

Socio-demographic characteristics of the study participants

Of 291 participants, 286 were involved in the study and five incomplete ones were discarded. As a result, 286 children were included in the analysis, yielding a completion rate of 98.3%. The mean age of the participants was 7.8 years old (± 3.64 SD), and half of the 146 (51%) children were male. More than half of the 176 (61.5%) children knew that they had HIV, and the vast majority (83.6%) lived in cities. Almost half of the 156 (54.5%) caregivers had a good understanding of the importance of ART (Table 1).

Clinical and treatment-related characteristics of children on ART

Approximately half of the 175 children (55%) had a CD4 count or percentage above the threshold. Sixty-one percent (61%) of the participants were in WHO stages I and II, while 16.8% had TB. Regarding ART duration, 252 participants (88.1%) had been on ART for more than 34 months. Additionally, 111 participants (39%) had anemia (hemoglobin <10 mg/dL). During data collection, viral load tests were conducted for 217 children (75.8%) within the past 12 months. Of these, 59 children (20.7%) had a high viral load ($\geq 1,000$ copies/mL) (Table 2).

Level of ART non-adherence

In this study, the overall proportion of ART non-adherence was 24.1% (95% CI: 19.2–29.0%) of the study participants.

Factors associated with poor adherence to ART

Bivariate and multivariate logistic regressions were used to fit all variables that met the chi-square assumption. In the bivariable logistic

TABLE 2 Clinical and treatment-related characteristics of children on antiretroviral therapy at South Wollo Zone Public hospitals, 2024.

Characteristics	Categories	Frequency	Percentage %
Weight for age	Normal	249	87%
	Underweight	37	13%
Height for age	Normal	251	88%
	Stunting	35	12%
CD4 counts or % level	Below threshold	129	45%
	Above threshold	157	55%
WHO clinical staging	I/II	174	61%
	III/IV	112	39%
Levels of HGB	> 10 mg/dL	111	39%
	≤ 10 mg/dL	175	61%
IPT	Given	205	72%
	Not given	81	28%
CPT	Given	154	54%
	Not given	132	46%
TB status positive	Yes	48	16.8%
	No	238	28%
Viral RNA copies per ml within 12 months	$\geq 1,000$ mL	59	20.7%
	$< 1,000$ mL	200	69.9%
	Not done	27	9.4%
Duration on ART	< 34 months	34	11.9%
	> 34 months	252	88.1%

Hemoglobin (Hgb) level, CPT (Co-trimoxazole Preventive Therapy), IPT (Isoniazid Preventive Therapy), antiretroviral therapy (ART), and Tuberculosis (TB).

regression analysis, age of the child, sex, residence, knowledge of the caregiver, HIV disclosure status, weight for age, height for age, HGB level, CD4 count or percentage, WHO stage, CPT user, IPT user, TB status, and duration of ART were each given a *p*-value of less than 0.25 and fitted into a multivariable logistic regression model. Positive TB status, diagnostic status not disclosure, and poor caregiver knowledge were found to be significantly associated with poor adherence at the multivariate level, with *p*-values of less than 0.05 (Table 3).

Discussion

Adherence is crucial for the success of antiretroviral therapy (ART), yet non-adherence remains a significant challenge, particularly among children receiving ART. This cross-sectional study aimed to assess the level of non-adherence to ART in children with HIV and identify the factors contributing to it.

According to our findings, the total proportion of ART non-adherence among the study participants was 24.1% (95% CI: 19.2 –29.0%). Furthermore, TB co-infection, HIV non-disclosure status, and poor caregiver knowledge were significantly related to poor adherence. This finding is consistent with research conducted in public hospitals in the northeast (21.4%) (11) and northwest (21.1%) (16) Ethiopia, Uganda (21%) (29), Nigeria (23.9%) (30), and Myanmar (23.8%) (31). However, this percentage is less than

TABLE 1 Socio-demographic characteristics of children on antiretroviral therapy at South Wollo Zone Public hospitals, 2024.

Characteristics	Categories	Frequency	Percentage
Age of the children (years)	< 5 years	47	16.4%
	5–9 years	36	12.6%
	≥ 10 years	203	71%
Sex	Male	146	51%
	Female	140	49%
Residence	Urban	37	13%
	Rural	249	87%
HIV disclosure status	Yes	176	61.5%
	No	110	38.5%
Knowledge of the caregiver about ART drugs	Good	156	54.5%
	Poor	130	45.5%

TABLE 3 Bivariate and multivariate analyses of factors associated with poor adherence to ART at South Wollo Zone Public Hospitals ($n = 286$).

Variable	Category	Level of adherence		COR, 95% CI	p -value	AOR, 95% CI	p -value
		Good	Poor				
Age of the children (years)	<5 years	35	12	1.13 (0.54–2.36)	0.72	–	
	5–9 years	26	10	1.27 (0.57–2.83)	0.54	–	
	≥10 years	156	47	1	–	–	
Sex	Male	112	34	1	–	–	
	Female	105	35	0.91 (0.53–1.56)	0.73	–	
Residence	Urban	23	14	1	–	1	0.21
	Rural	194	55	2.14 (1.03–4.45)	0.04	1.77 (0.75–4.17)	
Knowledge of the caregiver about ART drugs	Good	134	22	1	–	1	–
	Poor	83	47	3.44 (1.94–6.13)	0.00	2.18 (1.04–4.56)	0.03
HIV disclosure status	Yes	150	26	1	–	1	–
	No	67	43	3.70 (2.10–6.51)	0.00	2.69 (1.43–5.00)	0.00
Weight for age	Normal	195	54	1	–	1	–
	Underweight	22	14	2.46 (1.19–5.06)	0.01	1.34 (0.57–3.14)	0.49
Height for age	Normal	197	54	1	–	1	0.55
	Stunting	20	15	2.76 (1.31–5.70)	0.00	1.30 (0.53–3.18)	
CD4 counts or % level	Below threshold	96	33	1.15 (0.67–1.98)	0.60	–	
	Above threshold	121	36	1	–	–	
WHO clinical staging	I/II	138	36	1	–	1	–
	III/IV	79	33	1.60 (0.92–2.76)	0.09	1.07 (0.52–2.18)	0.16
Levels of HGB	> 10 mg/dL	135	40	1	–	–	
	≤10 mg/dL	82	29	1.19 (0.68–2.07)	0.52	–	
IP	Given	156	49	1	–	–	
	Not given	61	20	1.04 (0.57–1.89)	0.88	–	
CPT	Given	115	39	1	–	–	
	Not given	102	30	0.86 (0.50–1.49)	0.69	–	
TB status positive	Yes	19	29	7.55 (3.86–14.77)	0.00	4.10 (1.90–8.88)	0.00
	No	198	40	1	–	1	–
Duration on ART	<34 months	22	12	1	–	1	–
	>34 months	195	57	0.53 (0.25–1.14)	0.10	1.65 (0.65–4.19)	0.30

Bold values indicate statistically significant results ($p < 0.05$).

that of studies conducted in Jimma (36.2%) (32), Fiche Hospital (36%) (33), and Tikur Anbessa Hospital (65.2%) (10). On the other hand, this result is higher than that of research conducted in Ethiopia's Tigray region (15.2%) (25). This disparity could be explained by the differences in ART-adherence diagnostic techniques. Furthermore, inaccurate reporting is more common in low-income nations than in middle-income countries due to a shortage of skilled healthcare providers and caretakers. This variation considered socioeconomic level, study design, adherence measurement methods, sample size, and setting differences. This variation may reflect differences in local healthcare systems, patient demographics, or methodologies. Higher adherence rates in some studies could be due to better support systems, more effective adherence interventions, or differing standards of care. Conversely, the lower adherence rate could be linked to unique regional challenges or disparities in healthcare resources and support. These

differences highlight the need for context-specific strategies to address ART adherence and improve treatment outcomes across diverse settings.

This study result indicates that caregivers with poor knowledge about ART (antiretroviral therapy) drugs are 2.18 times more likely to experience non-adherence compared to those with better knowledge [AOR (: 95% CI) = 2.18 (1.04–4.56)]. This finding is consistent with the results of studies in the Oromia region (24), northeast Ethiopia (34), northern Ethiopia (25) and India (35). This result can be justified by the crucial role caregivers play in managing and supporting ART adherence. Caregivers with limited knowledge may struggle to understand the importance of adherence, proper medication administration, and potential side effects, which can lead to inconsistent or incorrect use of ART. This lack of knowledge can directly impact the effectiveness of the treatment and the patient's overall health, thereby increasing the likelihood of non-adherence.

Improving caregivers' knowledge about ART is essential for enhancing treatment adherence. Caregivers with a better understanding of ART are more likely to support proper medication use and adherence, which can lead to better health outcomes for the children. Therefore, targeted education and training programs for caregivers should be a priority to reduce non-adherence and improve the effectiveness of ART.

In this study, the odds of non-adherence among children with TB/HIV co-infection were more than four times higher than those in children without TB co-infection [AOR = 4.10, 95% CI (1.90–8.88)]. This finding is similar to those of investigations conducted in northwest Ethiopia (16), Nigeria (30), and Peru (36). The reason for this occurrence could be attributed to the administration of medication for the confection, therapy, and antiretroviral therapy in combination, which may lead to an increase in the number of pills required to be taken, interactions between drugs, and an increasing rise in the occurrence of unfavorable drug reactions. These factors collectively can hinder adherence to antiretroviral drugs (16). The increased risk of non-adherence in children with TB/HIV co-infection underscores the need for specialized support and management strategies. The interaction between treatments and the added burden of co-infection can significantly affect adherence. Targeted interventions and integrated care are crucial for improving adherence and overall treatment outcomes in these children.

This study found that children unaware of their HIV status (AOR = 2.69, 95% CI: 1.43–5.00) were more likely to exhibit poor adherence compared to those who were aware of their status. Similar findings have been reported in other studies (17, 18, 37, 38). Children who do not know their HIV status may lack understanding of the importance of their treatment regimen, which can result in lower motivation to adhere to prescribed ART. Awareness of their condition often encourages better adherence as it fosters a clearer understanding of the necessity of consistent medication for their health. This result aligns with similar studies, reinforcing the need for HIV status disclosure and education to improve adherence outcomes in pediatric patients (39). This result implies that HIV status disclosure is crucial for improving ART adherence in children.

Limitations of the study were we did not account for variables related to household dynamics, such as the quality of the caregiver-child relationship, instances of violence and maltreatment, or health system-related factors. Additionally, factors such as the mode of HIV transmission (vertical or acquired), alcohol abuse, depression, caregiver and patient education levels, the caregiver-patient relationship, age at first diagnosis, and parental HIV status were not considered, which may have influenced the results. Another limitation is that caregivers may inaccurately recall adherence behaviors or knowledge. Since the study was conducted in a specific region, the findings may not apply to other areas with differing healthcare systems, resources, or cultural contexts.

Conclusion and recommendation

According to the current study, the level of non-adherence to antiretroviral therapy remains high compared to the targets set by

the United Nations Joint Program on HIV/AIDS (UNAIDS) Project 95–95–95. TB status-positive (co-infection), diagnostic status not disclosed, and poor caregiver knowledge were discovered to be significantly related to poor adherence. Implement targeted education programs to improve caregiver knowledge about ART and its importance. Develop strategies to encourage and support the disclosure of diagnostic status to ensure better adherence. Strengthen integrated care approaches for children with TB/HIV co-infection to address the unique challenges they face in adhering to treatment. These measures can help improve adherence rates and overall health outcomes for affected children.

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 Wollo University and a permission letter was taken from South Wollo zone health office. 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 minors' legal guardians/next of kin.

Author contributions

EW: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. FB: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Writing – review & editing. MA: Formal analysis, Investigation, Methodology, Software, Supervision, Writing – review & editing. SM: Conceptualization, Investigation, Methodology, Project administration, Supervision, Writing – review & editing. GB: Conceptualization, Investigation, Methodology, Project administration, Resources, Supervision, Writing – review & editing. BD: Conceptualization, Data curation, Investigation, Methodology, Supervision, Writing – review & editing. MZ: Conceptualization, Data curation, Formal analysis, Project administration, Validation, Writing – review & editing. FA: Conceptualization, Investigation, Methodology, Software, Supervision, Writing – review & editing. EC: Formal analysis, Resources, Supervision, Visualization, Writing – review & editing.

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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.

References

1. WHO. HIV and AIDS. (2023). Available at: https://www.who.int/news-room/fact-sheets/detail/hiv-aids?gad_source=1&gclid=CjwKCAjw4_K0BhBsEiwAfVZ_-3ETu8iy6kBBPNHgRquo86fV2EQaei_a08vJdBT0yZeuMeK57Cm5xoCZksQAvD_BwE.
2. WHO. Available at: <https://www.who.int/teams/global-hiv-hepatitis-and-stis-programmes/hiv/treatment/treatment-and-care-in-children-and-adolescents>.
3. UNICEF. Children, HIV and AIDS: The world today and in 2030. (2019). Available at: <https://data.unicef.org/resources/children-hiv-and-aids-2030/>
4. Lulseged S. Pediatric HIV epidemic: status and prospects in Ethiopia. *Ethiopian journal of pediatrics and child health*. (2023) 18:1–4. doi: 10.4314/ejph.v18i1.1
5. Pegurri E, Konings E, Crandall B, Haile-Selassie H, Matinhure N, Naamara W, et al. The missed HIV-positive children of Ethiopia. *PLoS One*. (2015) 10:e0124041. doi: 10.1371/journal.pone.0124041
6. Unge C, Södergård B, Marrone G, Thorson A, Lukhwara A, Carter J, et al. Long-term adherence to antiretroviral treatment and program drop-out in a high-risk urban setting in sub-Saharan Africa: a prospective cohort study. *PLoS One*. (2010) 5:e13613. doi: 10.1371/journal.pone.0013613
7. Starace F, Massa A, Amico KR, Fisher JD. Adherence to antiretroviral therapy: an empirical test of the information-motivation-behavioral skills model. *Health Psychol*. (2006) 25:153–62. doi: 10.1037/0278-6133.25.2.153
8. AIDSinfo. Adherence to antiretroviral therapy in HIV-infected children and adolescents. (2021). Available at: <https://clinicalinfo.hiv.gov/en/guidelines/pediatric-arv/adherence-antiretroviral-therapy-hiv-infected-children-and-adolescents>.
9. CDC. CfDCAp. HIV treatment: How to adhere to antiretroviral therapy. (2021). Available at: <https://search.cdc.gov/search/?query=cfDCAp.%20hiv%20treatment%3A%20how%20to%20adverse%20antiretroviral%20therapy.%202021.&page=1>
10. Biressaw S, Abegaz WE, Abebe M, Taye WA, Belay M. Adherence to antiretroviral therapy and associated factors among HIV infected children in Ethiopia: unannounced home-based pill count versus caregivers' report. *BMC Pediatr*. (2013) 13:1–9. doi: 10.1186/1471-2431-13-132
11. Ketema AK, Shewangizaw WZ. Assessment of adherence to highly active antiretroviral therapy and associated factors among people living with HIV at Debrebirhan referral hospital and health center, Northeast Ethiopia: a cross-sectional study. *HIV AIDS (Auckl)*. (2015) 7:75–81. doi: 10.2147/HIV.S79328
12. Morowatisharifabad MA, Movahed E, Farokhzadian J, Nikoie R, Hosseinzadeh M, Askarishahi M, et al. Antiretroviral therapy adherence and its determinant factors among people living with HIV/AIDS: a case study in Iran. *BMC Res Notes*. (2019) 12:1–5. doi: 10.1186/s13104-019-4204-5
13. Nozaki I, Dube C, Kakimoto K, Yamada N, Simpungwe JB. Social factors affecting ART adherence in rural settings in Zambia. *AIDS Care*. (2011) 23:831–8. doi: 10.1080/09540121.2010.542121
14. Prendergast A, Tudor-Williams G, Jeena P, Burchett S, Goulder P. International perspectives, progress, and future challenges of paediatric HIV infection. *Lancet*. (2007) 370:68–80. doi: 10.1016/S0140-6736(07)61051-4
15. Davies M-A, Boule A, Fakir T, Nuttall J, Eley B. Adherence to antiretroviral therapy in young children in Cape Town, South Africa, measured by medication return and caregiver self-report: a prospective cohort study. *BMC Pediatr*. (2008) 8:1–12. doi: 10.1186/1471-2431-8-34
16. Gebreyesus F, Mitku D, Tareegn T, Temere B, Terefe T, Belete A, et al. Levels of adherence and associated factors among children on ART over time in northwest, Ethiopia: evidence from a multicenter follow-up study. *HIV/AIDS (Auckland, NZ)*. (2021) 13:829. doi: 10.2147/HIV.S323090
17. Feyera B, Letta S, Kumie A. Level of adherence and factors associated with antiretroviral therapy among HIV infected children in selected public hospitals, Addis Ababa, Ethiopia. *East African J Health Biomed. Sci*. (2016) 1:23–30.

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18. Mengesha MM, Embibel M, Gobena T, Tunje A, Jerene D, Hallström IK. Antiretroviral therapy non-adherence among children living with HIV in Dire Dawa, eastern Ethiopia: a case-control study. *BMC Pediatr*. (2022) 22:653. doi: 10.1186/s12887-022-03697-1
19. HIVinfo.NIH.gov. Guidelines for the use of antiretroviral agents in pediatric HIV infection (2024). Available at: <https://www.hiv.gov/>.
20. Ethiopia. National CONSOLIDATED guidelines for comprehensive HIV prevention, care and treatment (2018). Available at: <https://www.afro.who.int/sites/default/files/2019-04/National%20Comprehensive%20HIV%20Care%20%20Guideline%202018.pdf>.
21. Ethiopia. Federal Ministry of Health. National guidelines for comprehensive HIV prevention, care, and treatment (2017). 1226. Available at: <https://www.differentiatedservicedelivery.org/wp-content/uploads/POCKET-GUIDE-compressed-1.pdf>
22. Mussa FM, Massawe HP, Bhalloo H, Moledina S, Assenga E. Magnitude and associated factors of anti-retroviral therapy adherence among children attending HIV care and treatment clinics in Dar Es Salaam, Tanzania. *PLoS One*. (2022) 17:e0275420. doi: 10.1371/journal.pone.0275420
23. Alemayehu B, Etana B, Abebe M. Adherence to antiretroviral therapy and associated factors among children living with HIV in east Wallaga zone public health institutions, Ethiopia. *J Int Assoc Providers AIDS Care (JIAPAC)*. (2023) 22:23259582231215677. doi: 10.1177/23259582231215677
24. Gemechu GB, Hebo H, Kura Z. Children's adherence to antiretroviral therapy and associated factors: multicenter cross-sectional study. *HIV AIDS (Auckl)*. (2023) 15:423–34. doi: 10.2147/HIV.S407105
25. Tesfahunegn TB, Berhe N, Abraha TH, Hintsas S, Yohanes G, Desta K, et al. Adherence to antiretroviral therapy and associated factors among HIV-infected children in public health institutions of Adwa, Axum, and Shire towns of Tigray, Northern Ethiopia: A Cross-Sectional Study. *HIV AIDS (Auckl)*. (2023) 15:217–24. doi: 10.2147/HIV.S282938
26. Organization WH. Policy brief: Consolidated guidelines on HIV prevention, diagnosis, treatment and care for key populations. Geneva, Switzerland: World Health Organization (2017).
27. FMOH E. Guidelines for management of TB, DR-TB and leprosy in Ethiopia. Ethiopia Federal Ministry of Health Ethiopia: Addis Ababa (2018).
28. Weinberg JL, Kovarik CL. The WHO clinical staging system for HIV/AIDS. *AMA J Ethics*. (2010) 12:202–6. doi: 10.1001/virtualmentor.2010.12.3.cprl1-1003
29. Wadunde I, Tuhebwe D, Ediau M, Okure G, Mpimbaza A, Wanyenze RK. Factors associated with adherence to antiretroviral therapy among HIV infected children in Kabale district, Uganda: a cross sectional study. *BMC Res Notes*. (2018) 11:466. doi: 10.1186/s13104-018-3575-3
30. Ugwu R, Eneh A. Factors influencing adherence to paediatric antiretroviral therapy in Portharcourt, south-South Nigeria. *Pan Afr Med J*. (2014) 16. doi: 10.11604/pamj.2013.16.30.1877
31. Thandar M, Mon AS, Boonyaleepun S, Laohasiriwong W. Antiretroviral treatment adherence and associated factors among people living with HIV in developing country, Myanmar. *Int J Comm Med Public Health*. (2016) 3:1318–25. doi: 10.18203/2394-6040.ijcmph20161405
32. Abera A, Fenti B, Tesfaye T, Balcha F. Factors influencing adherence to antiretroviral therapy among people living with HIV/AIDS at ART Clinic in Jimma University teaching hospital, Southwest Ethiopia. *J Pharma Reports*. (2015) 1:2.
33. Feyissa A. Magnitude and associated factors of non-adherence to highly active antiretroviral therapy among children in fiche hospital, north Shewa, Ethiopia 2016. *J Pharm Care Health Syst*. (2017) 4

34. Arage G, Tessema GA, Kassa H. Adherence to antiretroviral therapy and its associated factors among children at south Wollo zone hospitals, Northeast Ethiopia: a cross-sectional study. *BMC Public Health*. (2014) 14:1–7. doi: 10.1186/1471-2458-14-365
35. Kendre GM, Gabhale YR, Shah ND, Jadhav VM, Nath K, Manglani MV. Adherence to antiretroviral therapy and factors affecting adherence among paediatric HIV patients. *Int J Contemp Pediatr Kendre*. (2017) 4:1962–8. doi: 10.18203/2349-3291.ijcp20174154
36. Leyva-Moral JM, Loayza-Enriquez BK, Palmieri PA, Guevara-Vasquez GM, Elias-Bravo UE, Edwards JE, et al. Adherence to antiretroviral therapy and the associated factors among people living with HIV/AIDS in northern Peru: a cross-sectional study. *AIDS Res Ther*. (2019) 16:1–12. doi: 10.1186/s12981-019-0238-y
37. Amankwah-Poku M, Klutsey DA, Asante KO. Disclosure and health-related outcomes among children living with HIV and their caregivers. *AIDS Res Ther*. (2021) 18:1–8. doi: 10.1186/s12981-021-00337-z
38. Ammon N, Mason S, Corkery J. Factors impacting antiretroviral therapy adherence among human immunodeficiency virus-positive adolescents in sub-Saharan Africa: a systematic review. *Public Health*. (2018) 157:20–31. doi: 10.1016/j.puhe.2017.12.010
39. Sumbi EM, Venables E, Harrison R, Garcia M, Iakovidis K, van Cutsem G, et al. “It’s a secret between us”: a qualitative study on children and care-giver experiences of HIV disclosure in Kinshasa, Democratic Republic of Congo. *BMC Public Health*. (2021) 21:1–9. doi: 10.1186/s12889-021-10327-5



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Socioeconomic determinants of low birth weight and its association with peripubertal obesity in Brazil

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Introduction: Low birth weight (LBW) is an early life adversity associated with various risk factors and metabolic dysfunction throughout life. However, the role of socioeconomic factors in the association between LBW and peripubertal health in low- and middle-income countries (LMICs) remains unclear. This ecological study investigated the factors contributing to LBW and its impacts in Brazil.

Methods: Data were collected from the Global Health Data Exchange as summary exposure values (SEVs), which serve as a proxy for population prevalence weighted by the relative risk. Additionally, information was sourced from official Brazilian government resources covering the years 1995 to 2017, resulting in a total of 338 state-year observations applied for temporal lagged analyses. First, we tested the SEV of 1-year lagged reproductive-age population (15–49 years) risk factors as exposures and the SEV of LBW as an outcome. In the second temporal lagged analysis, we tested the association between the SEV of LBW as the primary exposure and the SEV of high body mass index (HBMI) in peripubertal population 10 years later as the outcome. Fixed-effects multivariable linear regression models with lags were constructed, adjusting for socioeconomic covariates.

Results: The exposure of the reproductive-age population to smoking, alcohol, high systolic blood pressure, and HBMI was positively associated with the SEV of LBW. A diet high in sugar-sweetened beverages (SSB diet) was also positively associated, but the association disappeared when GDP per capita and access to primary care were added to the model. Regarding the repercussions of LBW, a 1-point increase in the SEV of LBW was associated with a 1.6-point increase in HBMI in the peripubertal population (95% CI: 0.66 to 2.55). However, this association disappeared after adjusting for GDP per capita and access to primary care, indicating their confounding roles.

Discussion: Our study highlights several risk factors in the adult population associated with LBW and its relationship with peripubertal HBMI. Interestingly, GDP per capita and access to primary care were found to be the socioeconomic determinants for birth outcomes as a result of exposure to the risk factors tested and the mid-term effects of LBW. These findings enhance our understanding of the role of socioeconomic factors contributing to LBW in LMICs and the need

for public policies addressing healthcare and welfare to reduce the burden of LBW in LMICs.

KEYWORDS

low birth weight, socioeconomic factors, peripubertal health, reproductive-age population, high body mass index, low- and middle income countries

1 Introduction

Low birth weight (LBW), whether due to preterm birth or fetal growth restriction, is one of the earliest outcomes of intrauterine malnutrition (1). It is defined as a birth weight lower than 2,500 g and is shown to increase the risk of death by over 20 times compared to normal-weight neonates (2). LBW is a well-known risk factor for several disorders, including overweight in both children and adults, type 2 diabetes, metabolic syndrome, and late cardiovascular disease (3, 4). The paradoxical condition of being born small, which leads to lasting effects of metabolic distress, has been studied since 1992, when Hales and Barker (5) established the thrifty phenotype concept after observing that birth weight influences the risk of type 2 diabetes and adiposity in adulthood. At a population level, another common paradoxical phenomenon is the double burden of malnutrition (DBM), i.e., the coexistence of undernutrition and overweight. This problem arises from the nutritional transitions exacerbating the demographic and epidemiological challenges in low- and middle-income countries (LMICs) (6).

Globally, one in four babies is born either prematurely or with low birth weight (1). In LMICs, intrauterine malnutrition is a prevalent issue, particularly due to the multifactor vulnerability to which the reproductive-age population is exposed (7). A joint report released in 2019 by the UNICEF and WHO indicated that between 2000 and 2015, an average of 75% of the world's LBW neonates were born in LMICs (8). In addition to posing a risk of death, LBW serves as a valuable public health indicator of maternal health, nutrition, and poverty (9). An adverse maternal intrauterine environment influenced by factors such as malnutrition, neighborhood disadvantage, smoking, or emotional stress leads to early, medium, and long-term repercussions (2–4, 9, 10). These effects can be explained by adaptive developmental plasticity, a permanent physiological change in the developmental trajectory influenced by external or internal factors, occurring through gene–environment interactions (11).

Brazil is an LMIC and a large continental nation in Latin America, with unique characteristics making it an appropriate setting to investigate sociodemographic and prenatal risk factors associated with LBW. Data from the Surveillance System of Risk and Protective Factors for Chronic Diseases by Telephone Survey (Vigitel) indicate that overweight affects over 50% of the Brazilian population, while specific subgroups have shown increasing prevalence of underweight, characterizing an active DBM. This phenomenon appears to be influenced by social factors such as educational attainment, socioeconomic status, and demographic disparities (12). Similarly, data from the Cardiovascular Risk Factors in Adolescents Study (ERICA) indicate that these social factors are associated with an average 26.3% prevalence of excessive weight in adolescents aged 12 to 17 years in the country (13), reinforcing the idea that environmental and social factors can lead to metabolic disorders. Although the association between LBW and DBM has been hardly explored, it is

reasonable to hypothesize the correlation between DBM and pubertal excessive weight in countries with a high prevalence of LBW.

In this regard, despite the consistent prevalence of LBW in Brazil, which nearly stands at 8.5% of all births (14), it remains unclear how the environmental and social factors influence the prevalence and the metabolic consequences of LBW. A broad understanding at the populational level of how modifiable factors lead to LBW and the subsequent repercussions of this condition on the health of future generations is essential for a thorough comprehension of its origins and for devising effective preventive strategies. Therefore, considering the life-long effects of LBW in general health, including late development of cardiometabolic diseases, and the scarcity of published data from LMICs, this study aimed to investigate the risk factors and socioeconomic covariates that potentially contribute to LBW occurrence and verify an outcome of this condition by determining the association between LBW and peripubertal excessive weight in Brazil.

2 Methods

2.1 Data source and study design

Data used in this ecological study were collected from publicly available datasets: the Global Health Data Exchange (GHDx), which is a comprehensive database on health-related variables also known as GBD study 2019 (15). Crude and age-standardized estimates of various measures of the burden of risk factors and LBW in Brazilian States from 1995 to 2017 were extracted from the GBD database¹ with no specific permissions required. In addition, official sources from the Brazilian government were used to collect data related to socioeconomic covariates, namely, poverty data that were collected from the Brazilian Ministry of Social Development, access to primary care and hospital support from the Brazilian Ministry of Health, and the Gini index and GDP per capita data from the Brazilian Institute of Geography and Statistics (IBGE).

GBD estimates incidence, prevalence, summary exposure value (SEV), mortality, years of life lost (YLLs), years lived with disability (YLDs), and disability-adjusted life-years (DALYs) due to 369 diseases and injuries, for both sexes, and for 204 countries and territories. Input data were extracted from censuses, household surveys, civil registration and vital statistics, disease registries, health service use, air pollution monitors, satellite imaging, disease notifications, and other sources (15). Among these estimations, SEV was used to compare the distribution of excess risk multiplied by exposure level to a population where everyone is at maximum risk. SEV represents a

¹ <http://ghdx.healthdata.org/gbd-results-tool>

prevalence-weighted measure of the relative risk associated with exposure to various disease-causing risk factors. The relative risk, derived from both primary research (published and unpublished) and secondary review studies, quantifies the likelihood of developing a disease or experiencing mortality or morbidity due to specific risk factor exposures. SEVs range from 0 to 100%, where 0 denotes the absence of excess risk in the population and 100% corresponds to the maximum level of exposure risk. An increasing SEV reflects a higher prevalence of the risk factor within the population, whereas a decreasing value indicates a reduction in its prevalence (16). Multivariable linear regression models were constructed from those datasets, as described in Section 2.4.

2.2 Risk factors

The prevalence of modifiable risk factors was computed as a summary exposure value (SEV) in GHDx 2019 (17), which denotes the prevalence weighted by the relative risk, demonstrating the extent of exposure by the risk level and the severity of that risk contribution to disease burden. Risk factors included are tobacco use (smoking), alcohol use (alcohol), low physical activity (LPA), diet high in trans fatty acids (TFA diet), diet high in sugar-sweetened beverages (SSB diet), increased levels of plasma glucose (glucose), high systolic blood pressure (HSBP), diet high in LDL cholesterol (HLDL), and high body mass index (HBMI). All data were age-standardized and stratified by sex.

2.3 Covariates

As previously described (18), we included the socioeconomic determinants and access to healthcare covariates in both models to bring the model closer to the social complexity in which individuals are included. The selected covariates were Gini index of household income, the main metric used for determining income inequality; gross domestic product (GDP) per capita in R\$ (Brazilian Reais), an income variable also capable of being associated with the population health (19); number of hospital beds per 1,000 inhabitants; and coverage of primary care (20) to account for access to healthcare. To assess poverty, Bolsa familia value in R\$ (Reais) per 1,000 individuals, a Brazilian state income transfer program for low-income families, was used (21). The covariates collected ranged from 2004 to 2016. To account for heteroskedasticity and autocorrelation, which are common when dealing with panel data, a correlation panel was created for each model including covariates and variables (Supplementary Tables 1, 2).

2.4 Statistical analysis

Multivariable linear regression models including data from all 26 Brazilian States, henceforth referred to as States, in different year-series totaling 338 State-year observations to each variable were performed using R software (22). Figure 1 summarizes the whole study population, data year-series, and covariates. Different models were constructed. First, a 1-year temporal lag model was utilized to assess the associations between reproductive-age population risk

factors (2004–2016), where each risk factor was used as an independent variable (predictor), and LBW (2005–2017), as a dependent variable. Then, a 10-year lag model was applied to evaluate the association between LBW (1995–2007) as an independent variable (predictor) and peripubertal high body mass index (HBMI) (2005–2017) as a dependent variable (outcome). Data were stratified by sex. Reproductive-age population was defined as men and women aged between 15 and 49 years (17), while peripubertal population was defined as boys and girls aged 10 to 14 years. For all variables and covariates in the selected time series, the retrieved dataset was complete, with no missing data. While risk factors and LBW were expressed as SEVs, other aforementioned covariates were expressed as prevalence and assumed as potential confounders.

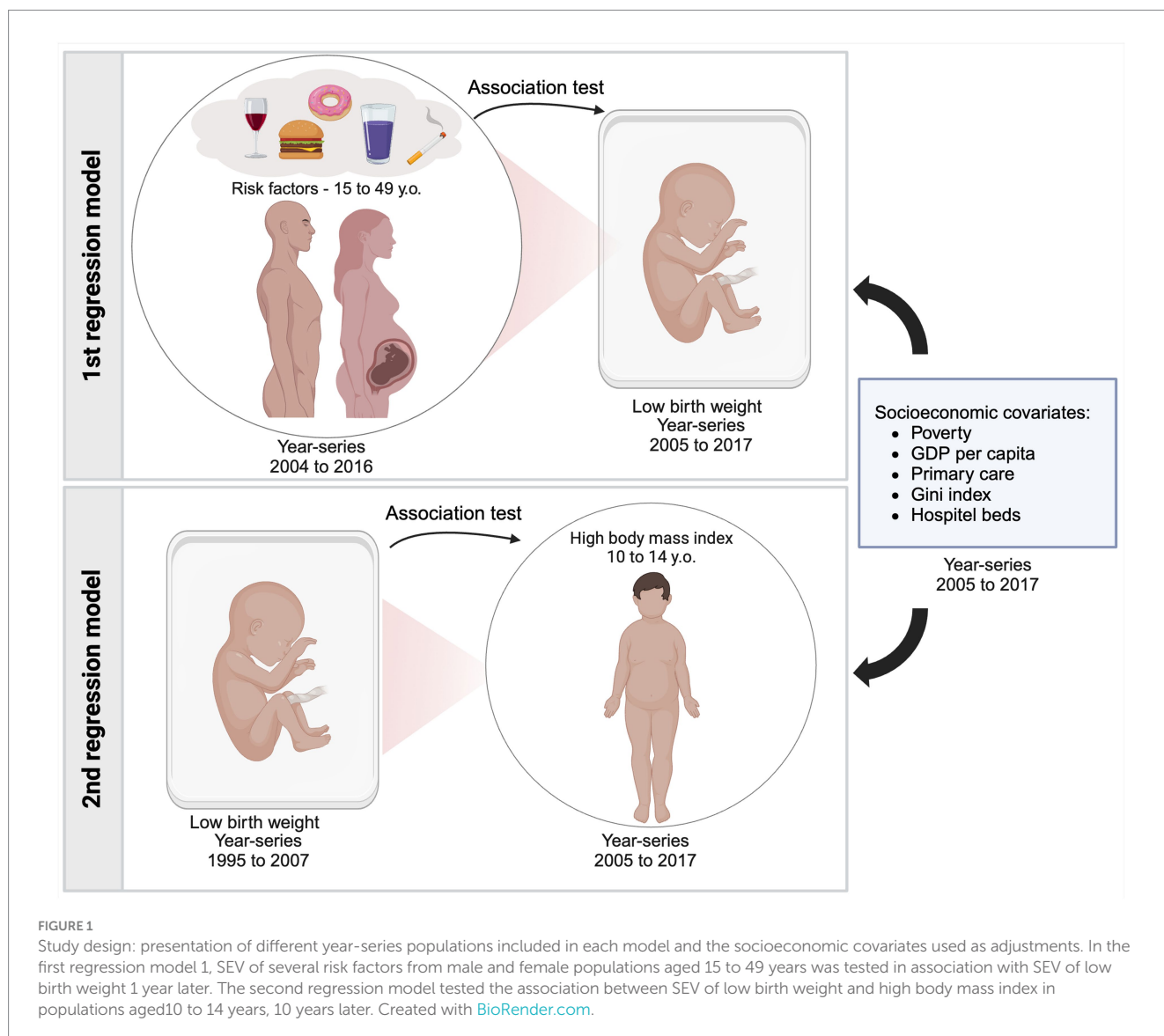
As a standard procedure for data processing, the analysis began with testing the crude association between the predictor and the outcome, without adjustment for covariates. If a positive association was observed, a new model was created by including all adjustment covariates. In cases where this adjustment consistently blocked the association, a stepwise adjustment procedure was applied, where covariates were added individually to the model. This stepwise approach allowed for identifying specific covariates responsible for blocking the association. In the context of multivariable linear regression analysis, this method facilitates in determining the covariate primarily influencing changes in the association. By isolating this key covariate, it is possible to identify its role in altering the outcomes and analyze the interplay between different exposures and their effects on the results (23).

State-fixed effects were employed to account for intrinsic cultural, geographical, and historical characteristics that may vary across States but are fixed over time. The fixed-effects model is a robust and conservative analytical instrument well suited for examining aggregated health data (18) and was estimated using ordinary least square (OLS), which is employed to predict unknown parameters in a linear regression model. The use of the fixed-effects model aided in reducing the likelihood of multiplicity in the model. The output of the model can be interpreted as changes in the dependent variable associated with a 1-point change in the SEV for a given risk factor over time and is presented as the estimated coefficients and their associated 95% confidence interval (2.5 and 97.5% bounds).

3 Results

3.1 Association between reproductive-age population risk factors and LBW

To assess whether the exposure of male and female reproductive-age populations to several risk factors would be associated with SEV of LBW of newborn boys and girls 1 year after the exposure, a 1-year temporal lag model was created and applied. A summary of the State-level data on risk factors, socioeconomic determinants, and SEV of LBW is presented in Supplementary Tables 3, 4. As shown in Table 1, multivariable linear regression analyses showed a direct positive association of alcohol, tobacco, and SSB diet with SEV of LBW for both sexes. HBMI is also positively associated with SEV of LBW, except for HBMI in men and SEV of LBW in boys. Regarding HSBP, reproductive-age women showed a significant association with SEV of LBW for both girls and boys, while



for men, HSBP was associated with SEV of LBW in boys but not girls (Table 1).

To enhance the robustness and accuracy of the analyses, the effects of socioeconomic covariates, Gini index, GDP per capita, hospital beds per 1,000 inhabitants, coverage of primary care, and poverty were incorporated as adjustments to the model, corresponding to the risk factors already identified as associated with LBW in Table 1. With such adjustments, as shown in Figure 2A, SEV for smoking was the only risk factor of the male population that sustained the association with LBW in both girls (0.26; 95% CI 0.06 to 0.4) and boys (0.31; 95% CI 0.1 to 0.5). In addition to smoking, SEV of HSBP in men was also associated with LBW, but only in girls (0.07; 95% CI 0.007 to 0.14). For the female population, several risk factors preserved the positive association with LBW for both girls and boys, which include SEVs of smoking (girls 0.28; 95% CI 0.1 to 0.4 and boys 0.24; 95% CI 0.1 to 0.37), alcohol (girls 0.43; 95% CI 0.01 to 0.8 and boys 0.6; 95% CI 0.26 to 1.00), and HSBP (girls 0.02; 95% CI 0.05 to 0.11 and boys 0.12; 95% CI 0.01 to 0.24). However, SEV of HBMI in women was associated with LBW only in boys (0.10; 95% CI 0.01 to 0.18) (Figure 2A).

High SSB diet was the only positive association to be lost after full adjustment with covariates, representing a consistent response for both male and female reproductive-age populations despite the newborn sex (Figure 2A). Therefore, we performed further analyses employing stepwise addition of individual socioeconomic determinants, allowing the identification of potential covariates that may be confounding the association. Figure 2B shows that the SEV for the number of hospital beds, Gini index, and poverty did not change the positive association between SSB diet and LBW. On the other hand, stepwise adjustment for SEV coverage of primary care for men (girls 0.05; 95% IC −0.05 to 0.1 and boys 0.09; 95% IC −0.007 to 0.2) and women (girls 0.03; 95% IC −0.04 to 0.1 and boys 0.07; 95% IC −0.001 to 0.1) at reproductive age avoided the association with LBW in newborns from both sexes. Similarly, adjustment for SEV of GDP per capita blocked the association of SEV of SSB diet in men with LBW in newborn boys (0.1; 95% IC −0.01 to 0.32) and girls (0.1; 95% IC −0.06 to 0.3), while in women, it only prevented the association with LBW in girls (0.07; 95% IC −0.041 to 0.1) (Figure 2B).

Altogether, our data regarding socioeconomic and modifiable risk factors among male and female reproductive-age populations leading

TABLE 1 Multivariable linear regression from several risk factors of the male and female reproductive-age population with SEV of LBW in newborn boys and girls.

Reproductive-age risk factors	Newborn girls		Newborn boys	
	Coefficient (95% CI)	p-value	Coefficient (95% CI)	p
Women				
Alcohol	0.71 (0.23; 1.19)	0.003	0.92 (0.48; 1.37)	0.0001
SSB diet	0.08 (0.02; 0.14)	0.007	0.11 (0.06; 0.16)	0.0001
TFA diet	0.05 (−0.42; 0.14)	0.281	0.04 (−0.05; 0.13)	0.395
HBMI	0.15 (0.04; 0.27)	0.008	0.18 (0.10; 0.27)	0.0001
Glucose	−0.35 (−1.4; 0.69)	0.508	−0.35 (−1.2; 0.49)	0.411
HDL	−0.02 (−0.40; 0.34)	0.883	0.10 (−0.31; 0.52)	0.618
HSBP	0.23 (0.11; 0.35)	0.0001	0.21 (0.10; 0.33)	0.0001
LPA	−0.07 (−0.38; 0.23)	0.62	−0.26 (−0.59; 0.06)	0.11
Smoking	0.31 (0.18; 0.43)	0.0001	0.32 (0.19; 0.45)	0.0001
Men				
Alcohol	0.48 (0.09; 0.86)	0.01	0.65 (0.28; 1.03)	0.0005
SSB diet	0.1 (0.02; 0.19)	0.01	0.14 (0.07; 0.21)	0.0001
TFA diet	0.06 (−0.01; 0.14)	0.092	0.07 (0; 0.15)	0.057
HBMI	0.11 (−0.01; 0.25)	0.07	0.15 (0.04; 0.27)	0.005
Glucose	−0.05 (−1.0; 0.9)	0.918	−0.05 (−0.72; 0.71)	0.988
HDL	−0.06 (−0.36; 0.35)	0.97	0.14 (−0.22; 0.51)	0.448
HSBP	0.12 (0.00; 0.24)	0.051	0.11 (0.05; 0.23)	0.03
LPA	0.01 (−0.23; 0.26)	0.91	−0.07 (−0.35; 0.2)	0.50
Smoking	0.32 (0.15; 0.49)	0.0002	0.37 (0.23; 0.52)	0.0001

Bold values correspond to statistically significant *p*-values (*p* ≤ 0.05).

to LBW 1 year later supporting a sexually dimorphic association, once variables in women, such as HBMI and HSBP, appear to be more steadily associated with LBW in women than in men. Moreover, the exposure to SSB diet *per se* is associated with LBW, albeit the improvement of primary care or GDP per capita is possibly able to nullify it.

3.2 Association between LBW and peripubertal high body mass index

After analyzing the risk factors associated with LBW, we next proceeded to investigate how/whether LBW *per se* is associated with HBMI in the peripubertal age population. Thus, the second model data from SEV of LBW in newborn girls and boys and SEV of HBMI in peripubertal girls and boys using the same time series were applied in the multilinear models as shown in Figure 3. Between 1995 and 2007, the countrywide average SEV of LBW decreased by 17% in female (7.8 to 6.6, Figures 3A,B) and 15% in male (7.18 to 6.11, Figures 3C,D) neonates. In the meantime, the 10-year lagged (2005 to 2017) countrywide average SEV of HBMI in adolescents aged 10 to 14 years increased by 43% in girls (19 to 27.1, Figures 3E,F) and 52% in boys (17.7 to 27, Figures 3G,H), depicting an inversely proportional behavior of those variables over time in Brazil.

To test the State-fixed association between LBW and pubertal HBMI, crude and multivariable linear regressions were performed

adjusting for covariates models, as previously described. When unadjusted, each 1-point increase in SEV of LBW was associated with a consistent increase of peripubertal SEV of HBMI in girls (1.6; 95% CI 0.66 to 2.55) and boys (2; 95% CI 0.8 to 3.2) (Figure 4). However, in multivariable analysis including all covariates, such association was lost, regardless of sex. To recognize the socioeconomic covariates that exerted a greater influence in the adjustment, the stepwise addition of covariates was performed. The individual adjustment for poverty, hospital beds, or Gini index did not block the association between LBW and HBMI between 10 and 14 years. Meanwhile, after adjusting for GDP per capita, both girls (0.2; 95% CI −0.5 to 1) and boys with LBW (0.3; 95% CI −0.4 to 1.1) were no longer associated with peripubertal HBMI. A similar result was obtained after adjusting for the coverage of primary care for both girls (0.6; 95% CI −0.4 to 1.7) and boys (1.1; 95% CI −0.07 to 2.2), suggesting that GDP per capita and primary care appear to be confounders to the burden of peripubertal HBMI among girls and boys born small (Figure 4).

4 Discussion

The current study has shed light on the role of income per capita and access to primary care regarding the LBW rates in Brazil. Moreover, these social determinants also acted in the double burden of malnutrition, influencing LBW and peripubertal HBMI 10 years

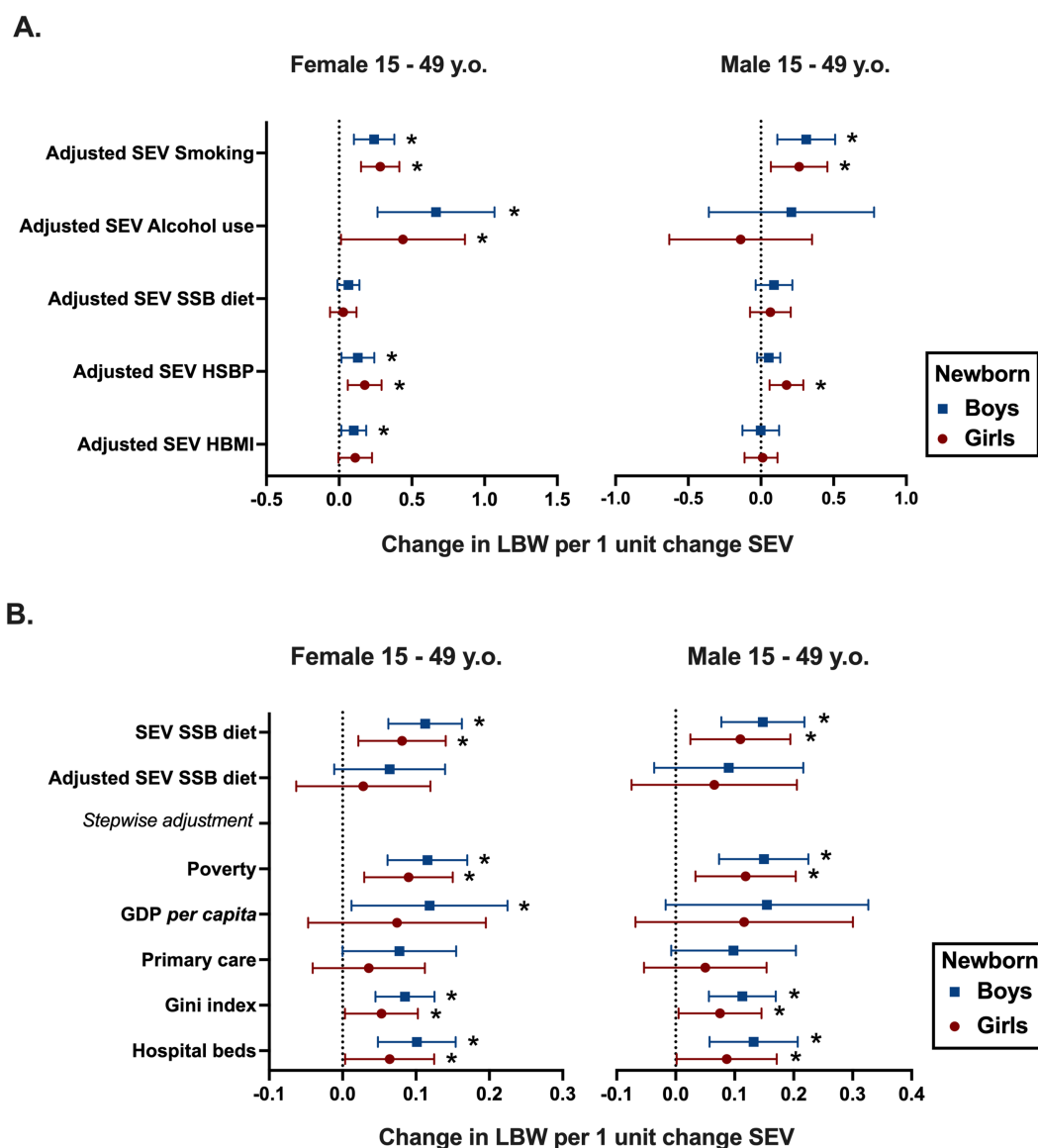


FIGURE 2

Risk factors of the female and male reproductive-age population (15–49 years old) associated with LBW in Brazilian States. (A) Multivariable linear regression analysis shows the risk factors of the male and female reproductive-age population associated with SEV of LBW in newborn boys and girls when fully adjusted for socioeconomic covariates. (B) Fully adjusted and Unadjusted regression models of SEV SSB diet with SEV LBW, followed by Stepwise adjustment from female and male population. Socioeconomic covariates: Gini index of household income; gross domestic product (GDP) per capita in R\$ (Brazilian Reais); number of hospitals beds per 1,000 inhabitants; coverage of primary care; and Log Bolsa familia as poverty. The variables State- and year-fixed effects are included in the model. Risk factors are exhibited as follows: smoking as tobacco use, alcohol use, HSBP as high systolic blood pressure, SSB diet as diet high in sugar-sweetened beverages, and HBMI as high body mass index. * $p < 0.05$.

later. This main result is supported by the evidence that the association between the exposure of reproductive-age population to an SSB-rich diet and the occurrence of LBW was decreased in models including GDP per capita or coverage of primary care, which also prevented the association between LBW and HBMI 10 years later. It is noteworthy that these covariates blocked the association between the exposure of reproductive-age men and LBW in neonates from both sexes, highlighting the negative impact of paternal exposure on fetal health outcomes. Overall, the findings herein presented emphasize the need for public health policies addressing the reproductive-age population from both sexes to prevent LBW and its repercussions for future generations, especially in LMICs.

The detrimental effects of maternal smoking, alcohol use, HSBP, and HBMI prior to or during pregnancy on fetal health have been well documented, with evidence demonstrating a higher risk of preterm birth and LBW in several populations (24–33). On the other hand, emerging data have also highlighted the role of paternal preconception exposure to diverse risk factors negatively impacting fetal growth and lifelong health outcomes in the offspring (34–36). Therefore, considering both male and female exposure, we first created models directly associating female and male reproductive-age population risk factors with LBW, without adjustments. Our findings based on Brazilian States data align with those of previous studies. They supported a positive association of both male and female exposure to

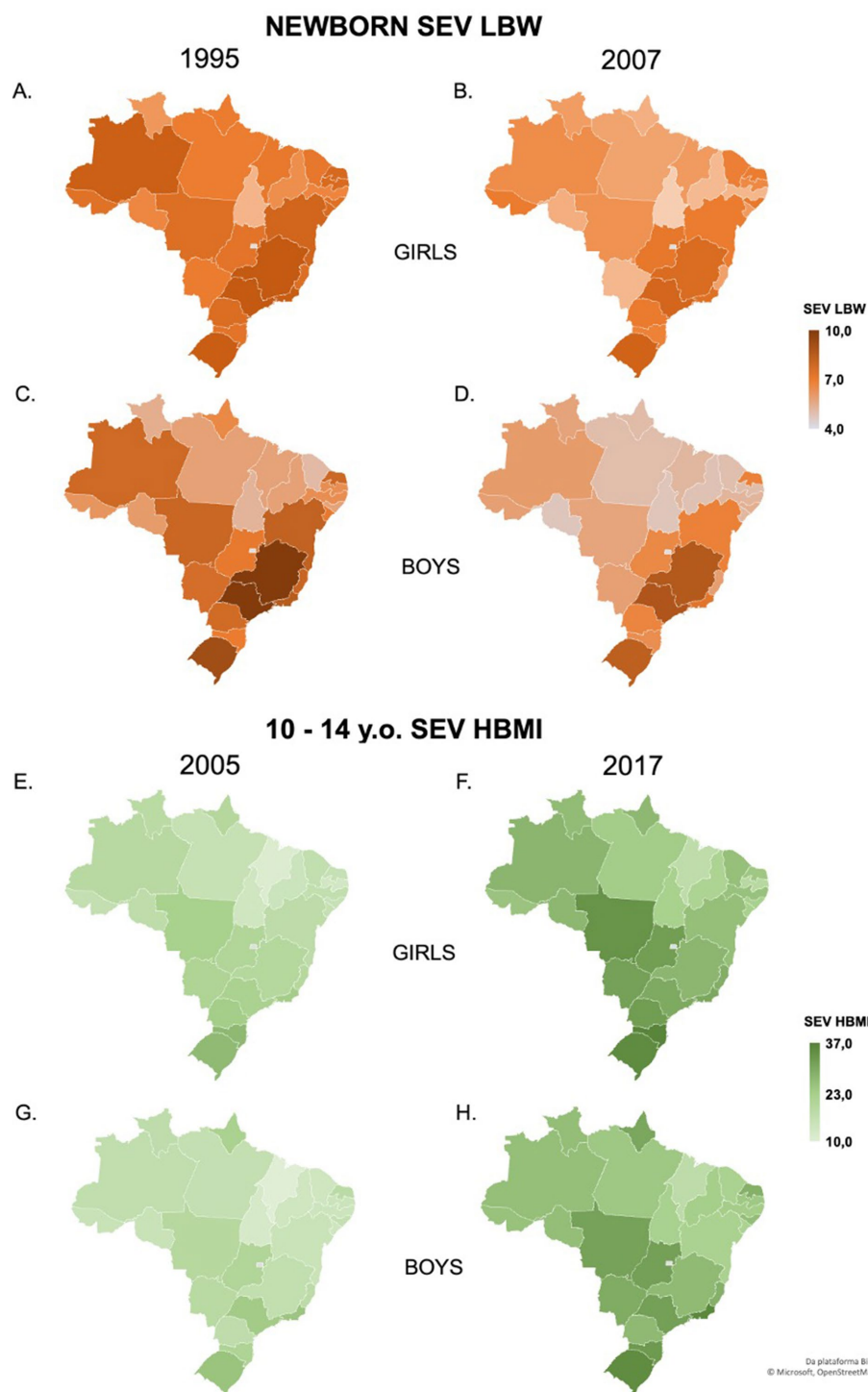


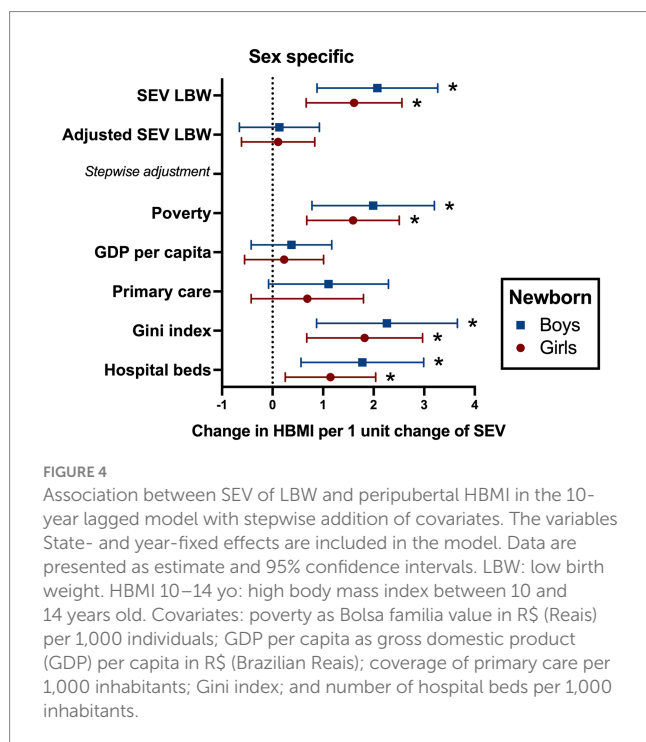
FIGURE 3

Summary exposure value (SEV) distribution of male and female SEV of LBW and peripubertal SEV of HBMI in Brazilian States in the 10-year lagged model. The maps display the SEV of LBW from 1995 (A) to 2007 (B) for girls, and 1995 (C) to 2007 (D) for boys. SEV of HBMI 10–14 years old from 2005 (E) to 2017 (F) for girls and 2005 (G) to 2017 (H) for boys. LBW: low birth weight; HBMI: high body mass index. Data were obtained from the Global Health Data Exchange (GHDx).

smoking, alcohol use, and HSBP with SEV LBW 1 year later, corroborating the association between LBW and male exposure to such risk factors.

Regarding HBMI in reproductive-age population, our results showed that pre-existent excess weight in women is positively

associated with LBW, corroborating with previous studies from Korean, Polish, and Danish populations which showed that maternal preconceptional obesity increased the risk of LBW (24, 37, 38). When associating HBMI in men with LBW, we found a positive association with newborn boys, but not for newborn girls,



suggesting a sex-specific role for paternal HBMI on LBW. Noteworthy, some studies have found a positive association between postconceptional obesity and maternal gain during gestation and a higher risk of the offspring being born large for gestational age or macrosomic (39, 40). Such data support distinct roles for the impact of maternal obesity on birth weight, depending on the time it occurs. Meanwhile, data concerning the impact of paternal obesity on such outcomes are still elusive despite the current debate about the paternal origins of health and disease (POHaD) (35, 36).

Transgenerational inheritance depends on genetic, epigenetic, and environmental aspects, varying in different populations, socioeconomic scenarios, and the aforementioned risk factor exposures (41). Thus, to bring our model closer to a real environment, socioeconomic adjustments at State-level data were added. In accordance with the historical association of maternal smoking or alcohol use with LBW in several populations (25, 30, 41–44), our data sustained this positive association even after adjustments were added. However, for alcohol use in men, the association with LBW was lost when socioeconomic data were added. Notwithstanding, when adjusted, female HSBP remained associated with LBW, corroborating the recent findings by Ishikuro et al. (32) in the Japanese population. Despite the inherent limitations of our population-based dataset, which precluded us from directly linking parents and offspring within individual-level associations, it does allow us to speculate that the same health- and lifestyle-associated risk factors apply for the understanding of preconceptional etiology of LBW and their role as transgenerational risk factors for non-communicable chronic diseases.

Considering malnutrition as one of the fundamental aspects of the environment, it is crucial to not reduce it to calorie intake, since it includes the assessment of macro- and micronutrient intake, as well as healthy or unhealthy food consumption, as classified by the Prime Diet Quality Score (PDQS) (28, 45). Unhealthy food includes

SSB diet, and their inadequate consumption during pregnancy can impair fetal growth and development (28, 46). In a prospective study on Norwegian women, Englund-Ögge et al. (47) demonstrated that the lower the maternal education level, the higher is the positive association with maternal SSB intake, maternal HBMI, and preterm birth. Similarly, our unadjusted model showed that exposure of men and women to a diet high in SSB was positively associated with LBW, even though this association was lost when all the socioeconomic covariates were added. On the other hand, stepwise adjustments identified GDP per capita and access to primary care as the covariates responsible for preventing the association between a diet high in SSB and LBW in the Brazilian States, strengthening the evidence that socioeconomic status can modulate the impact of SSB ingestion on gestational outcomes.

Social disadvantage, especially low income, has been associated with intrauterine impairment of brain development, while increasing the access to social welfare programs as a way to reduce the burden of social disadvantage has the capacity to detain such outcomes (10, 48). This finding aligns with our results since access to primary care and GDP per capita played a pivotal role in the association of the exposure of reproductive-age population to SSB with LBW, highlighting the relevance of socioeconomic status and healthcare for perinatal health. Although the data presented herein are not sufficient to assert the overall protective effect of increased access to primary care and higher income per capita against LBW occurrence, they consistently suggest that in a context of high SSB intake, they may protect the fetus from being born small, a major consequence of intrauterine malnutrition, with a positive impact on its lifelong health status.

When investigating the mid-term repercussions of being born small, there was a positive association between LBW and HBMI in peripubertal girls and boys 10 years later, which was lost if income per capita and access to primary care were added to the model. This finding is corroborated by the concept of the developmental origins of health and disease (DOHaD), which has long hypothesized and examined the biological relationship between LBW and body weight gain throughout the lifespan (49, 50). Numerous studies have implicated LBW as a risk factor for obesity development in different population groups (4, 49, 51–53). However, this study puts a spotlight on the unique role of primary care and GDP per capita in attenuating the association between being born with LBW and increasingly gaining weight over time. According to our data, Brazilian States with better access to primary care and higher income per capita were able to mitigate the mid-late metabolic effects of low birth weight, which supports the increasing notion that LBW is not a deterministic condition in terms of health or disease but rather a risk factor. LBW may lead to either a negative or non-negative outcome, depending on genetic, environmental, and socioeconomic status, as we have presented (4, 54–56).

Brazil is an LMIC historically marked by poverty and income inequality, with above 50% of the population facing some level of food insecurity (57), which helps explain the consistent rates of LBW over the years (~8.5%) (14). However, there are scarce data on the health status of those LBW newborns throughout their life cycle. Having said that, studies including long-term follow-up of children born small to assess the lasting effects of this condition in different scenarios are needed, as well as interventional research aiming to circumvent the metabolic disability. In addition to the limitations of our study,

including that analyzed data were from a few years ago, because of lacking some recent year-series information in Brazilian sources, the study's findings advocate for comprehensive public health interventions aimed at preventing the reproductive-age population exposure to well-known risk factors causing intrauterine malnutrition. Nonetheless, our data highlight the intricate interplay of socioeconomic factors and healthcare in influencing birth outcomes and call for targeted strategies to enhance male and female healthcare, ultimately fostering healthier outcomes for both mothers and their offspring.

Overall, this study provides evidence from an LMIC, Brazil, where alcohol consumption, smoking, high systolic blood pressure, high body mass index, and diet high in sugar-sweetened beverages in the population between 15 and 49 years old were associated with LBW in a State level. In addition, LBW is associated with a high body mass index of children between 10 and 14 years old. Remarkably, in both models, income and primary care played a pivotal role, suggesting that rich societies with high access to healthcare were favored to overcome the harmful effects of LBW on peripubertal metabolic health.

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

Ethical approval was not required for the studies involving humans because this study did not require approval from an Ethics Committee since only data from publicly available secondary databases were used. 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 because this study did not require approval from an Ethics Committee since only data from publicly available secondary databases were used.

Author contributions

FL-S: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Validation, Writing – original draft, Writing – review & editing. RG: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software,

Validation, Writing – original draft, Writing – review & editing. SA-C: Data curation, Formal analysis, Validation, Writing – review & editing. CR: Methodology, Supervision, Validation, Writing – review & editing. AP: Conceptualization, Funding acquisition, Project administration, Resources, Supervision, Validation, Writing – review & editing.

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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.

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Supplementary material

The Supplementary material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fpubh.2025.1424342/full#supplementary-material>

References

- Ashorn P, Ashorn U, Muthiani Y, Aoubaker S, Askari S, Bahl R, et al. Small vulnerable newborns—big potential for impact. *Lancet*. (2023) 401:1692–706. doi: 10.1016/S0140-6736(23)00354-9
- 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
- Miguel PM, Pereira LO, Silveira PP, Meaney MJ. Early environmental influences on the development of Children's brain structure and function. *Dev Med Child Neurol*. (2019) 61:1127–33. doi: 10.1111/dmcn.14182
- Power C, Li L, Manor O, Smith GD. Combination of low birth weight and high adult body mass index: at what age is it established and what are its determinants? *J Epidemiol Community Health*. (2003) 57:969–73. doi: 10.1136/jech.57.12.969

5. Hales CN, Barker DJ. Type 2 (non-insulin-dependent) diabetes mellitus: the thrifty phenotype hypothesis. *Diabetologia*. (1992) 35:595–601. doi: 10.1007/BF00400248
6. Popkin BM, Corvalan C, Grummer-Strawn LM. Dynamics of the double burden of malnutrition and the changing nutrition reality. *Lancet*. (2020) 395:65–74. doi: 10.1016/S0140-6736(19)32497-3
7. Marete I, Ekhuagere O, Bann CM, Bucher SL, Nyongesa P, Patel AB, et al. Regional trends in birth weight in low-and middle-income countries 2013–2018. *Reprod Health*. (2020) 17:1–8. doi: 10.1186/s12978-020-01026-2
8. World Health Organization. Unicef-who low birthweight estimates: Levels and trends 2000–2015. Geneva: World Health Organization (2019).
9. Collins JW, Wambach J, David RJ, Rankin KM. Women's lifelong exposure to neighborhood poverty and low birth weight: A population-based study. *Matern Child Health J*. (2009) 13:326–33. doi: 10.1007/s10995-008-0354-0
10. Lean RE, Smyser CD, Brady RG, Triplett RL, Kaplan S, Kenley JK, et al. Prenatal exposure to maternal social disadvantage and psychosocial stress and neonatal white matter connectivity at birth. *Proc Natl Acad Sci*. (2022) 119:e2204135119. doi: 10.1073/pnas.2204135119
11. Lu A, Petrullo L, Carrera S, Feder J, Schneider-Crease I, Snyder-Mackler N. Developmental responses to early-life adversity: evolutionary and mechanistic perspectives. *Evol Anthropol*. (2019) 28:249–66. doi: 10.1002/evan.21791
12. Meller FO, Schäfer AA, Santos LP, Quadra MR, Miranda VIA. Double burden of malnutrition and inequalities in the nutritional status of adults: A population-based study in Brazil, 2019. *Int J Public Health*. (2021) 66:609179. doi: 10.3389/ijph.2021.609179
13. Lima NMS, Leal VS, Oliveira JS, Andrade MIS, Santos NF, Pessoa JT, et al. Excess weight in adolescents and associated factors: data from the Erica study. *J Pediatr*. (2021) 97:676–84. doi: 10.1016/j.jpeds.2021.02.008
14. Saúde M. Sistema De Informação Sobre Nascidos Vivos. (2022). Available online at: <http://tabnet.datasus.gov.br/cgi/tabcgi.exe?sinasc/cnv/nvuf.def> (Accessed November 12, 2023).
15. Vos T, Lim SS, Abbafati C, Abbas KM, Abbasi M, Abbasifard M, et al. 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
16. Murray CJ, Aravkin AY, Zheng P, Abbafati C, Abbas KM, Abbasi-Kangevari M, et al. 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
17. Global Burden of Disease Collaborative Network. Global Burden of Disease Study 2019 (GBD 2019) Reference Life Table. Seattle, United States of America: Institute for Health Metrics and Evaluation (IHME) (2021). doi: 10.6069/1D4Y-YQ37
18. Gaspar RS, Rossi L, Hone T, Dornelles AZ. Income inequality and non-communicable disease mortality and morbidity in Brazil states: A longitudinal analysis 2002–2017. *Lancet Regl Health Am*. (2021) 2:100042. doi: 10.1016/j.lana.2021.100042
19. Backlund E, Sorlie PD, Johnson NJ. The shape of the relationship between income and mortality in the United States: evidence from the National Longitudinal Mortality Study. *Ann Epidemiol*. (1996) 6:12–20. doi: 10.1016/1047-2797(95)00090-9
20. Hone T, Saraceni V, Medina Coeli C, Trajman A, Rasella D, Millett C, et al. Primary healthcare expansion and mortality in Brazil's urban poor: A cohort analysis of 1.2 million adults. *PLoS Med*. (2020) 17:e1003357. doi: 10.1371/journal.pmed.1003357
21. Shei A, Costa F, Reis MG, Ko AI. The impact of Brazil's Bolsa Familia conditional cash transfer program on Children's health care utilization and health outcomes. *BMC Int Health Hum Rights*. (2014) 14:1–9. doi: 10.1186/1472-698X-14-10
22. R Development Core Team. R: A language and environment for statistical Computing. Vienna: R Foundation for Statistical computing (2010).
23. Wallisch C, Dunkler D, Rauch G, De Bin R, Heinze G. Selection of variables for multivariable models: opportunities and limitations in quantifying model stability by resampling. *Stat Med*. (2021) 40:369–81. doi: 10.1002/sim.8779
24. Lewandowska M. Maternal obesity and risk of low birth weight, fetal growth restriction, and macrosomia: multiple analyses. *Nutrients*. (2021) 13:1213. doi: 10.3390/nu13041213
25. O'Callaghan FV, O'Callaghan M, Najman JM, Williams GM, Bor W. Maternal alcohol consumption during pregnancy and physical outcomes up to 5 years of age: A longitudinal study. *Early Hum Dev*. (2003) 71:137–48. doi: 10.1016/S0378-3782(03)00003-3
26. Popova S, Dozet D, Pandya E, Sanches M, Brower K, Segura L, et al. Effectiveness of brief alcohol interventions for pregnant women: A systematic literature review and Meta-analysis. *BMC Pregnancy Childbirth*. (2023) 23:1–17. doi: 10.1186/s12884-023-05344-8
27. Rumrich I, Vähäkangas K, Viluksela M, Gissler M, de Ruyter H, Hänninen O. Effects of maternal Smoking on body size and proportions at birth: A register-based cohort study of 1.4 million births. *BMJ Open*. (2020) 10:e033465. doi: 10.1136/bmjopen-2019-033465
28. Yang J, Wang M, Tobias DK, Rich-Edwards JW, Darling AM, Abioye AI, et al. Dietary diversity and diet quality with gestational weight gain and adverse birth outcomes, results from a prospective pregnancy cohort study in urban Tanzania. *Matern Child Nutr*. (2022) 18:e13300. doi: 10.1111/mcn.13300
29. Yu Z, Han S, Zhu J, Sun X, Ji C, Guo X. Pre-pregnancy body mass index in relation to infant birth weight and offspring overweight/obesity: A systematic review and Meta-analysis. *PLoS One*. (2013) 8:e61627. doi: 10.1371/journal.pone.0061627
30. Day NL, Jasperse D, Richardson G, Robles N, Sambamoorthi U, Taylor P, et al. Prenatal exposure to alcohol: effect on infant growth and morphologic characteristics. *Pediatrics*. (1989) 84:536–41. doi: 10.1542/peds.84.3.536
31. Dessi A, Corona L, Pintus R, Fanos V. Exposure to tobacco smoke and low birth weight: from epidemiology to metabolomics. *Expert Rev Proteomics*. (2018) 15:647–56. doi: 10.1080/14789450.2018.1505508
32. Ishikuro M, Obara T, Murakami K, Ueno F, Noda A, Onuma T, et al. The association between blood pressure control in women during pregnancy and adverse perinatal outcomes: the Tmm Birthree cohort study. *Hypertens Res*. (2024) 47:1216–22. doi: 10.1038/s41440-023-01570-x
33. Lewandowska M, Więckowska B, Sztorc L, Sajdak S. Smoking and Smoking cessation in the risk for fetal growth restriction and low birth weight and additive effect of maternal obesity. *J Clin Med*. (2020) 9:3504. doi: 10.3390/jcm9113504
34. Houfflynn S, Matthys C, Soubry A. Male obesity: epigenetic origin and effects in sperm and offspring. *Curr Mol Biol Rep*. (2017) 3:288–96. doi: 10.1007/s40610-017-0083-5
35. Soubry A. Pohad: why we should study future fathers. *Environ Epigenet*. (2018) 4:7. doi: 10.1093/eeep/dvy007
36. Watkins AJ, Rubini E, Hosier ED, Morgan HL. Paternal programming of offspring health. *Early Hum Dev*. (2020) 150:105185. doi: 10.1016/j.earhumdev.2020.105185
37. Han Y, Ha E, Park H, Kim Y, Lee S. Relationships between pregnancy outcomes, biochemical markers and pre-pregnancy body mass index. *Int J Obes*. (2011) 35:570–7. doi: 10.1038/ijo.2010.162
38. Rode L, Nilas L, Wøjdemann K, Tabor A. Obesity-related complications in Danish single cephalic term pregnancies. *Obstet Gynecol*. (2005) 105:537–42. doi: 10.1097/01.AOG.0000152304.39492.1c
39. Gilboa SM, Correa A, Alverson CJ. Use of spline regression in an analysis of maternal Prepregnancy body mass index and adverse birth outcomes: does it tell us more than we already know? *Ann Epidemiol*. (2008) 18:196–205. doi: 10.1016/j.annepidem.2007.09.005
40. Park S, Sappenfield WM, Bish C, Salihu H, Goodman D, Bensyl DM. Assessment of the Institute of Medicine Recommendations for weight gain during pregnancy: Florida, 2004–2007. *Matern Child Health J*. (2011) 15:289–301. doi: 10.1007/s10995-010-0596-5
41. Accordini S, Calciano L, Johannessen A, Portas L, Benediktsdóttir B, Bertelsen RJ, et al. A three-generation study on the Association of Tobacco Smoking with asthma. *Int J Epidemiol*. (2018) 47:1106–17. doi: 10.1093/ije/dyy031
42. Brooke OG, Anderson HR, Bland JM, Peacock JL, Stewart CM. Effects on birth weight of Smoking, alcohol, caffeine, socioeconomic factors, and psychosocial stress. *Br Med J*. (1989) 298:795–801. doi: 10.1136/bmj.298.6676.795
43. Kuzma JW, Sokol RJ. Maternal drinking behavior and decreased intrauterine growth. *Alcohol Clin Exp Res*. (1982) 6:396–402. doi: 10.1111/j.1530-0277.1982.tb04998.x
44. U. S. Surgeon General's Advisory Committee on Smoking and Health. Smoking and Health: Report of the Advisory Committee to the Surgeon General of the Public Health Service Washington, D.C.: U.S. Department of Health, Education and Welfare, Public Health Service; (1964). Available at: <https://collections.nlm.nih.gov/ext/document/101584932X202/PDF/101584932X202.pdf> (Accessed November 29, 2023).
45. Kramer MS, Kakuma R. Energy and protein intake in pregnancy. *Cochrane Database Syst Rev*. (2003) 4:CD000032–CD.
46. Madzorera I, Isanaka S, Wang M, Msamanga GI, Urassa W, Hertzmark E, et al. Maternal dietary diversity and dietary quality scores in relation to adverse birth outcomes in Tanzanian women. *Am J Clin Nutr*. (2020) 112:695–706. doi: 10.1093/ajcn/nqaa172
47. Englund-Ögge L, Brantsæter AL, Haugen M, Sengpiel V, Khatibi A, Myhre R, et al. Association between intake of artificially sweetened and sugar-sweetened beverages and preterm delivery: A large prospective cohort study. *Am J Clin Nutr*. (2012) 96:552–9. doi: 10.3945/ajcn.111.031567
48. Abo Hamza E, Tindle R, Pawlak S, Bedewy D, Moustafa AA. The impact of poverty and socioeconomic status on brain, behaviour, and development: A unified framework. *Rev Neurosci*. (2024) (00) 35:597–617. doi: 10.1515/revneuro-2023-0163
49. Ravelli G-P, Stein ZA, Susser MW. Obesity in young men after famine exposure in utero and early infancy. *N Engl J Med*. (1976) 295:349–53. doi: 10.1056/NEJM197608122950701
50. Terry T. Fibroblastic overgrowth of persistent tunica Vascularis Lenticis in infants born prematurely: ii. Report of cases—clinical aspects. *Trans Am Ophthalmol Soc*. (1942) 40:262–84. doi: 10.1016/S0002-9394(42)91858-0
51. Jaramillo-Ospina A, Casanella P, Garmendia ML, Andersen R, Levitan RD, Meaney MJ, et al. Interactions between a polygenic risk score for plasma docosahexaenoic fatty acid concentration, eating behaviour, and body composition in children. *Int J Obes*. (2022) 46:977–85. doi: 10.1038/s41366-022-01067-6
52. Liu J, Au Yeung SL, He B, Kwok MK, Leung GM, Schooling CM. The effect of birth weight on body composition: evidence from a birth cohort and a Mendelian randomization study. *PLoS One*. (2019) 14:e0222141. doi: 10.1371/journal.pone.0222141

53. Rasmussen EL, Malis C, Jensen CB, Jensen J-EB, Storgaard H, Poulsen P, et al. Altered fat tissue distribution in young adult men who had low birth weight. *Diabetes Care*. (2005) 28:151–3. doi: 10.2337/diacare.28.1.151
54. Gamazon ER, Wheeler HE, Shah KP, Mozaffari SV, Aquino-Michaels K, Carroll RJ, et al. A gene-based association method for mapping traits using reference transcriptome data. *Nat Genet*. (2015) 47:1091–8. doi: 10.1038/ng.3367
55. Portella AK, Papantoni A, Paquet C, Moore S, Rosch KS, Mostofsky S, et al. Predicted Drd4 prefrontal gene expression moderates snack intake and stress perception in response to the environment in adolescents. *PLoS One*. (2020) 15:e0234601. doi: 10.1371/journal.pone.0234601
56. Potter-Dickey A, Letourneau N, Silveira PP, Ntanda H, Giesbrecht GF, Hart M, et al. Associations among parental caregiving quality, cannabinoid receptor 1 expression-based polygenic scores, and infant-parent attachment: evidence for differential genetic susceptibility? *Front Neurosci*. (2021) 15:704392. doi: 10.3389/fnins.2021.704392
57. da Silva PA, da Silva VMB, Lemos YS, da Cunha LNA, Andrade RA, de Sales Santos BM, et al. Insegurança Alimentar Em Tempos De Pandemia Do Covid-19 No Brasil. *Rev Literat Res Soc Dev*. (2022) 11:31809. doi: 10.33448/rsd-v11i9.31809



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A protocol for estimating health burden posed by early life exposure to ambient fine particulate matter and its heavy metal composition: a mother–child birth (ELitE) cohort from Central India

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Background: Pregnant women and children are vulnerable to air pollution-related adverse health effects, especially those residing in low-resource and high-exposure settings like India. However, evidence regarding the effects of early-life exposure to air particulate matter (PM) on childhood growth/developmental trajectory is contradictory; evidence about specific constituents of PM, like heavy metals, is limited. Similarly, there are few Indian cohorts investigating PM exposure and the incidence of acute respiratory infection during infancy. This study protocol aims to fill these critical gaps in knowledge.

Methods: We aim to establish a mother–child birth cohort through the enrolment of 1,566 pregnant women residing in two urban areas of central India. Antenatally, we will collect socioeconomic, demographic, and clinical information and details of confounding variables from these pregnant women, who will then be followed up until childbirth to assess their exposure to air PM. Biomonitoring will also be conducted to evaluate heavy metal exposure. At birth, pregnancy outcomes will be noted, followed by postnatal follow-up of live-born children until the first year of life to assess their achievement of growth/development milestones and exposure to pollutants. We will also estimate the incidence of Acute Respiratory Infections (ARI) during infancy.

Discussion: This manuscript describes the protocol for an Indian mother–child air pollution birth cohort study that aims to generate comprehensive evidence regarding the adverse effects of early-life (i.e., both pre- and post-natal) exposure to air PM and its constituent heavy metals among Indian children. This study will provide an epidemiological basis for further understanding in this

context. Finally, by reporting our carefully planned study methods/outcome measures, which are comparable to those of published and ongoing birth cohorts, we aim to serve as the starting point for similar cohorts in the future, which, when considered together, would generate enough evidence to facilitate context-specific policy-making and development of appropriate prevention and mitigation strategies.

KEYWORDS

acute respiratory infection, air pollution, birth cohort, child development, growth, heavy metals, India, particulate matter

1 Introduction

Air pollution is the most significant worldwide threat to human health and life expectancy, with 7 million global deaths being attributable to its exposure (1, 2). The United Nations Environment Programme (UNEP) reported that the vast majority of people worldwide reside in places where the concentration of particulate matter (PM) pollutants in the air exceeds the stringent permissible limits prescribed in the 2021 air quality guidelines of the World Health Organization (WHO) (3, 4). People living in India and other low- and middle-income countries, particularly pregnant women and children, are at significantly higher health risk (5–7). Therefore, the WHO–United Nations Children’s Fund (UNICEF)–Lancet Commission, in its 2020 report focussing on the future of the global child population, has stressed evidence generation and subsequent interventions to safeguard the health of children, especially in high pollution exposure settings, to expedite the fulfillment of the 48 child-related Sustainable Development Goal (SDG) indicators (8, 9).

Air pollution adversely affects pregnancy, fetal growth, and development (10–12). However, evidence regarding the effects of early-life (i.e., pre- and post-natal) exposure to air particulate matter on the childhood growth trajectory is contradictory. Some studies demonstrate an increased relative risk of childhood stunting, wasting, and being underweight (13–15). At the same time, others have also reported a higher risk of childhood obesity and raised body mass index (BMI) (16, 17). Even among infants, published evidence is contradictory. For example, a Colorado-based prospective cohort study reported higher adiposity among exposed infants at the 5th-month follow-up (18). Similar results were reported by a Chinese birth cohort (19). In contrast, a cohort study from Ghana reported lower length-for-age (stunting) and weight-for-length (wasting) z-scores among exposed infants (15). On the other hand, a recent randomized trial conducted in four low- and middle-income countries that substituted biomass burning with clean cooking fuel, leading to a reduction in antenatal personal exposure levels, reported no difference in the risk of stunting in infants (20). Therefore, further research is required to provide confirmatory evidence. This ambiguity in evidence might be because few studies have investigated the differential effect of chemical constituents of particulate matter, which are a heterogeneous mixture of multiple components with varying toxicity profiles (21). Particularly, there is a paucity of longitudinal research investigating the association between early-life exposure to multiple heavy metals and aberrations in childhood growth or development (22, 23). Considering the magnitude of the public health burden posed by air pollution and child growth/

developmental abnormalities in low- and middle-income countries such as India (24), where annually more than 250 million under-five children fail to attain their optimum developmental potential (25), this study protocol aims to generate comprehensive evidence in this context to complement the limited India-specific evidence published so far (26–28).

Another adverse effect of prenatal air pollution exposure is the alteration of immune mechanisms in children (29–31), which can increase the risk of infectious diseases such as acute respiratory infections (ARIs). Evidence supporting this link is mainly based on studies conducted in high-income countries (32). The burden of childhood ARI is enormous in India, which is one of the top 15 countries globally in terms of the prevalence of ARI and subsequent childhood mortality, with 0.4 million under-five children dying annually from ARI-related diseases (33). However, Indian evidence on air pollution-induced childhood ARI is mainly limited to cross-sectional surveys or ecological retrospective data analysis. Further, these studies have used proxy measures such as questionnaire data to elicit either household exposures (34, 35) or ambient air pollution (36, 37). Thus, considering these knowledge gaps, this study protocol also focuses on identifying the association of variation in the incidence of ARI till one year of age among children exposed during early life to different levels of air PM and its heavy metal content.

2 Aims and objectives

We aim to establish an urban mother–child birth cohort in central India. The data collected from this cohort will enable us to understand the health burden posed by early life exposure (i.e., pre- and post-natal) to air PM and its heavy metal composition in Indian children and the role of such environmental exposure in the multifactorial aetiology of our chosen study outcomes. The specific objectives being addressed in this research are:

1. To investigate the variation in achievement of growth/developmental milestones during the infancy period of children attributable to different levels of early life exposure to air pollution
2. To assess the incidence of acute respiratory infections during the infancy period of children attributable to different levels of early-life exposure to air pollution
3. To find the association of exposure to selected heavy metals (as represented by blood concentration) among pregnant women /children with assessed morbidity outcomes of children.

3 Materials and methods

During the drafting of this manuscript, details were reported as per the STROBE checklist, which was modified to suit requirements specific to the protocol of cohort studies (see [Supplementary material](#)).

3.1 Study design

This is the protocol for a population-based prospective cohort study. During the first phase of this study, which will be implemented over three years, we will establish the mother–child birth cohort and conduct regular follow-ups for exposure and clinical assessments of study participants during the antenatal and 1-year postnatal period (see [Figure 1](#)). In the next phase, the established cohort will be followed up annually by securing further funding.

3.2 Study setting

The cohort population will be enrolled within the boundaries of urban local bodies (municipal corporations) of two selected cities (Bhopal and Ujjain) of Madhya Pradesh (MP), a large province located in central India (see [Figure 2](#)). The process of finalizing these two cities to establish the cohort has been detailed in [Supplementary material \(Data Sheet 1\)](#). MP is a large province with a total population exceeding 72 million (38), of which around 25% reside in urban areas (39). MP has thirty-two cities, with Bhopal and Ujjain ranking as the second and fifth most populous cities in the province, respectively (40). The child population accounts for 12.02 and 11.45% of the total population of these two cities, respectively (41, 42). The average literacy rate of the total population (Bhopal: 83.47% versus Ujjain: 84.43%, both of which are at a higher level than the Indian average of 74.04%) and proportion of slum population (Bhopal: 26.68% versus Ujjain: 23.32% both of which are at a higher level than the Indian

Study Measures	Enrollment	Gestational FU	Gestational FU	Gestational FU	Post delivery	1 month FU	2 month FU	3 month FU	4 month FU	5 month FU	6 month FU	7 month FU	8 month FU	9 month FU	10 month FU	11 month FU	12 month FU
Information about Pregnant Women																	
Eligibility for inclusion in study	✓																
Residential Address and other identifying details	✓																
Age, education, occupation	✓																
Obstetric History (Current and past pregnancy details)	✓																
Medical history of comorbidities and prescription drug use	✓																
Tobacco use, smoking, alcohol, physical activity and diet	✓																
ANC visits (gestational follow up)		✓	✓	✓													
Preganancy loss (Spontaneous abortion, abortion, stillbirth)		✓	✓	✓	✓												
Hospital/clinic for ANC and delivery	✓	✓	✓	✓	✓												
Information about Household Characteristics																	
Household Roster; Socioemographics & Socioeconomic status	✓																
Built environmental assessment	✓																
Indoor exposures like smoking and type of cooking	✓																
Water and Sanitation: clean water, indoor plumbing, latrine	✓																
Information about Children																	
Health status at birth: APGAR score, NICU admission					✓												
Neonatal assessment: length, weight, HC, MAC					✓												
Birth order and family (including siblings) medical history					✓												
Growth and development						✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Clinical assessment for ARI						✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Clinical assessment for other morbidities						✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Feeding practices						✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Immunization						✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Environmental assessment																	
Personal Exposure Monitoring (pregnant women and children)	✓			✓					✓					✓			
Blood heavy metal sampling (pregnant women and children)	✓																✓
Retrieval of previous years air PM data (Public sources)	✓																
PM and heavy metal monitoring (Ambient air)																	→
LUR-based PM exposure estimation at residential address																	→

FIGURE 1

Overview of activities to be conducted in the study (Activities under the study are listed on each row and the timing of each activity is indicated by a tick mark in the cells corresponding to the column headings showing the phase of study such as enrolment, gestational follow-up, post-birth and month-wise follow-up (FU) in the infancy period. Ambient air particulate matter/heavy metal assessment and land-use regression (LUR) modeling will be done over the entire study period and have been shown using arrows. ANC, antenatal care; APGAR, scoring given to child after birth based on appearance, pulse, grimace, activity, and respiration; ARI, acute respiratory infection; HC, head circumference; LUR, land use regression; MAC, mid-arm circumference; NICU, neonatal intensive care unit; PM, particulate matter).

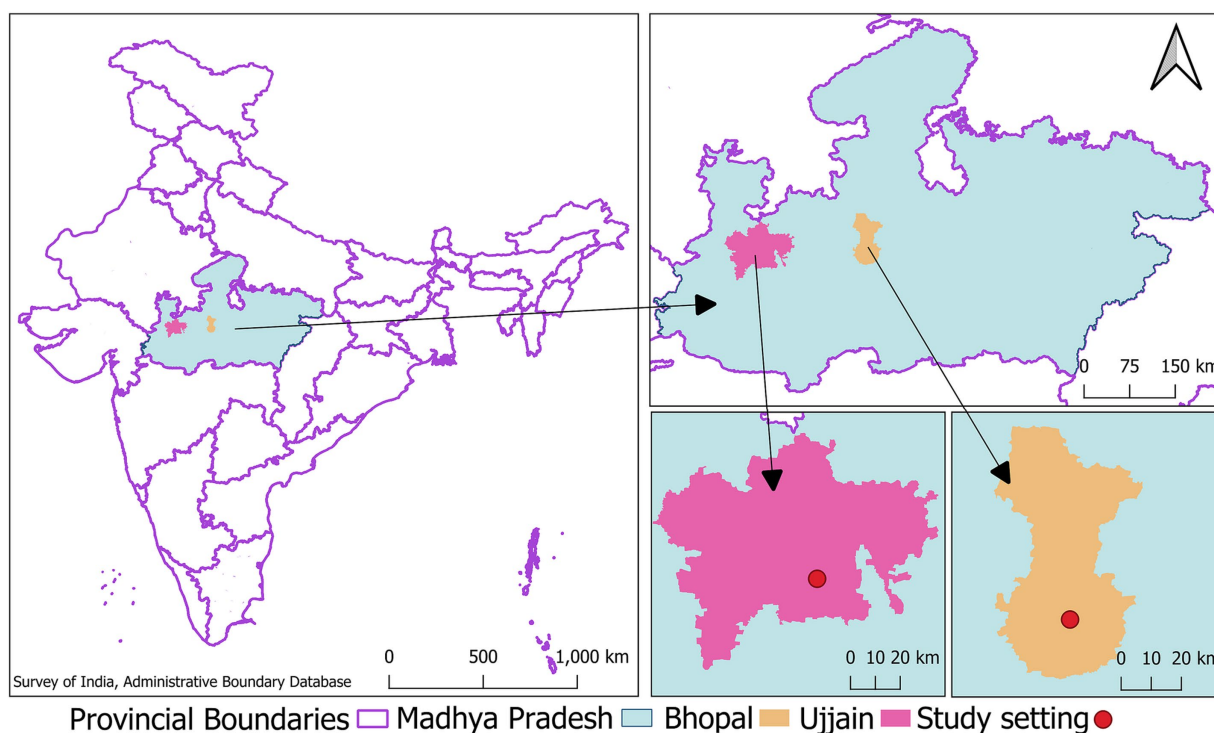


FIGURE 2

Map showing the location of study cities the image shows clockwise the map of India with the location of the central Indian province of Madhya Pradesh demarcated in green, inset of Madhya Pradesh showing the location of study cities- Bhopal and Ujjain (This image was developed by the research team in the QGIS software (Version 3.28.15). The India map with state and provincial boundaries and point location of Indian District Head Quarters (indicating location of cities) was retrieved from the survey of india- administrative boundary database available at https://onlinemaps.surveyofindia.gov.in/Digital_Product_Show.aspx).

average of 5.41%) in these two cities are comparable, highlighting that the socioeconomic scenario of these two cities are similar (41, 42).

3.3 Study population

Consenting pregnant women ($n = 783$ from each city), aged ≥ 18 years, with documented gestational age less than or equal to 16th week, who have been primarily residing in the study cities for at least the past year (and have no imminent plan to shift residence for more than a continuous period of one month away from their current address during the study period) will be enrolled. We will exclude pregnant women who have a history of using any assisted reproductive technology or who have been diagnosed with a high-risk pregnancy where complications are anticipated (43). We will also exclude pregnant women with occupation or lifestyle factors that are reported by previous studies to be sources of exposure to high levels of PM (44–46). Women with pregnancy loss, preterm birth, and term neonates with birth asphyxia and diagnosed congenital anomalies will be identified using relevant records and withdrawn from further follow-up. Details of operational definitions to be used for excluding participants at the time of enrolment and during follow-up phases have been described in [Supplementary Table S1](#).

3.3.1 Sample size calculation

The calculated sample size is 571 mother–child pairs. Our main objective is to investigate the effect of early-life exposure to air

pollution on child growth/development. Stunting, a prevalent manifestation of chronic malnutrition, is one of the significant indicators for delay in the achievement of growth/developmental milestones in children (47). Hence, we have calculated the sample size by assuming a power of 80%, a two-sided confidence level of 95%, and by using data available from a recent publication (48). This article estimated an odds ratio (OR) of 1.74 for stunting among under-five children with long-term exposure to $PM_{2.5}$. We applied relevant continuity correction and inflation to account for participant exclusions during follow-up and anticipated non-response/participant attrition. Thus, we will enroll 783 pregnant women in each study city (1,566 participants in total) to establish the final cohort of 571 mother–child pairs. Further details of sample size calculation have been enumerated in [Supplementary material \(Data Sheet 2\)](#). We will continue to use the same cohort for our subsequent objectives.

3.3.2 Sampling strategy

We will obtain information about eligible pregnant women in the study area from community health workers (CHWs), who are usually the first point of contact for antenatal care (ANC) among Indian pregnant women (49, 50). Before the launch of the study, we will identify and enlist, with the help of relevant district-level offices, all the CHWs working in both study cities under the Integrated Child Development Scheme (ICDS) and National Health Mission (NHM) (51, 52). These include Anganwadi workers (AWW) and Accredited Social Health Activists (ASHA), respectively (49, 50). We will approach all CHWs to gain their consent to cooperate, and those

willing will be briefed about the study participant enrollment procedure.

We will contact pregnant women identified by CHWs at their homes or at the nearest Anganwadi Centre [community maternal and child care centre in India functioning under the ICDS (53)] to describe our study, confirm their eligibility using a pre-designed checklist, and finally obtain written informed consent. After administration of written informed consent (including consent for follow-up of their child for one year), pregnant women will be enrolled for participation in the study.

3.4 Data collection

3.4.1 Exposure data collection

A multi-pronged strategy will be used to collect individual and neighborhood-level exposure data. To begin with, historical data on the neighborhood-level concentration of air PM (PM_{10} and $PM_{2.5}$) covering the two study cities will be retrieved from available open-access sources. For example, in India, in addition to using satellite-derived aerosol optical depth as a source for PM data, the Central Pollution Control Board (CPCB) provides freely available information from its network of fixed-site automatic monitors (continuous ambient air quality monitoring stations - CAAQMS) and gravimetric samplers under the National Air Quality Monitoring Program (NAMP) (54, 55). Using the city-level air PM data, we will develop an exposure database at a high spatial scale using the Land Use Regression (LUR) model for both cities. LUR has been widely used to predict the concentration of air pollutants (measured through distant fixed site monitors and/or remote sensing data) at target locations (i.e., the residential addresses of the selected participants) (56–58). We will develop our LUR model to assign ambient $PM_{2.5}$ and PM_{10} exposure to each participant based on the geocodes of their residence. We will follow the methodologies previously published for urban area LUR models, such as that under the ESCAPE project (59) and for Indian cities (60, 61). Accordingly, in our LUR model, we will use data for a range of geographic, population, and emission source-specific predictor variables retrieved from open access sources, including satellite data, local authorities, and/or collected from field-level verification. For example, data on land use, road network, population density, elevation, meteorological, and other relevant variables will be used, in line with previous studies (56–58). We will adopt a supervised forward addition linear regression approach for model development and perform diagnostics on the fitted models to maintain the linear regression. Finally, we will assess the performance of the developed model by adopting a 10-fold cross-validation approach (62). In addition, we will also measure the personal exposure to air PM (PM_{10} and $PM_{2.5}$) of each enrolled pregnant woman once in each trimester after enrolment to increase the accuracy of PM exposure data while accounting for participant mobility. For these measurements, low-cost battery-operated portable sensors will be used, as has been reported in previous studies (63, 64).

For the heavy metal component of our study, we will conduct biomonitoring of study participants. Blood samples collected from enrolled pregnant women and their live-born children will be analyzed through Inductively coupled plasma optical emission spectroscopy (ICP-OES) using the hot-acid digestion method given by the United States Environmental Protection Agency (USEPA) (65).

We will limit our analysis to those heavy metals that are known to adversely affect childhood growth and development and are found in the ambient air of study cities during our air sampling and subsequent composition study. For this, we will refer to previous large-scale studies conducted in Spain, China, and other countries, as well as published systematic reviews (66–70), to compile a list of heavy metals with known adverse effects on childhood growth and development. Simultaneously, we will conduct air PM composition analysis focussing on identifying heavy metals that exceed the permissible limits in the ambient air following CPCB methodology (71) for sampling and, subsequently, USEPA guidelines for laboratory analysis (65).

3.4.2 Outcome and covariates data collection

3.4.2.1 Pregnant women

In the first (baseline) visit to households of eligible and consenting pregnant women, the detailed residential address (including contact details and geographic coordinates), as well as details of the participant and her household members, will be collected at the time of enrolment. Briefly, we will collect information on age, education, occupation, lifestyle factors, medical history (including details of current/past pregnancy and prescription drug use), and relevant family history from the pregnant women. The maternal height and weight will be recorded at the baseline visit. Detailed data about previous pregnancies (if any) will include parity status, birth intervals between consecutive births, and history of anemia/malaria/urinary tract infection/other infections/any other complications in a past pregnancy. In addition, the demographic details, socioeconomic characteristics, water, sanitation, hygiene, and environmental factors related to her household will be collected. The enrolled pregnant women will be followed up once in each trimester in the remaining period of gestation to collect information regarding the occurrence of spontaneous abortion/miscarriage and the details of scheduled antenatal check-ups undergone by the pregnant women. We will note their preference for a hospital/healthcare facility where they would opt for childbirth.

3.4.2.2 Live-born children

3.4.2.2.1 Early neonatal period

According to the information regarding the calculated expected date of delivery (EDD) obtained during the baseline visit, the pregnant women will be contacted within 1 week of the EDD to collect information on pregnancy/birth outcomes (date of childbirth to calculate the child's chronological age, live birth versus stillbirth, gestational age at birth and congenital anomalies). After getting information about the birth, study staff will visit the hospital/house of the mother to collect anthropometric data of the baby (preferably within 72 h of birth) to supplement the information obtained from hospital/medical records. In cases where the mother/child cannot be contacted within 72 h of birth, we will try to collect relevant data about the child as early as possible before the 1st-month follow-up visit.

3.4.2.2.2 Monthly follow-up of the child till 1st year of age

All eligible live-born children will be followed up at their homes/nearest Anganwadi centre. To ensure timely and smooth data collection, follow-up visits will be scheduled in a manner that these

visits coincide with routine house-to-house visits carried out by CHWs under different ongoing national programs [such as Home-based newborn care (HBNC) and Home-Based Care for Young Child Programme (HBYC) under NHM and “Poshan Abhiyan” (72), “Dastak Abhiyan” specific to MP (73)]. In each monthly follow-up visit, anthropometry, achievement of developmental milestones, and acute morbidity profile will be recorded. Additional information about at-birth APGAR score, weight, length, head, and mid-arm circumference will be collected in the 5th visit (child age 1 month). Blood samples for heavy metal analysis and the data on child immunization and feeding practices will be collected in the 17th visit (during the 12th month of the child's age).

3.4.2.3 Details of data to be collected

The list of domains, variables, and measurement timing of this study are described in subsequent paragraphs and shown in Figure 1.

3.4.2.3.1 Exposure variables

The main exposure/independent variables to be investigated in this study are mean (daily/monthly/annual) concentration of particulate matter (PM₁₀ and PM_{2.5}) for the specific geo-location of each study participant and mean levels of heavy metal in blood samples of participants (pregnant women and children).

3.4.2.3.2 Study outcomes

The primary study outcomes are related to childhood growth and development, as shown in Tables 1, 2. In addition, we will also estimate the incidence rate of ARIs (number of episodes of ARI during infancy/total number of children under follow-up). We modified the Integrated Management of Childhood Illness definition for ARI [given by WHO/UNICEF (74)] which has been used previously (75) to create an operational definition of ARI for this study. Modification was done by incorporating the signs and symptoms mentioned in the Integrated Management of Neonatal and Childhood Illness (IMNCI), Ministry of Health & Family Welfare, Government of India. Accordingly, ARI will be defined as cough or difficulty in breathing with or without any general danger signs, with or without any chest indrawing, stridor, and fast breathing. Depending upon the site of inflammation determined by the paediatrician based on clinical signs and symptoms, it will be classified as ARI of the upper respiratory tract and ARI of the lower respiratory tract. Further, depending upon the severity, ARI will be classified as per IMNCI guidelines into “No Pneumonia: cough or cold,” “Pneumonia,” and “Severe Pneumonia or Very Severe Disease.” Based on previous research, we will define each episode of ARI to last for two weeks (75). When a child who has had no symptoms for at least one week develops signs and symptoms of ARI, we will treat that as a new episode (75).

3.4.2.3.3 Confounding variables/effect modifiers

We will collect information for a wide range of covariates identified from a detailed literature review. We will collect information using questionnaires and case report forms developed for this study. Wherever possible, relevant questions will be adapted from pre-existing validated questionnaires. To minimize attrition over time, we will ensure that an optimal number of questions will be asked without missing out on important information.

Child-specific details will be retrieved from discussions with care providers and by consulting available hospital records. Briefly, we will record information such as age, gender, birth order, status of

immunization [i.e., as per the National Immunization Schedule (NIS) of the Universal Immunization Programme (UIP) in India (76)], history of anaemia and other acute morbidities (defined as per the Integrated Disease Surveillance Project (IDSP) (77) of the Government of India), relevant medical history, including at-birth details of APGAR score, length, weight, head circumference, mid-arm circumference, neonatal intensive care unit (NICU) admission, co-morbidities and family history.

We will collect family-specific information in the form of a household roster detailing the age, education, occupation, relevant medical history, and tobacco/alcohol consumption [using standard questions provided by the WHO STEPwise instrument (78)] of family members. Then, the household socioeconomic status (SES) will be categorized based on scores assigned using the latest revision of the Kuppuswamy Scale (79). Household water sanitation and hygiene assessment will be done using a pre-tested structured questionnaire which the study team has developed by adapting questions from the “Core questions on drinking-water and sanitation for household surveys” given by WHO/UNICEF (80).

In addition to the data collected at baseline, current pregnancy-related information will also be collected from the pregnant women. After birth, during monthly follow-ups with the child, the mother will be asked about breastfeeding and complementary feeding (after the child attains 6 months of age) practices. For data collection on complementary feeding, we will use relevant questions from a questionnaire previously used in Indian settings (81).

Finally, information about other environmental factors, such as the built environment and other indoor exposures, will be collected by adapting questions about built environmental factors such as ventilation, building material, area and construction of the house, and fuels used for cooking or heating from the ‘household questionnaire’ of the National Family Health Survey, India 2019–20 (NFHS – 5) and the ‘house-listing and housing census schedule’ of census 2011 (82, 83). Additionally, we will leverage the field experience gained by the study team in designing and using an exposure questionnaire in a previous cohort study conducted in central India, focussing on the impact of the built environment on population health (84–86).

3.5 Data management

We will formulate a Data Collection and Management Committee (DCMC) consisting of the team's principal investigator and other senior investigators. This committee will ensure that during the implementation of this research, the national guidelines for biomedical research data collection and management (87), are followed stringently to maintain the quality of data collection and analysis. For example, equipment used in the study will be routinely calibrated, and laboratory testing will be conducted using high-quality reagents. Research staff will be adequately trained before the start of project work. We will validate the study questionnaires, which have been developed by adapting questions from standardized tools, and these will be pilot-tested before use. DCMC will also handle requisite communication with the ethics committee and other ethical considerations, including data dissemination. The DCMC will ensure proper management of data. Filled questionnaires will be stored in secure locked cabinets, while online or computer-based information will be kept safe using passwords accessible only to the research team. All data forms will have a unique identifier, which will be used to link

TABLE 1 Operational definitions, indicators, and measurement methods to be used for child growth-related outcome measures.

Outcome	Operational definition	Variable/indicator	Measurement method
Small for gestational age (SGA)	As per the WHO definition of SGA given by the 1995 WHO expert committee, infants having a birth weight for gestational age below the 10th percentile based on a sex-specific reference population (139, 140).	Proportion of children diagnosed as SGA at birth (proxy of in-utero growth of the child)	Based on hospital records-verified by study staff
Low birth weight (LBW)	Infants with a birth weight of less than 2,500 g, regardless of gestational age at the time of birth (141, 142).	The proportion of children diagnosed as LBW at birth (proxy of in-utero growth of the child)	Based on hospital records-verified by study staff
Overweight/ obese	Children's body mass index (BMI - calculated as weight in kilograms divided by height in metres squared) will be plotted on WHO BMI charts and those with a BMI above the 95th percentile will be classified as obese and overweight will indicate those children whose BMI falls between the 85th and 95th percentile (143, 144).	The proportion of overweight/ obese (based on BMI for age) infants at the end of the first year of life.	Monthly measurement of height/ length, weight, and calculation of BMI
Underweight, wasted and stunted	Z-scores for growth indicators (length/height-for-age, weight-for-age, weight-for-length/height, BMI-for-age) will be estimated by comparing each child's height/length and weight with WHO growth standards as shown in the image below (which has been adapted from the WHO child growth standards: training course on child growth assessment) (145). Based on where their calculated z-scores lie with respect to the median value of the standard reference population, children will be categorized as: - Underweight: 'weight for age' below minus two standard deviations (-2SD) - Severely underweight: 'weight for age' below minus three standard deviations (-3SD) - Stunted: 'height/length for age' below minus two standard deviations (-2SD) - Severely Stunted: height/length for age' below minus three standard deviations (-3SD) - Wasted: 'weight for height/length' below minus two standard deviations (-2SD)	Proportion of children with abnormal Z-scores for aforementioned growth indicators (i.e., underweight, severely underweight, stunted, severely stunted, wasted and severely wasted) at the end of the first year of life.	Z-scores for growth indicators (length/height-for-age, weight-for-age, weight-for-length/height, BMI-for-age) obtained from comparison of each child's height/length and weight with WHO growth standards

collected information on exposures, outcomes, and confounders to ensure accurate data integration while maintaining participant confidentiality. Data entry done by research staff will be supervised by the DCMC, who will randomly verify the entered data to check for data entry mistakes. We will use multiple imputation methods to manage missing data.

3.6 Statistical analysis and reporting

The data will be entered using open access online applications from which the data will be downloaded and exported to SPSS statistics software (Version 25) and the latest versions of R packages/R studio for analysis. Data will be summarized using descriptive statistics like mean/standard deviation (SD) or median/ Interquartile range. For categorical variables, summary estimates will be reported using frequency with percentages and within two selected study settings. An initial analysis will compare aggregated data between cities with high and low pollution levels. For this, relative risk (RR) and attributable risk (AR) will be calculated

through the relevant equations using the probability of outcome (incidence/proportion) among the high pollution group (exposed) divided by the probability of outcome among the low air pollution group (relatively unexposed).

The next level of analysis will be based on the range of the estimates of $PM_{2.5}$ / PM_{10} exposure concentrations and blood heavy metal levels found in the study participants (i.e., pregnant women/ live-born children). We will use relevant correlation coefficients to assess possible correlations between environmental variables- $PM_{2.5}$ / PM_{10} /blood heavy metal levels and the health outcomes – growth indicator related z scores/development quotient/ARI episodes (Pearson or Spearman).

Finally, multivariable logistic regression model analyses will be used to study the relationship between environmental variables- $PM_{2.5}$ / PM_{10} / blood heavy metal levels and the health outcomes in binary forms – growth/development/ARI. Briefly, multiple linear mixed-effects regression model analyses will be used to study the relationship between the levels of early-life exposure (concentration of environmental pollutants- $PM_{2.5}$ / PM_{10} concentration/ heavy metals in pregnant women and the child participant- monthly means for the former and cumulative

TABLE 2 Operational definitions, indicators, and measurement methods to be used for child development-related outcome measures.

Outcome	Operational definition	Variable/Indicator	Measurement method
Development progress	The developmental level of the child will be assigned a score ASQ-3 (146, 147). ASQ-3 has been widely used in many countries as a field-based parent-completed screening tool to assess five developmental domains (148). It has also been previously used and validated in the Indian population (149, 150). Developmental Quotient (DQ) is calculated by dividing Developmental Age by Chronological Age and multiplying it by 100 (151, 152). Developmental Age (DA): Each child will be assigned a DA at each follow-up visit for each of the 5 developmental domains, i.e., gross motor, fine motor, adaptive/cognitive, language and personal-social developmental domains. Study staff under the supervision of a paediatrician will estimate DA according to the achievement of domain-specific developmental milestones. Chronological Age (CA): the actual age of the child calculated from his/her date of birth	Domain-specific and mean score of ASQ-3 obtained monthly - Proportion of children with delayed achievement of development milestones at the end of the first year of life. - Domain-specific monthly developmental level of each infant obtained through Development quotient calculation	Ages and stages questionnaires- third edition (ASQ-3) questionnaire (146, 147) Questionnaire developed by authors and pilot-tested in an ongoing built environmental child cohort (84)

mean- i.e., in-utero maternal exposure summed with infancy period exposure to heavy metal) and child health outcomes- mean anthropometric data (height, weight, head, and mid-arm circumference) and developmental level (obtained from developmental quotient/mean score on ASQ-3 scale) of each participant (live-born children) while adjusting for confounders. Similar regression equations will be used to analyze the association between exposure and delay in achieving growth and developmental milestones. Subsequently, the PM_{2.5}, PM₁₀ data and other environmental/sociodemographic data will be used in a logistic regression model of ARI symptoms within a distributed lag nonlinear modeling framework (DLNM) (88, 89). This approach will test the associations of PM_{2.5} /PM₁₀ exposure over the preceding time periods and the distribution of growth z-scores / occurrences of ARI events (90–92).

Analyses will be performed separately for each child’s morbidity outcomes, such as growth/developmental parameters/domain. All analyses will adjust for different confounding variables included in the study. Details of such confounders for statistical adjustment will consist of gender, family size, socioeconomic status, gynecological/obstetrics/ other relevant medical history, and data from environmental assessments of the households (built environmental attributes). We will also adjust for the effect of low birth weight and small-for-gestational-age on the studied association (Supplementary material). We will also conduct sensitivity analyses to test the robustness of our findings, for example, analysing a subset with complete data and comparing the results with the entire dataset where missing data imputations have been done.

3.7 Ethical considerations

This study was reviewed and approved by the Institutional Ethics Committee (Human), National Institute for Research in Environmental Health (vide approval letter number: ICMR-NIREH/ BPL/IEC/2023–24/1307 dated 16/02/2024). At the beginning of the research, we will obtain written informed consent from the pregnant women for both their and their child’s participation, allowing data collection and scientific dissemination. If we identify any pregnant women or children with signs of illness or health complications during our survey, we will refer them to a nearby government hospital. We will inform the study participants and their families about the study’s final findings through meetings organized in the community with the help of the CHWs. We will also disseminate the findings scientifically through the publication of peer-reviewed articles.

4 Discussion

The ELitE birth cohort study will be a relevant addition to the currently sparse evidence base about the long-term effects of early-life exposure to air pollutants among Indian children. Owing to physiological pulmonary adaptation during pregnancy, women inhale a higher volume of air and the pollutants in it in each respiratory cycle (93). Adverse health effects in the mother coupled with the now-acknowledged potential of PM to cross the placenta cause placental malfunctioning as well as other direct and indirect environmental insults to the susceptible developing fetus (94–98). Postnatally, multiple factors such as higher baseline ventilation rates, predominance of mouth-breathing bypassing nasal clearance of

particles, and immature immune/pulmonary systems contribute to both higher risk of PM exposure and increased inhaled doses post similar levels of exposure in children who have different deposition and clearance probabilities than adults (99). Hence, pregnant women and children, particularly those living in low-resource, high-exposure settings like India, are especially vulnerable to the adverse health effects of air pollution. Therefore, it is essential to collect prospective longitudinal data to document and understand these impacts over time.

The adverse effects of PM exposure on child growth/developmental trajectory have been shown by epidemiological studies, albeit with contradictory findings (13–17). However, the biological mechanisms mediating these effects are not well explored, leading to perpetuating ambiguity (100). Recently, Sinharoy et al. (101) attempted to elucidate the pathophysiological framework underlying the exposure-response relationship between air pollution and stunting. Authors posited that antenatal exposure via oxidative stress and inflammation leads to mitochondrial dysfunction, decreased DNA methylation, and shortened telomere length, all of which contribute to placental dysfunction and poor foetal growth (101). Further, authors argue that adverse effects on developing immune and pulmonary systems affecting the child's susceptibility to infections compounded by alterations in appetite versus bodily requirements and dietary metabolite absorptions vis-à-vis loss, particularly that of vitamin D, can contribute to post-natal growth failure leading to stunting (101). Other researchers have also reported similar mechanisms (102, 103). Growth failures due to chronic malnutrition during early childhood can independently translate into developmental delay (104, 105).

On the other end of this spectrum, research has found links between PM exposure and adiposity. The association between PM and obesity is well-established among older children and adults, as shown by a recent review (106). It is said to be mediated via many mechanisms ranging from oxidative stress/inflammation and epigenetic changes to perturbations in metabolic and intestinal flora balance (106). However, the common postulation explaining this dichotomy in the PM effect on growth trajectory reasoned that children with early-life growth restriction are at higher risk of metabolic diseases, including obesity, at a later phase in life as per the developmental origins of health and disease (107, 108). However, recent evidence challenges this mode of reasoning since obesity and higher adiposity have been noted among exposed infants (18, 19). Another line of thinking has evolved, which contemplates that the phenotype of fetal growth restriction in an antenatally exposed mother could be immediately followed by rapid weight gain in the infancy period (109). However, the overall paucity of longitudinal evidence precludes the drawing of any conclusions. The study presented here will help fill in the existing gap in knowledge owing to the scarcity of longitudinal evidence by establishing a birth cohort consisting of mother-child pairs from two urban areas of central India. Although findings are not expected to be generalizable globally, the prospective follow-up data collected in this cohort study will provide strong evidence for planning and policymaking in this field.

This study has multiple advantages owing to its multi-disciplinary research team, which aids in comprehensive information collection and enhances the validity of the study's findings. Such a strength would be crucial since we deal with child growth and development, a

complex multidimensional concept (110, 111). Children are vulnerable to the effects of the complex interplay between a multitude of factors ranging from environmental and psychosocial to genomic insults (112). These factors are hypothesized to begin their effect even before conception (113). Therefore, researchers are increasingly acknowledging the concept of the “exposome,” first introduced in 2005, as the entirety of all non-genomic influences from conception to death owing to the internal effects from the human bodily environment and external influences encompassing harmful exposures to chemical pollutants/infectious pathogens, health behavioral factors linked to tobacco/alcohol consumption, physical activity or diet and even societal, economic, psychological and spiritual factors (114, 115). However, accounting for all potential exposure and confounder variables is a humongous task demanding high-end infrastructure, cost-intensive analytic methods, and high-dimensional data computational facility, all limited in low-resource settings (116). Therefore, although we have not been able to incorporate multiple exposures such as residential greenness, high-decibel community noise, water/food pollutants such as pesticides, endocrine disrupting chemicals, etc., with known effects on child growth/developmental trajectory and morbidity profile (117–123), and “omic” technologies; we have planned for this longitudinal transgenerational study with follow-up at regular intervals and biological sampling to initiate the investigation in this field in India. As evidence from similar cohorts begins to accumulate, the opportunity for robust data analysis will expand. In the future, the evidence base can be strengthened by merging collected exposure and health outcome data with advanced analyses of stored biological samples, similar to the approach used by the EXPOsOMICS research group (124).

A limitation of this exposure-response cohort is the potential of missing personal exposure information in the first trimester. Considering operational feasibility, the 16th week was chosen as the cut-off for pregnant women's enrolment and the start of exposure assessment in the antenatal period. Previous research has shown that most women in India report their first antenatal care visit within a median time of 16 weeks of gestation, and only 19.6% of pregnancies are detected and registered within the first trimester (125, 126). Hence, it is likely that we will be enrolling most of our pregnant participants in the gestational period of the 12th–16th week, and our field-data-based exposure assessment will fail to account for the complete picture of first-trimester exposure. This can be a significant limitation since it is plausible that the sensitive window for exposure in this context can be during the first trimester. Data analyzed from the INMA Spanish birth cohort showed that the z-score for length at the 6th month of the child's age reduced by 6% for every 10- $\mu\text{g}/\text{m}^3$ increase in antenatal NO_2 exposure during the first trimester (127). Block and Calderón-Garcidueñas (128) also stated that first-trimester exposure to organic constituents of PM, such as polycyclic aromatic hydrocarbons, had a maximal effect on fetal growth when compared with later exposures. This limitation affects birth cohorts in low- and middle-income countries in Asia and Africa. For example, a rural Ghanaian pregnancy cohort investigating air pollution and childhood growth trajectory enrolled pregnant women at or before the 24th week of gestation (15). Authors would have been facing similar constraints as us since the median time to first visit for antenatal care among African women has been reported to be 5 months (129).

We have attempted to overcome this limitation by incorporating past exposure open-access data (such as CPCB ground monitoring

stations/satellite-based estimates) of $PM_{2.5}$ into our constructed LUR models. Previous studies have used this method. For example, the recently published Californian population-based prospective pregnancy cohort study (MADRES) enrolled pregnant women with a gestational age of less than 30 weeks and obtained air pollution exposure information using data from the United States Environmental Protection Agency Air Quality System to model daily participant exposure beginning from 2 years before pregnancy (130). However, using only LUR modeling-based exposure assessment suffers from ecological fallacy (131). Final estimation is highly dependent upon the density of monitoring stations from which PM data can be used to train the models and the granularity of data for predictor variables and, thus, cannot accurately differentiate between individual-specific exposure, particularly when their residential addresses are clustered close together (132, 133). Hence, data triangulation by adding personally measured and biomonitoring data would increase confidence in the overall exposure assessment (134). We have thus adopted a multi-pronged strategy to estimate the study participants' accurate exposure information.

Finally, to ensure the highest level of internal validity of our study, we will attempt to overcome the biases inherent in adopting a cohort study design (135, 136). For example, to control for attrition bias, loss-to-follow-up will be minimized through better rapport building with the study participants with the support of CHWs. Published evidence acknowledges the crucial role played by CHWs, who are usually residents of the locality where they work and, hence, have an established rapport with their beneficiaries (137, 138). By seeking the active cooperation of CHWs through appropriate incentivization, we will be leveraging this trust built with the community. Hence, we expect attrition to be minimal in the study. In addition, we will also systematically document the characteristics (including the reasons for withdrawal) of those participants who decline further follow-up. Although not wholly amenable to control, other selection biases like non-response bias and healthy entrant bias will be accounted for by asking for and recording relevant information about those pregnant women who refuse to participate in the study when approached for consent (135, 136). Similarly, information and confounding bias will be minimized by ensuring the use of validated pilot-tested questionnaires and appropriate collection of data on exposure, outcome, and confounding variables by trained research staff (135, 136).

5 Conclusion

This manuscript outlines the methodology for establishing an Indian mother–child air pollution birth cohort and its follow-up. The study addresses critical gaps in existing evidence on the adverse effects of early-life exposure to air PM and its heavy metal constituents among Indian children. While resource limitations may restrict comprehensive exposure assessment and reduce the generalisability of our findings to all sub-populations within India and other low- and middle-income countries, the study's strengths will provide a valuable epidemiological foundation for advancing knowledge in this area. By detailing our rigorously planned study methods and outcome measures, which align with established and ongoing birth cohorts, we aim to serve as a foundation for future cohorts. Collectively, such efforts can generate robust evidence to inform context-specific

policies and the development of effective prevention and mitigation strategies.

Ethics statement

The studies involving humans were approved by Institutional (Human) Ethics Committee, National Institute for Research in Environmental Health, Bhopal, Madhya Pradesh, India. 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

TT: Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing, Conceptualization, Data curation, Formal analysis, Funding acquisition. VY: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. UM: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. VD: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. RT: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. RA: Conceptualization, Formal analysis, Funding acquisition, Investigation, Methodology, Resources, Supervision, Validation, Writing – original draft, Writing – review & editing. DR: Data curation, Formal analysis, Software, Validation, Writing – review & editing. SR: Formal analysis, Investigation, Methodology, Software, Supervision, Validation, Writing – review & editing. SS: Formal analysis, Funding acquisition, Investigation, Methodology, Supervision, Validation, Writing – review & editing. SD: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. YS: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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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.

References

- World Health Organization (WHO). Ambient (outdoor) air pollution. (2018). Available online at: [https://www.who.int/news-room/fact-sheets/detail/ambient-\(outdoor\)-air-quality-and-health](https://www.who.int/news-room/fact-sheets/detail/ambient-(outdoor)-air-quality-and-health) (Accessed June 17, 2020).
- Greenstone M, Hasenkopf C. Air quality life index (AQLI) - 2023 annual update. Chicago: Energy Policy Institute at the University of Chicago (EPIC) (2023).
- World Health Organization. *WHO global air quality guidelines: Particulate matter (PM_{2.5} and PM₁₀), ozone, nitrogen dioxide, sulfur dioxide and carbon monoxide*. World Health Organization. (2021). Available online at: (Accessed June 2, 2024) <https://www.who.int/publications/i/item/9789240034228>.
- Climate and Clean Air Coalition, Scientific and Technical Advisory Panel (STAP) of the International Day of Clean Air for blue skies. UNEP Air Pollution Action Note – Data you need to know. (2023). Available online at: <https://www.unep.org/interactives/air-pollution-note> (Accessed February 6, 2024).
- Braga AL, Saldiva PH, Pereira LA, Menezes JJ, Conceição GM, Lin CA, et al. Health effects of air pollution exposure on children and adolescents in São Paulo, Brazil. *Pediatr Pulmonol*. (2001) 31:106–13. doi: 10.1002/1099-0496(200102)31:2<106::aid-ppul1017>3.0.co;2-m
- Sly PD, Flack F. Susceptibility of children to environmental pollutants. *Ann N Y Acad Sci*. (2008) 1140:163–83. doi: 10.1196/annals.1454.017
- Landrigan PJ, Fuller R, Acosta NJ, Adeyi O, Arnold R, Baldé AB, et al. The lancet commission on pollution and health. *Lancet*. (2018) 391:462–512. doi: 10.1016/S0140-6736(17)32345-0
- Clark H, Coll-Seck AM, Banerjee A, Peterson S, Dalglish SL, Ameratunga S, et al. A future for the world's children? A WHO–UNICEF–Lancet Commission. *Lancet*. (2020) 395:605–58. doi: 10.1016/S0140-6736(19)32540-1
- UNICEF Division of Data, Analytics, Planning and Monitoring – Data and Analytics Section. Progress on Children's well-being: Centring child rights in the 2030 agenda – For every child, a sustainable future. New York: United Nations Children's Fund (UNICEF) (2023).
- Kannan S, Misra DP, Dvonch JT, Krishnakumar A. Exposures to airborne particulate matter and adverse perinatal outcomes: a biologically plausible mechanistic framework for exploring potential effect modification by nutrition. *Environ Health Perspect*. (2006) 114:1636–42. doi: 10.1289/ehp.9081
- Pedersen M, Giorgis-Allemand L, Bernard C, Aguilera I, Andersen A-MN, Ballester F, et al. Ambient air pollution and low birthweight: a European cohort study (ESCAPE). *Lancet Respir Med*. (2013) 1:695–704. doi: 10.1016/S2213-2600(13)70192-9
- Veras M, Waked D, Saldiva P. Safe in the womb? Effects of air pollution to the unborn child and neonates. *J Pediatr*. (2022) 98:S27–31. doi: 10.1016/j.jpeds.2021.09.004
- Goyal N, Canning D. Exposure to ambient fine particulate air pollution in utero as a risk factor for child stunting in Bangladesh. *Int J Environ Res Public Health*. (2017) 15:E22. doi: 10.3390/ijerph15010022
- Ranathunga N, Perera P, Nandasena S, Sathiakumar N, Kasturiratne A, Wickremasinghe AR. Effects of indoor air pollution due to solid fuel combustion on physical growth of children under 5 in Sri Lanka: a descriptive cross sectional study. *PLoS One*. (2021) 16:e0252230. doi: 10.1371/journal.pone.0252230
- Boamah-Kaali E, Jack DW, Ae-Ngibise KA, Quinn A, Kaali S, Dubowski K, et al. Prenatal and postnatal household air pollution exposure and infant growth trajectories: evidence from a rural Ghanaian pregnancy cohort. *Environ Health Perspect*. (2021) 129:117009. doi: 10.1289/EHP8109
- Lin L, Li T, Sun M, Liang Q, Ma Y, Wang F, et al. Global association between atmospheric particulate matter and obesity: a systematic review and meta-analysis. *Environ Res*. (2022) 209:112785. doi: 10.1016/j.envres.2022.112785
- Chiu Y-HM, Hsu H-HL, Wilson A, Coull BA, Pendo MP, Baccarelli A, et al. Prenatal particulate air pollution exposure and body composition in urban preschool children: examining sensitive windows and sex-specific associations. *Environ Res*. (2017) 158:798–805. doi: 10.1016/j.envres.2017.07.026
- Starling AP, Moore BF, Thomas DSK, Peel JL, Zhang W, Adgate JL, et al. Prenatal exposure to traffic and ambient air pollution and infant weight and adiposity: the healthy start study. *Environ Res*. (2020) 182:109130. doi: 10.1016/j.envres.2020.109130
- Zhou S, Lin L, Bao Z, Meng T, Wang S, Chen G, et al. The association of prenatal exposure to particulate matter with infant growth: a birth cohort study in Beijing, China. *Environ Pollut*. (2021) 277:116792. doi: 10.1016/j.envpol.2021.116792
- Checkley W, Thompson LM, Sinharoy SS, Hossen S, Moulton LH, Chang HH, et al. Effects of cooking with liquefied petroleum gas or biomass on stunting in infants. *N Engl J Med*. (2024) 390:44–54. doi: 10.1056/NEJMoa2302687
- Park M, Joo HS, Lee K, Jang M, Kim SD, Kim I, et al. Differential toxicities of fine particulate matters from various sources. *Sci Rep*. (2018) 8:17007. doi: 10.1038/s41598-018-35398-0
- Michael T, Kohn E, Daniel S, Hazan A, Berkovitch M, Brik A, et al. Prenatal exposure to heavy metal mixtures and anthropometric birth outcomes: a cross-sectional study. *Environ Health*. (2022) 21:139. doi: 10.1186/s12940-022-00950-z
- Yao L, Liu L, Dong M, Yang J, Zhao Z, Chen J, et al. Trimester-specific prenatal heavy metal exposures and sex-specific postpartum size and growth. *J Expo Sci Environ Epidemiol*. (2022) 33:895–902. doi: 10.1038/s41370-022-00443-8
- Dey S. Impact of air pollution on child health in India and the way forward. *Indian Pediatr*. (2022) 59:447–50. doi: 10.1007/s13312-022-2532-3
- Black MM, Walker SP, Fernald LCH, Andersen CT, DiGirolamo AM, Lu C, et al. Lancet early childhood development series steering committee early childhood development coming of age: science through the life course. *Lancet Lond Engl*. (2017) 389:77–90. doi: 10.1016/S0140-6736(16)31389-7
- Balakrishnan K, Ghosh S, Thangavel G, Sambandam S, Mukhopadhyay K, Puttaswamy N, et al. Exposures to fine particulate matter (PM_{2.5}) and birthweight in a rural-urban, mother-child cohort in Tamil Nadu, India. *Environ Res*. (2018) 161:524–31. doi: 10.1016/j.envres.2017.11.050
- Goyal N, Canning D. The association of in-utero exposure to ambient fine particulate air pollution with low birth weight in India. *Environ Res Lett*. (2021) 16:054034. doi: 10.1088/1748-9326/abf18e
- Spears D, Dey S, Chowdhury S, Scovronick N, Vyas S, Apte J. The association of early-life exposure to ambient PM_{2.5} and later-childhood height-for-age in India: an observational study. *Environ Health*. (2019) 18:62. doi: 10.1186/s12940-019-0501-7
- Baiz N, Slama R, Béné M-C, Charles M-A, Kolopp-Sarda M-N, Magnan A, et al. Maternal exposure to air pollution before and during pregnancy related to changes in newborn's cord blood lymphocyte subpopulations. The EDEN study cohort. *BMC Pregnancy Childbirth*. (2011) 11:87. doi: 10.1186/1471-2393-11-87
- Herr CEW, Dostal M, Ghosh R, Ashwood P, Lipsett M, Pinkerton KE, et al. Air pollution exposure during critical time periods in gestation and alterations in cord blood lymphocyte distribution: a cohort of livebirths. *Environ Health Glob Access Sci Source*. (2010) 9:46. doi: 10.1186/1476-069X-9-46
- Rychlik KA, Sillé FCM. Environmental exposures during pregnancy: mechanistic effects on immunity. *Birth Defects Res*. (2019) 111:178–96. doi: 10.1002/bdr2.1469

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Supplementary material

The Supplementary material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fpubh.2025.1485417/full#supplementary-material>

32. Darrow LA, Klein M, Flanders WD, Mulholland JA, Tolbert PE, Strickland MJ. Air pollution and acute respiratory infections among children 0–4 years of age: an 18-year time-series study. *Am J Epidemiol.* (2014) 180:968–77. doi: 10.1093/aje/kwu234
33. Hasan MM, Saha KK, Yunus RM, Alam K. Prevalence of acute respiratory infections among children in India: regional inequalities and risk factors. *Matern Child Health J.* (2022) 26:1594–602. doi: 10.1007/s10995-022-03424-3
34. Mondal D, Paul P. Effects of indoor pollution on acute respiratory infections among under-five children in India: evidence from a nationally representative population-based study. *PLoS One.* (2020) 15:e0237611. doi: 10.1371/journal.pone.0237611
35. Singh PK, Sinha P, Singh N, Singh L, Singh S. Does secondhand smoke exposure increase the risk of acute respiratory infections among children aged 0–59 months in households that use clean cooking fuel? A cross-sectional study based on 601 509 households in India. *Indoor Air.* (2022) 32:e12980. doi: 10.1111/ina.12980
36. Chakrabarti S, Khan MT, Kishore A, Roy D, Scott SP. Risk of acute respiratory infection from crop burning in India: estimating disease burden and economic welfare from satellite and national health survey data for 250 000 persons. *Int J Epidemiol.* (2019) 48:1113–24. doi: 10.1093/ije/dyz022
37. George PE, Thakkar N, Yasobant S, Saxena D, Shah J. Impact of ambient air pollution and socio-environmental factors on the health of children younger than 5 years in India: a population-based analysis. *Lancet Reg Health Southeast Asia.* (2024) 20. doi: 10.1016/j.lansea.2023.100328
38. Madhya Pradesh Population 2011–2020. pp. 100328. Available online at: <https://www.census2011.co.in/census/state/madhya+pradesh.html> (Accessed August 3, 2020).
39. States Uts - Madhya Pradesh - Know India: National Portal of India. Available online at: <https://knowindia.gov.in/states-uts/madhya-pradesh.php> (Accessed August 3, 2020).
40. List of Most populated cities in India. Available online at: <https://www.census2011.co.in/city.php> (Accessed February 7, 2024).
41. Bhopal City Population. (2024). Literacy and Hindu Muslim Population. Available online at: <https://www.census2011.co.in/census/city/302-bhopal.html> (Accessed February 7, 2024).
42. Ujjain City Population. (2024). Literacy and Hindu Muslim Population. Available online at: <https://www.census2011.co.in/census/city/296-ujjain.html> (Accessed February 7, 2024).
43. Kuppusamy P, Prusty RK, Kale DP. High-risk pregnancy in India: prevalence and contributing risk factors – a national survey-based analysis. *J Glob Health.* (2023) 13:04116. doi: 10.7189/jogh.13.04116
44. Langlois PH, Hoyt AT, Desrosiers TA, Lupo PJ, Lawson CC, Waters MA, et al. Maternal occupational exposure to polycyclic aromatic hydrocarbons and small for gestational age offspring. *Occup Environ Med.* (2014) 71:529–35. doi: 10.1136/oemed-2013-101833
45. Norlén F, Gustavsson P, Wiebert P, Rylander L, Albin M, Westgren M, et al. Occupational exposure to inorganic particles during pregnancy and birth outcomes: a nationwide cohort study in Sweden. *BMJ Open.* (2019) 9:e023879. doi: 10.1136/bmjopen-2018-023879
46. Quansah R, Jaakkola JJK. Paternal and maternal exposure to welding fumes and metal dusts or fumes and adverse pregnancy outcomes. *Int Arch Occup Environ Health.* (2009) 82:529–37. doi: 10.1007/s00420-008-0349-6
47. Soliman A, De Sanctis V, Alaraj N, Ahmed S, Alyafei F, Hamed N, et al. Early and long-term consequences of nutritional stunting: from childhood to adulthood. *Acta Bio Medica Atenei Parm.* (2021) 92:e2021168. doi: 10.23750/abm.v92i1.11346
48. Li X, Li Y, Yu B, Nima Q, Meng H, Shen M, et al. Urban-rural differences in the association between long-term exposure to ambient particulate matter (PM) and malnutrition status among children under five years old: a cross-sectional study in China. *J Glob Health.* (2023) 13:04112. doi: 10.7189/jogh.13.04112
49. Agarwal S, Curtis SL, Angeles G, Speizer IS, Singh K, Thomas JC. The impact of India's accredited social health activist (ASHA) program on the utilization of maternity services: a nationally representative longitudinal modelling study. *Hum Resour Health.* (2019) 17:68. doi: 10.1186/s12960-019-0402-4
50. Nadella P, Subramanian SV, Roman-Urrestarazu A. The impact of community health workers on antenatal and infant health in India: a cross-sectional study. *SSM - Popul Health.* (2021) 15:100872. doi: 10.1016/j.ssmph.2021.100872
51. Ministry of Women & Child Development. Annual report 2017–18: chapter 3: child development. (2018). Available online at: <https://wcd.nic.in/sites/default/files/AR%202017-18%20Chapter%203.pdf> (Accessed June 24, 2023).
52. NHM. Guidelines on accredited social health Activists (ASHA). (2005). Available online at: <https://nhm.gov.in/images/pdf/communitisation/task-group-reports/guidelines-on-asha.pdf> (Accessed June 24, 2023).
53. Integrated Child Development Services (ICDS) Scheme. (2005). Available online at: <http://icds-wcd.nic.in/icds.aspx> (Accessed May 29, 2022).
54. Scientific & Technical Activity: (Information Technology): Continuous Ambient Air Quality Monitoring Stations (CAAQMS). (2021). Available online at: https://cpqb.nic.in/uploads/it_technical_activity.pdf (Accessed July 7, 2023).
55. CPCB. Central Pollution Control Board- Monitoring Network: Operating Stations under National Air Quality Monitoring Programme (NAMP). (2024). Available online at: https://cpqb.nic.in/uploads/Stations_NAMP.pdf (Accessed February 9, 2024).
56. Aguilera I, Garcia-Esteban R, Iñiguez C, Nieuwenhuijsen MJ, Rodríguez À, Paez M, et al. Prenatal exposure to traffic-related air pollution and ultrasound measures of fetal growth in the INMA Sabadell cohort. *Environ Health Perspect.* (2010) 118:705–11. doi: 10.1289/ehp.0901228
57. Iñiguez C, Esplugues A, Sunyer J, Basterrechea M, Fernández-Somoano A, Costa O, et al. Prenatal exposure to NO₂ and ultrasound measures of fetal growth in the Spanish INMA cohort. *Environ Health Perspect.* (2016) 124:235–42. doi: 10.1289/ehp.1409423
58. Luo D, Kuang T, Chen Y-X, Huang Y-H, Zhang H, Xia Y-Y. Air pollution and pregnancy outcomes based on exposure evaluation using a land use regression model: a systematic review. *Taiwan J Obstet Gynecol.* (2021) 60:193–215. doi: 10.1016/j.tjog.2021.01.004
59. Eeftens M, Beelen R, de Hoogh K, Bellander T, Cesaroni G, Cirach M, et al. Development of land use regression models for PM_{2.5}, PM_{2.5} absorbance, PM₁₀ and PM_{coarse} in 20 European study areas; results of the ESCAPE project. *Environ Sci Technol.* (2012) 46:11195–205. doi: 10.1021/es301948k
60. Katoch V, Kumar A, Imam F, Sarkar D, Knibbs LD, Liu Y, et al. Addressing biases in ambient PM_{2.5} exposure and associated health burden estimates by filling satellite AOD retrieval gaps over India. *Environ Sci Technol.* (2023) 57:19190–201. doi: 10.1021/acs.est.3c03355
61. Tiwari S, Kumar A, Mantri S, Dey S. Modelling ambient PM_{2.5} exposure at an ultra-high resolution and associated health burden in megacity Delhi: exposure reduction target for 2030. *Environ Res Lett.* (2023) 18:044010. doi: 10.1088/1748-9326/acc261
62. Xu H, Bechle MJ, Wang M, Szpiro AA, Vedal S, Bai Y, et al. National PM_{2.5} and NO₂ exposure models for China based on land use regression, satellite measurements, and universal kriging. *Sci Total Environ.* (2019) 655:423–33. doi: 10.1016/j.scitotenv.2018.11.125
63. Ha S, Nobles C, Kanner J, Sherman S, Cho S-H, Perkins N, et al. Air pollution exposure monitoring among pregnant women with and without asthma. *Int J Environ Res Public Health.* (2020) 17:4888. doi: 10.3390/ijerph17134888
64. Wu J, Xiao X, Li Y, Yang F, Yang S, Sun L, et al. Personal exposure to fine particulate matter (PM_{2.5}) of pregnant women during three trimesters in rural Yunnan of China. *Environ Pollut.* (2020) 256:113055. doi: 10.1016/j.envpol.2019.113055
65. USEPA. Compendium of methods for the determination of inorganic compounds in ambient air. Compendium of Method IO-3.2, EPA/625/R-96/010a. (1999). <https://www.epa.gov/amtic/compendium-methods-determination-inorganic-compounds-ambient-air> Available online at: (Accessed March 7, 2023).
66. García-Villarino M, Signes-Pastor AJ, Karagas MR, Riaño-Galán I, Rodríguez-Dehli C, Grimalt JO, et al. Exposure to metal mixture and growth indicators at 4–5 years. A study in the INMA-Asturias cohort. *Environ Res.* (2022) 204:112375. doi: 10.1016/j.envres.2021.112375
67. Heng YY, Asad I, Coleman B, Menard L, Benki-Nugent S, Hussein Were F, et al. Heavy metals and neurodevelopment of children in low and middle-income countries: a systematic review. *PLoS One.* (2022) 17:e0265536. doi: 10.1371/journal.pone.0265536
68. Ma J, Geng S, Sun Q, Zhang X, Han L, Yao X, et al. Exposure to metal mixtures and young children's growth and development: a biomonitoring-based study in eastern China. *Ecotoxicol Environ Saf.* (2023) 268:115726. doi: 10.1016/j.ecoenv.2023.115726
69. Notario-Barandiaran L, Díaz-Coto S, Jimenez-Redondo N, Guxens M, Vrijheid M, Andiarana A, et al. Latent childhood exposure to mixtures of metals and neurodevelopmental outcomes in 4–5-year-old children living in Spain. *Expo Health.* (2024) 16:1053–66. doi: 10.1007/s12403-023-00610-8
70. Zeng X, Xu X, Qin Q, Ye K, Wu W, Huo X. Heavy metal exposure has adverse effects on the growth and development of preschool children. *Environ Geochem Health.* (2019) 41:309–21. doi: 10.1007/s10653-018-0114-z
71. Guidelines for the measurement of ambient air pollutants: Guidelines for Manual Sampling & Analyses. Delhi: Central Pollution Control Board (CPCB) (2013).
72. HBNC & HBYC National Health Mission. Available online at: <https://nhm.gov.in/index4.php?lang=1&level=0&linkid=491&lid=760> (Accessed February 9, 2024).
73. Dastak Abhiyan guidelines- National Health Mission (M.P.). Available online at: <https://www.nhmmp.gov.in/DastakDownload.aspx> (Accessed February 9, 2024).
74. WHO-UNICEF. Model IMCI handbook: Integrated management of childhood illness. (2006). <https://www.who.int/publications-detail-redirect/9241546441> (Accessed November 30, 2023).
75. Broor S, Parveen S, Bharaj P, Prasad VS, Srinivasulu KN, Sumanth KM, et al. A prospective three-year cohort study of the epidemiology and virology of acute respiratory infections of children in rural India. *PLoS One.* (2007) 2:e491. doi: 10.1371/journal.pone.0000491
76. Ministry of Health and Family Welfare, Government of India. National Immunization Schedule (NIS) for Infants, Children and Pregnant Women. Available online at: <https://main.mohfw.gov.in/sites/default/files/245453521061489663873.pdf> (Accessed May 27, 2022).
77. About IDSP: Integrated Disease Surveillance Programme (IDSP). Available online at: <https://idsp.nic.in/index4.php?lang=1&level=0&linkid=313&lid=1592> (Accessed May 29, 2022).
78. WHO STEPwise approach to surveillance. (2022). Available online at: <https://www.who.int/europe/tools-and-toolkits/who-stepwise-approach-to-surveillance> (Accessed December 5, 2022).

79. Saleem S. Modified Kuppuswamy socioeconomic scale updated for the year Indian *J Forensic Community Med.* (2020) 7:1–3. doi: 10.18231/j.ijfcm.2020.001
80. WHO/UNICEF. Core questions on drinking-water and sanitation for households surveys. (2006). Available online at: <https://www.who.int/publications-detail-direct/9241563265> (Accessed November 29, 2023).
81. Garg A, Chadha R. Index for measuring the quality of complementary feeding practices in rural India. *J Health Popul Nutr.* (2009) 27:763–71. doi: 10.18231/j.ijfcm.2021.001
82. India - Census of India 2011 - Houselisting and Housing Census Schedule - English. (2011). Available online at: <https://censusindia.gov.in/nada/index.php/catalog/40450> (Accessed February 9, 2024).
83. National Family Health Survey (NFHS-5) 2019-21- Questionnaire. (2015). Available online at: <https://dhsprogram.com/pubs/pdf/frind3/frind3-vol2.pdf> (Accessed December 5, 2022).
84. Sabde YD, Trushna T, Mandal UK, Yadav V, Sarma DK, Aher SB, et al. Evaluation of health impacts of the improved housing conditions on under-five children in the socioeconomically underprivileged families in Central India: a 1-year follow-up study protocol. *Front Public Health.* (2022) 10:973721. doi: 10.3389/fpubh.2022.973721
85. Sabde YD, Yadav V, Pakhare AP, Kumar S, Joshi A, Joshi R. Association of tobacco use with the tobacco-related built environment: an ecological study from urban slums of Bhopal, India. *Glob Health Res Policy.* (2023) 8:3. doi: 10.1186/s41256-023-00287-1
86. Sabde Y, Mandal UK, Yadav V, Trushna T, Tiwari RR, Sabde Y, et al. Effect of the built environment on the cumulative incidence of acute diarrheal diseases: a community-based cohort study from underprivileged areas of Bhopal, India. *Cureus.* (2024) 16:e55942. doi: 10.7759/cureus.55942
87. National Ethical Guidelines for Biomedical and Health Research Involving Human Participants. New Delhi, India: Indian Council Of Medical Research (2017).
88. Gasparrini A, Armstrong B, Kenward MG. Distributed lag non-linear models. *Stat Med.* (2010) 29:2224–34. doi: 10.1002/sim.3940
89. Gasparrini A, Leone M. Attributable risk from distributed lag models. *BMC Med Res Methodol.* (2014) 14:55. doi: 10.1186/1471-2288-14-55
90. Larson PS, Espira L, Glenn BE, Larson MC, Crowe CS, Jang S, et al. Long-term PM_{2.5} exposure is associated with symptoms of acute respiratory infections among children under five years of age in Kenya, 2014. *Int J Environ Res Public Health.* (2022) 19:2525. doi: 10.3390/ijerph19052525
91. Lei C, Lou CT, Io K, SiTou KI, Ip CP, HongJin U, et al. Viral etiology among children hospitalized for acute respiratory tract infections and its association with meteorological factors and air pollutants: a time-series study (2014–2017) in Macao. *BMC Infect Dis.* (2022) 22:588. doi: 10.1186/s12879-022-07585-y
92. Niu Z, Habre R, Chavez TA, Yang T, Grubbs BH, Eckel SP, et al. Association between ambient air pollution and birth weight by maternal individual- and neighborhood-level stressors. *JAMA Netw Open.* (2022) 5:e2238174. doi: 10.1001/jamanetworkopen.2022.38174
93. Chang J, Streitman D. Physiologic adaptations to pregnancy. *Neurol Clin.* (2012) 30:781–9. doi: 10.1016/j.ncl.2012.05.001
94. Stillerman KP, Mattison DR, Giudice LC, Woodruff TJ. Environmental exposures and adverse pregnancy outcomes: a review of the science. *Reprod Sci Thousand Oaks Calif.* (2008) 15:631–50. doi: 10.1177/1933719108322436
95. Dadvand P, Parker J, Bell ML, Bonzini M, Brauer M, Darrow LA, et al. Maternal exposure to particulate air pollution and term birth weight: a multi-country evaluation of effect and heterogeneity. *Environ Health Perspect.* (2013) 121:267–373. doi: 10.1289/ehp.1205575
96. Bové H, Bongaerts E, Slenders E, Bijnsens EM, Saenen ND, Gyselaers W, et al. Ambient black carbon particles reach the fetal side of human placenta. *Nat Commun.* (2019) 10:3866. doi: 10.1038/s41467-019-11654-3
97. Bongaerts E, Lecante LL, Bové H, Roeflaers MBJ, Ameloot M, Fowler PA, et al. Maternal exposure to ambient black carbon particles and their presence in maternal and fetal circulation and organs: an analysis of two independent population-based observational studies. *Lancet Planet Health.* (2022) 6:e804–11. doi: 10.1016/S2542-5196(22)00200-5
98. Zhu N, Ji X, Geng X, Yue H, Li G, Sang N. Maternal PM_{2.5} exposure and abnormal placental nutrient transport. *Ecotoxicol Environ Saf.* (2021) 207:111281. doi: 10.1016/j.ecoenv.2020.111281
99. Bateson TF, Schwartz J. Children's response to air pollutants. *J Toxicol Environ Health A.* (2008) 71:238–43. doi: 10.1080/15287390701598234
100. Dimitrova A, Marois G, Kiesewetter G, Rafaj P, SKCS P, Olmos S, et al. Projecting the impact of air pollution on child stunting in India—synergies and trade-offs between climate change mitigation, ambient air quality control, and clean cooking access. *Environ Res Lett.* (2022) 17:104004. doi: 10.1088/1748-9326/ac8e89
101. Sinharoy SS, Clasen T, Martorell R. Air pollution and stunting: a missing link? *Lancet Glob Health.* (2020) 8:e472–5. doi: 10.1016/S2214-109X(20)30063-2
102. Backes CH, Nelin T, Gorr MW, Wold LE. Early life exposure to air pollution: how bad is it? *Toxicol Lett.* (2013) 216:47–53. doi: 10.1016/j.toxlet.2012.11.007
103. Dewey KG, Mayers DR. Early child growth: how do nutrition and infection interact? *Matern Child Nutr.* (2011) 7:129–42. doi: 10.1111/j.1740-8709.2011.00357.x
104. Martins VJB, Toledo Florêncio TMM, Grillo LP, Franco M, Do CP MPA, APG C, et al. Long-lasting effects of undernutrition. *Int J Environ Res Public Health.* (2011) 8:1817–46. doi: 10.3390/ijerph8061817
105. Mustakim MRD, Irwanto IR, Irmawati M, Setyoboedi B. Impact of stunting on development of children between 1–3 years of age. *Ethiop J Health Sci.* (2022) 32:569–78. doi: 10.4314/ejhs.v32i3.13
106. Shi X, Zheng Y, Cui H, Zhang Y, Jiang M. Exposure to outdoor and indoor air pollution and risk of overweight and obesity across different life periods: a review. *Ecotoxicol Environ Saf.* (2022) 242:113893. doi: 10.1016/j.ecoenv.2022.113893
107. Barker DJ. The fetal and infant origins of adult disease. *BMJ.* (1990) 301:1111. doi: 10.1136/bmj.301.6761.1111
108. Mandy M, Nyirenda M. Developmental origins of health and disease: the relevance to developing nations. *Int Health.* (2018) 10:66–70. doi: 10.1093/inthealth/ihy006
109. Fleisch AF, Rifas-Shiman SL, Koutrakis P, Schwartz JD, Kloog I, Melly S, et al. Prenatal exposure to traffic pollution: associations with reduced fetal growth and rapid infant weight gain. *Epidemiol Camb Mass.* (2015) 26:43–50. doi: 10.1093/EDE.0000000000000203
110. Black MM, Lutter CK, Trude ACB. All children surviving and thriving: re-envisioning UNICEF's conceptual framework of malnutrition. *Lancet Glob Health.* (2020) 8:e766–7. doi: 10.1016/S2214-109X(20)30122-4
111. Haisma H, Yousefzadeh S, Boele Van Hensbroek P. Towards a capability approach to child growth: a theoretical framework. *Matern Child Nutr.* (2017) 14:e12534. doi: 10.1111/mcn.12534
112. Esposito G, Azhari A, Borelli JL. Gene × environment interaction in developmental disorders: where do we stand and What's next? *Front Psychol.* (2018) 9:2036. doi: 10.3389/fpsyg.2018.02036
113. Lecorguill M, Schipper MC, O'Donnell A, Aubert AM, Tafflet M, Gassama M, et al. Impact of parental lifestyle patterns in the preconception and pregnancy periods on childhood obesity. *Front Nutr.* (2023) 10:1166981. doi: 10.3389/fnut.2023.1166981
114. Wild CP. Complementing the genome with an “exposome”: the outstanding challenge of environmental exposure measurement in molecular epidemiology. *Cancer Epidemiol Biomark Prev Publ Am Assoc Cancer Res Cosponsored Am Soc Prev Oncol.* (2005) 14:1847–50. doi: 10.1158/1055-9965.EPI-05-0456
115. Zhang X, Gao P, Snyder MP. The Exposome in the era of the quantified Self. *Annu Rev Biomed Data Sci.* (2021) 4:255–77. doi: 10.1146/annurev-biodatasci-012721-122807
116. Stingone JA, Buck Louis GM, Nakayama SF, Vermeulen RCH, Kwok RK, Cui Y, et al. Toward greater implementation of the Exposome research paradigm within environmental epidemiology. *Annu Rev Public Health.* (2017) 38:315–27. doi: 10.1146/annurev-publhealth-082516-012750
117. Bliznashka L, Roy A, Jaacks LM. Pesticide exposure and child growth in low- and middle-income countries: a systematic review. *Environ Res.* (2022) 215:114230. doi: 10.1016/j.envres.2022.114230
118. Chilipweli PM, Ngowi AV, Manji K. Maternal pesticide exposure and child neuro-development among smallholder tomato farmers in the southern corridor of Tanzania. *BMC Public Health.* (2021) 21:171. doi: 10.1186/s12889-020-10097-6
119. Di Pietro G, Forcucci F, Chiarelli F. Endocrine disruptor chemicals and Children's health. *Int J Mol Sci.* (2023) 24:2671. doi: 10.3390/ijms24032671
120. Raess M, Valeria Maria Brentani A, Flückiger B, de Antas L, de Campos B, Fink G, et al. Association between community noise and children's cognitive and behavioral development: a prospective cohort study. *Environ Int.* (2022) 158:106961. doi: 10.1016/j.envint.2021.106961
121. Predieri B, Iughetti L, Bernasconi S, Street ME. Endocrine disrupting chemicals' effects in children: what we know and what we need to learn? *Int J Mol Sci.* (2022) 23:11899. doi: 10.3390/ijms231911899
122. Lin L, Li Q, Yang J, Han N, Chen G, Jin C, et al. The associations of residential greenness with fetal growth in utero and birth weight: a birth cohort study in Beijing, China. *Environ Int.* (2020) 141:105793. doi: 10.1016/j.envint.2020.105793
123. Dadvand P, Nieuwenhuijsen MJ, Esnaola M, Fornis J, Basagaña X, Alvarez-Pedrerol M, et al. Green spaces and cognitive development in primary schoolchildren. *Proc Natl Acad Sci.* (2015) 112:7937–42. doi: 10.1073/pnas.1503402112
124. Vineis P, Chadeau-Hyam M, Gmuender H, Gulliver J, Herceg Z, Kleinjans J, et al. The exposome in practice: design of the EXPOsOMICS project. *Int J Hyg Environ Health.* (2017) 220:142–51. doi: 10.1016/j.ijheh.2016.08.001
125. Patel PB, Rupani MP, Patel SS. Antenatal care registration and predicting factors of late registration among pregnant women. *Trop Dr.* (2013) 43:9–12. doi: 10.1177/0049475513480772
126. Tripathy A, Mishra PS. Inequality in time to first antenatal care visits and its predictors among pregnant women in India: an evidence from national family health survey. *Sci Rep.* (2023) 13:4706. doi: 10.1038/s41598-023-31902-3
127. Clemente DBP, Casas M, Janssen BG, Lertxundi A, Santa-Marina L, Iñiguez C, et al. Prenatal ambient air pollution exposure, infant growth and placental mitochondrial

DNA content in the INMA birth cohort. *Environ Res.* (2017) 157:96–102. doi: 10.1016/j.envres.2017.05.018

128. Block ML, Calderón-Garcidueñas L. Air pollution: mechanisms of Neuroinflammation & CNS disease. *Trends Neurosci.* (2009) 32:506–16. doi: 10.1016/j.tins.2009.05.009

129. Fentaw KD, Fenta SM, Biresaw HB, Mulugeta SS. Time to first antenatal care visit among pregnant women in Ethiopia: secondary analysis of EDHS 2016; application of AFT shared frailty models. *Arch Public Health.* (2021) 79:192. doi: 10.1186/s13690-021-00720-2

130. Ji N, Johnson M, Eckel SP, Gauderman WJ, Chavez TA, Berhane K, et al. Prenatal ambient air pollution exposure and child weight trajectories from the 3rd trimester of pregnancy to 2 years of age: a cohort study. *BMC Med.* (2023) 21:341. doi: 10.1186/s12916-023-03050-y

131. Wakefield J, Shaddick G. Health-exposure modeling and the ecological fallacy. *Biostat Oxf Engl.* (2006) 7:438–55. doi: 10.1093/biostatistics/kxj017

132. Liang L, Gong P, Cong N, Li Z, Zhao Y, Chen Y. Assessment of personal exposure to particulate air pollution: the first result of City health outlook (CHO) project. *BMC Public Health.* (2019) 19:711. doi: 10.1186/s12889-019-7022-8

133. Mölter A, Lindley S. Developing land use regression models for environmental science research using the XLUR tool – more than a one-trick pony. *Environ Model Softw.* (2021) 143:105108. doi: 10.1016/j.envsoft.2021.105108

134. Trushna T, Dhiman V, Raj D, Tiwari RR. Effects of ambient air pollution on psychological stress and anxiety disorder: a systematic review and meta-analysis of epidemiological evidence. *Rev Environ Health.* (2021) 36:501–21. doi: 10.1515/revh-2020-0125

135. Sedgwick P. Bias in observational study designs: prospective cohort studies. *BMJ.* (2014) 349:g7731. doi: 10.1136/bmj.g7731

136. Stenson JF, Kepler CK. Bias in prospective research and how to avoid it. *Clin Spine Surg.* (2019) 32:254–5. doi: 10.1097/BSD.0000000000000767

137. Mishra A. “Trust and teamwork matter”: community health workers’ experiences in integrated service delivery in India. *Glob Public Health.* (2014) 9:960–74. doi: 10.1080/17441692.2014.934877

138. Shrivastava R, Singh A, Khan A, Choubey S, Restivo Haney J, Karyotaki E, et al. Stress alleviation methods for community-based health ActiVists (SAMBHAV): development of a digital program for stress reduction for community health workers in rural India. *SSM - Ment Health.* (2023) 4:100230. doi: 10.1016/j.ssmmh.2023.100230

139. de Onis M, Habicht JP. Anthropometric reference data for international use: recommendations from a World Health Organization expert committee. *Am J Clin Nutr.* (1996) 64:650–8. doi: 10.1093/ajcn/64.4.650

140. Physical status: the use and interpretation of anthropometry. Report of a WHO expert committee. *World Health Organ Tech Rep Ser.* (1995):854.

141. Cutland CL, Lackritz EM, Mallett-Moore T, Bardaji A, Chandrasekaran R, Lahariya C, et al. Low birth weight: case definition & guidelines for data collection, analysis, and presentation of maternal immunization safety data. *Vaccine.* (2017) 35:6492–500. doi: 10.1016/j.vaccine.2017.01.049

142. ICD-11 for Mortality and Morbidity Statistics. <https://icd.who.int/dev11/l-m/en#/http%3a%2f%2fd.who.int%2fcd%2fentity%2f1950379483> (Accessed November 6, 2023).

143. Himes JH, Dietz WH. Guidelines for overweight in adolescent preventive services: recommendations from an expert committee. The expert committee on clinical guidelines for overweight in adolescent preventive services. *Am J Clin Nutr.* (1994) 59:307–16. doi: 10.1093/ajcn/59.2.307

144. Ayele DG, ASR A, MOM M. Determinants of under-five children body mass index in Sudan; application of quantile regression: a systematic review. *Iran J Public Health.* (2021) 50:1–10. doi: 10.18502/ijph.v50i1.5067

145. WHO Child Growth Standards: Training Course on Child Growth Assessment. Training Course on Child Growth Assessment WHO Child Growth Standards. Geneva (Switzerland): World Health Organization. (2008). Available online at: <https://www.who.int/publications-detail-redirect/9789241595070> (Accessed November 6, 2023).

146. Squires J, Bricker D. Ages & Stages Questionnaires® (Third Edition). (ASQ-3™ [Database record]). APA PsycTests. (2009). doi: 10.1037/t11523-000

147. Drotar D, Stancin T, Dworkin PH, Sices L, Wood S. Selecting developmental surveillance and screening tools. *Pediatr Rev.* (2008) 29:e52–8. doi: 10.1542/pir.29-10-e52

148. Small JW, Hix-Small H, Vargas-Baron E, Marks KP. Comparative use of the ages and stages questionnaires in low- and middle-income countries. *Dev Med Child Neurol.* (2019) 61:431–43. doi: 10.1111/dmcn.13938

149. Juneja M, Mohanty M, Jain R, Ramji S. Ages and stages questionnaire as a screening tool for developmental delay in Indian children. *Indian Pediatr.* (2012) 49:457–61. doi: 10.1007/s13312-012-0074-9

150. Gulati S, Israni A, Squires J, Singh A, Madaan P, Kamila G, et al. Socio-cultural adaptation and validation of ages and stages questionnaire (ASQ 3) in Indian children aged 2 to 24 months. *Indian Pediatr.* (2023) 60:908–12. doi: 10.1007/s13312-023-3034-7

151. Brown KA, Parikh S, Patel DR. Understanding basic concepts of developmental diagnosis in children. *Transl Pediatr.* (2020) 9:S9–S22. doi: 10.21037/tp.2019.11.04

152. Gupta P, Menon PSN, Ramji S, Lodha R. PG textbook of pediatrics. 1st ed. New Delhi: Jaypee Brothers Medical Publishers (P), Ltd (2015). 3 p.

Glossary

ANC - Antenatal Care

APGAR - Scoring Given to Child after Birth based on Appearance, Pulse, Grimace, Activity, and Respiration

AR - Attributable Risk

ARI - Acute Respiratory Infection

ASHA - Accredited Social Health Activists

ASQ-3 - Ages and Stages Questionnaire- Third Edition

AWW - Anganwadi Workers

AQI - Air Quality Index

BMI - Body Mass Index

CAAQMS - Continuous Ambient Air Quality Monitoring Stations

CA - Chronological Age

CHW - Community Health Workers

CPCB - Central Pollution Control Board

DA - Developmental Age

DCMC - Data Collection and Management Committee

DNA - Deoxyribonucleic Acid

DQ - Developmental Quotient

DLNM - Distributed Lag Non-Linear Model

EDD - Expected Date of Delivery

EDXRF - Energy-Dispersive X-Ray Fluorescence

GIS - Geographic Information System

HBNC - Home-Based Newborn Care

HBYC - Home-Based Care for Young Child Programme

HVAS - High Volume Air Sampler

ICD - International Classification of Disease

ICDS - Integrated Child Development Scheme

ICP-OES - Inductively Coupled Plasma Optical Emission Spectroscopy

IDSP - Integrated Disease Surveillance Project

IMNCI - Integrated Management of Neonatal and Childhood Illness

LBW - Low Birth Weight

LMP - Last Menstrual Period

LUR - Land Use Regression

MP - Madhya Pradesh

NAAQS - National Ambient Air Quality Standards

NFHS - National Family Health Survey

NHM - National Health Mission

NICU - Neonatal Intensive Care Unit

NIS - National Immunization Schedule

NO₂ - Nitrogen Dioxide

OR - Odds Ratio

PM - Particulate Matter

PM₁₀ - Particulate Matter with Aerodynamic Diameter < 10 µm

PM_{2.5} - Particulate Matter with Aerodynamic Diameter < 2.5 µm

RR - Relative Risk

SD - Standard Deviation

SDG - Sustainable Development Goal

SES - Socio-Economic Status

SGA - Short For Gestational Age

SO₂ - Sulphur Dioxide

UIP - Universal Immunization Programme

UNICEF - United Nations Children's Fund

UNEP - United Nations Environment Programme

USEPA - United States Environmental Protection Agency

WHO - World Health Organisation

Measurement units

m - Metre

ml - Millilitre (1 mL = 10⁻³litre)

µm - Micrometre (1 µm = 10⁻⁶ m)

kg - Kilogram

g - Gram (1 g = 10⁻³kilogram)

µg - Microgram (1 µg = 10⁻⁶ g).



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Perinatal outcomes in Malta between 2008 and 2022: a comparison of three 5 yearly epochs

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Background: Perinatal and neonatal mortality rates are quality indicators of antenatal, neonatal and postnatal care. This study describes perinatal outcomes for Malta over the 15 year period 2008–2022 to inform future practice and healthcare provision.

Methodology: Aggregate anonymous data on perinatal outcomes from 2008 to 2022 were obtained from the National Obstetric Information System (NOIS), Directorate for Health Information and Research (DHIR). Data for each variable was grouped into three 5-year intervals (2008–2012, 2013–2017 and 2018–2022) to investigate trends over time.

Results: Total births increased over time (p -value 0.008), mainly driven by singleton pregnancies (p -value 0.004), while multiple pregnancies remained stable. Live births increased (p -value 0.008), however, there was no statistically significant difference in stillbirth rate. There were no statistically significant changes in post-term, preterm or low birthweight deliveries (p -value 0.73). The neonatal mortality rate showed a downward trend from 4.92 per 1,000 live births for the years 2008–2012 to 3.92 per 1,000 births for the 2018–2022 epoch, but this could not be statistically confirmed. Data for ART pregnancies was only available as of 2013, analysis of which showed a significant increase in trend over the years with a p -value of <0.05 .

Conclusion: This study's findings highlight important public health implications for Malta and the world. The stable rates of preterm and low birth weight, and the decline in stillbirths, suggest improvements in maternal and infant health. However, Malta still lags behind the rest of Europe. This along with the overall increase in the number of births, may be attributed to the growing number of immigrants within the pregnant population, who have specific healthcare needs which need specific attention. These results can help inform public health policies and improve maternity and neonatal services in Malta and regions with similarly increasing immigrant populations.

KEYWORDS

perinatal, neonatal, outcomes, Malta, public health

Introduction

Perinatal and neonatal health outcomes, including mortality rates, are crucial indicators of a country's social, health, and economic conditions (1). Many perinatal and neonatal deaths are preventable, making these outcomes key quality indicators for antenatal, obstetric, and postnatal care (2). Monitoring changes in birth rates and adverse outcomes during the perinatal and early childhood periods is essential for improving child health and evaluating interventions at both national and global levels (1, 2).

In 1999, the European Union launched the EURO-PERISTAT network to create a high-quality perinatal health information system for decision-making in European countries. Key indicators such as gestational age, birthweight, neonatal mortality rate, and parity guide healthcare policies. The network has since collected data from 31 European countries, including Malta (2).

Malta has experienced a steady decline in perinatal and neonatal mortality rates over the past few decades, in line with European trends (2). However, its perinatal mortality rate, around 7.0 per 1,000 total births, is slightly higher than the EU average of approximately 6.0 per 1,000, indicating a need for improvement in maternal and neonatal healthcare outcomes (2) (Figure 1).

This study details perinatal outcomes in Malta from 2008 to 2022, comparing them with rates in other developed countries. The findings aim to provide insights into Malta's standing among similar European nations, informing future policy and healthcare practices.

The Maltese Islands are an archipelago in the middle of the Mediterranean, with an estimated population of 542,000 as of the year 2022, with children up to the age of five comprising 6.7% of the total population (3). Tertiary neonatal care in Malta is centralized at one general hospital, making it a unique case for studying healthcare systems. Although Malta is part of the EU, it has historically underperformed in health outcomes. Its resource-constrained healthcare system, geographic isolation, and aging population are compounded by a significant influx of immigrants with specific healthcare needs. This context is crucial for developing policies and providing effective perinatal care, especially since immigrants are disproportionately represented in the pregnancy cohort.

This study provides an overview of births and neonatal outcomes in Malta over the past 15 years, examining trends in perinatal and neonatal outcomes. It aims to guide public health policy and resource allocation to reduce mortality rates. Malta's healthcare system serves as a valuable case study for enhancing maternal and neonatal care in similarly sized European countries.

Studying perinatal outcomes in 5-year epochs over 15 years captures significant trends and provides statistical stability. This approach smooths short-term fluctuations from factors like seasonal variations, facilitating clearer insights into healthcare quality and interventions. It aligns with practices of major health organizations for international comparisons and effectively assesses the long-term effects of health policies, such as improvements in maternal and childcare. This method supports policymakers in evaluating the impact of healthcare reforms over time.

Methods

Consent

Data on perinatal outcomes were obtained from the National Obstetric Information System (NOIS) within the Directorate for

Health, Information and Research, Malta. This study utilized anonymized, non-identifiable registry data prepared in accordance with General Data Protection Regulation (GDPR) requirements and EUROPERISTAT published data. Ethical review was not required because the research involved secondary use of existing anonymized registry data and did not involve direct interaction with human subjects.

Population and measurements

Data from NOIS for the 15-year period - 2008 till 2022 were used. NOIS collects information on all in-hospital deliveries occurring in the various hospitals across the Maltese Islands as well as births that incidentally occur outside of the hospital and are then transferred to the hospital. It is estimated that less than 1% of births may be missing from the data registered – these include planned home deliveries that did not require transfer to the hospital for further care.

Data tables for each of the years (2008–2022) included the number of total and live births, gender, numbers of singleton and multiple births, number of live and stillbirths, gestation at birth, birth weight, and number of neonatal deaths. The number of assisted reproduction technology pregnancies, outcomes, and admissions to the neonatal intensive care (NICU) immediately post-delivery were obtained for the years 2018 to 2022 since this data was only available for these years.

Data analysis

Data were analyzed using SPSS and Microsoft Excel to ensure accurate statistical evaluation of the dataset. The data for each variable were grouped into three 5-year epochs: 2008–2012, 2013–2017, and 2018–2022. This grouping was done to minimize year-on-year fluctuations, which could result from small sample sizes in individual years. By dividing the data into these three epochs, the analysis could provide a more reliable overview of trends over time, ensuring more stable comparisons between groups.

Handling of variables

Categorical Variables were analyzed using Chi-square tests. The Shapiro Wilk was used to determine whether the distribution of continuous variables satisfied or violated the normality assumption.

Gestational age was analyzed using one-way ANOVA to assess whether the mean gestational age differed significantly across the three time periods.

The difference of two-proportion test was used to compare the proportions of neonates admitted to the NICU in each epoch (i.e., the proportion of NICU admissions in the 2008–2012 period compared to the 2013–2017 and 2018–2022 periods).

Hypothesis testing

A 0.05 level of significance was used for all statistical tests. If a *p*-value was above 0.05, the null hypothesis was accepted, indicating no significant difference or relationship between the variables and the

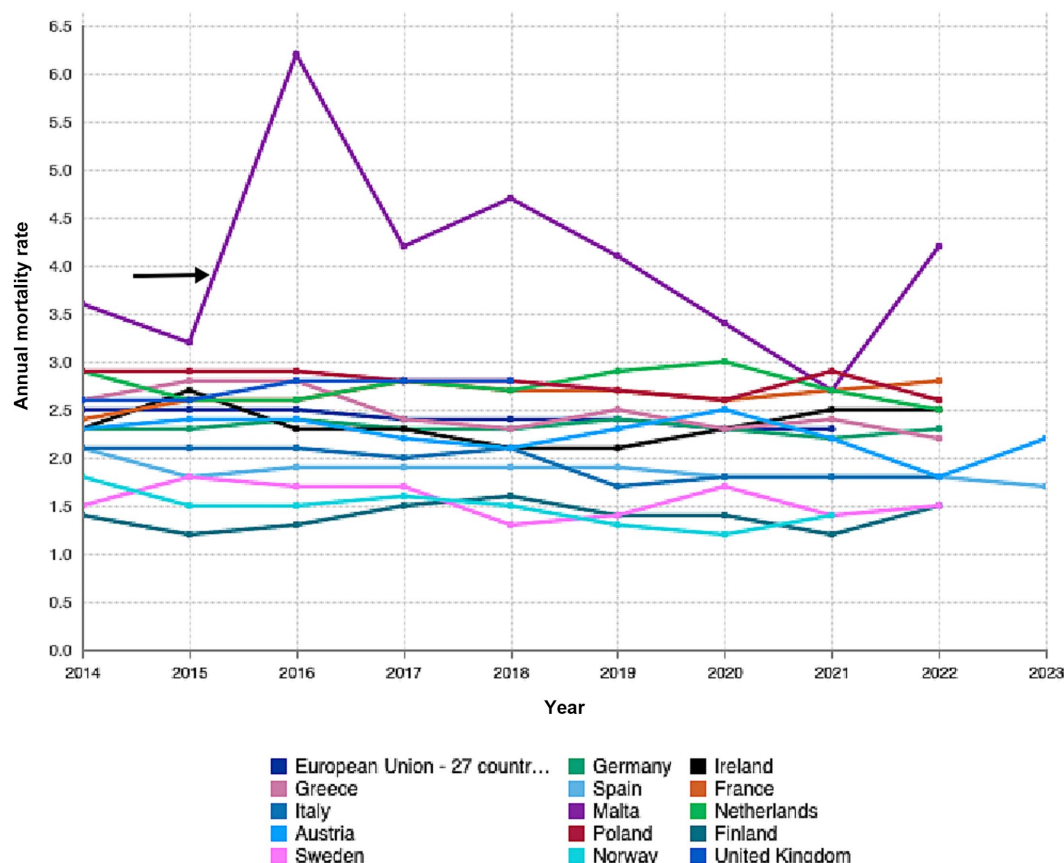


FIGURE 1

Graph sourced from Eurostat showing annual rates for fetal, peri- and neonatal mortality rates by country of occurrence. Adapted with permission from "Fetal, peri- and neonatal mortality rates by country of occurrence by Eurostat", by eurostat licensed under CC BY 4.0.

epochs. On the other hand, a p value below 0.05 rejects the null hypothesis.

(47.79–48.22%) for all the individual years with a p -value of <0.0001 . Male: female ratio throughout the period of study resulted to be 1.08:1.

Results

Total births

When births were categorized within five-year epochs (2008–2012, 2013–2017 and 2018–2022) and the three periods compared, the number of neonates increased significantly throughout the three phases as demonstrated by a p -value of 0.008 (Figure 2).

A regression model was fitted to relate the total number of births with time. The regression coefficient (26.5) indicated that on average, the total number births, increases by 26.5 every year. This increment is significant since the p -value is 0.001.

Gender

Comparison of mean frequencies showed that both the number of female and male neonates increased significantly throughout all 5-year phases, with a p -value of 0.009 for females and a p -value of 0.022 for males (Table 1). Moreover, throughout the 15 years studied, the proportion of male babies (51.48–52.21%) was invariably significantly larger than the proportion of female newborn babies

Parity

The number of singleton neonates increased significantly throughout the 3 phases with a p -value of 0.004 (Table 2). On the other hand, no significant difference could be demonstrated for multiple births. Figure 3 demonstrates annual data for singleton and multiple births over the past 15 years. A significant decrease in triplet pregnancies was noted for the 2013–2017 epoch (Table 3, Figure 4). In our population, data for fertilization methods resulting in twin or triplet pregnancies was only available from 2013 onwards. In our population, 56% of triplet births were a result of assisted pregnancies and deliveries compared with 38% occurring spontaneously in non-assisted pregnancies with successful delivery (Figure 5).

Assisted reproduction technology (ART) pregnancies and effects on total births

Data for ART pregnancies was only available as of 2013, analysis of which showed a significant increase in trend over the years with a p -value of <0.05 . The most noteworthy differences were those between the years of 2021 and 2022, with a significant increase for artificial

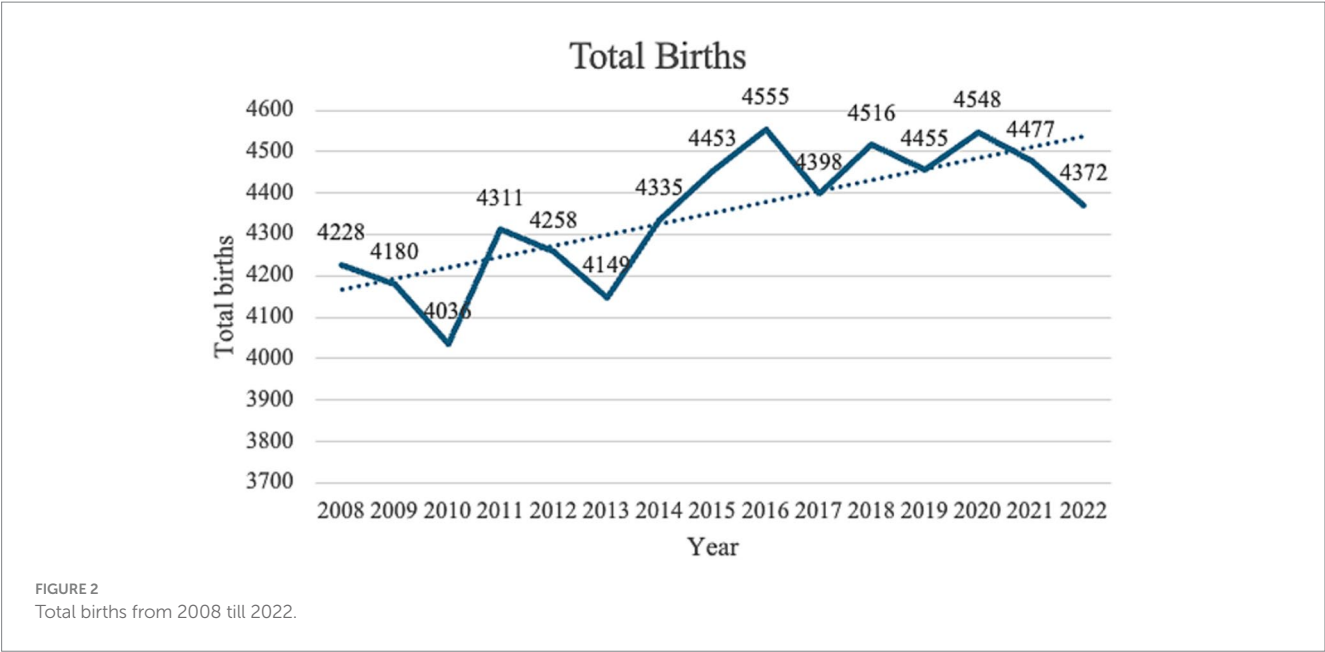


TABLE 1 Mean frequencies for neonates categorised according to gender.

Variables	Year	Number of deliveries per epoch	Mean	Standard deviation	p-value
Female	2008–2012	10,133	2026.60	50.585	0.009
	2013–2017	10,462	2092.40	85.967	
	2018–2022	10,853	2170.60	30.320	
Male	2008–2012	10,879	2175.80	63.152	0.022
	2013–2017	11,428	2285.60	81.773	
	2018–2022	11,515	2303.00	52.048	

Analysis performed using Chi-square testing. Bold values indicate statistically significant *p*-values.

TABLE 2 Mean frequencies for neonates categorised according to parity.

Variable	Year	Mean	Standard deviation	p-value
Singleton	2008–2012	4050.40	106.359	0.004
	2013–2017	4228.40	140.008	
	2018–2022	4336.20	68.240	
Multiple	2008–2012	73.40	5.899	0.813
	2013–2017	74.20	14.618	
	2018–2022	81.00	31.559	

Bold values indicate statistically significant *p*-values.

insemination (+2.59% from 2021), IVF and ICSI (+7.12% from 2021) being observed for the year 2022. On the other hand, an 8.75% decrease in ovulation induction was observed in 2022 compared to 2021. There were no significant changes noted for the previous years (Table 4).

Live vs stillbirth births

The number of live births was noted to increase significantly throughout the years with a *p*-value of 0.008 (Table 5).

There was no statistically significant decline in stillbirth rate across the years studied. Even though a drop in stillbirth rate was

noted between 2018 to 2022, from 7 per 1,000 total births to 5 per 1,000 total births, this was not statistically significant (Table 6). Analysis of trends in stillbirth outcomes (antepartum vs. intrapartum) throughout the years, revealed a significant majority of stillbirths being reported as antepartum as demonstrated in Figure 6.

Gestation

The absolute number of neonates born between 37 and 40⁺⁶ weeks was noted to have increased significantly throughout the 15 year period (*p* = 0.003). There were no other significant changes noted for

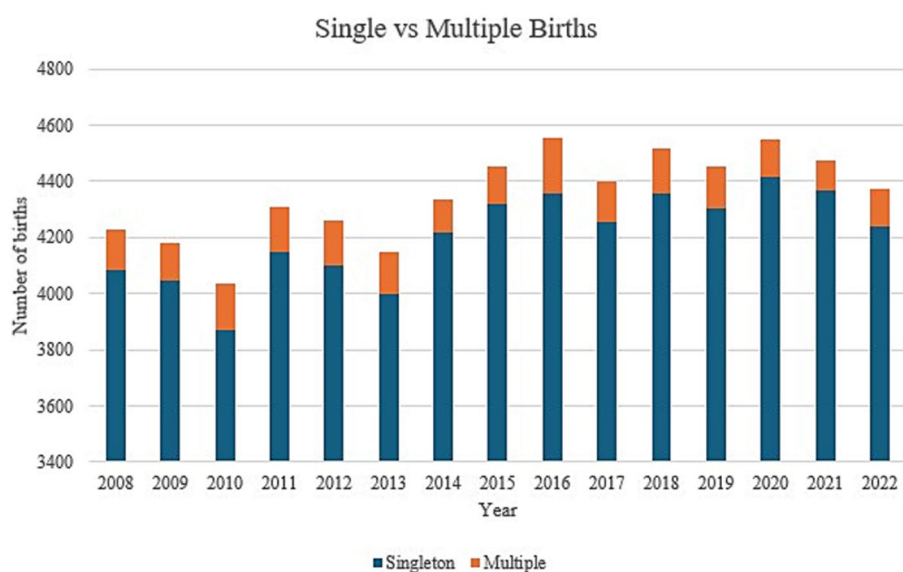


FIGURE 3
Trends in singleton and multiple births from 2008 till 2022.

TABLE 3 Number of twins and triplets for 2008–2022 categorised in five-year time epochs.

Plurality	2008–2012	2013–2017	2018–2022	<i>p</i> -value
Twins	680	733	654	0.450
Triplets	81	15	33	0.002

Bold values indicate statistically significant *p*-values.

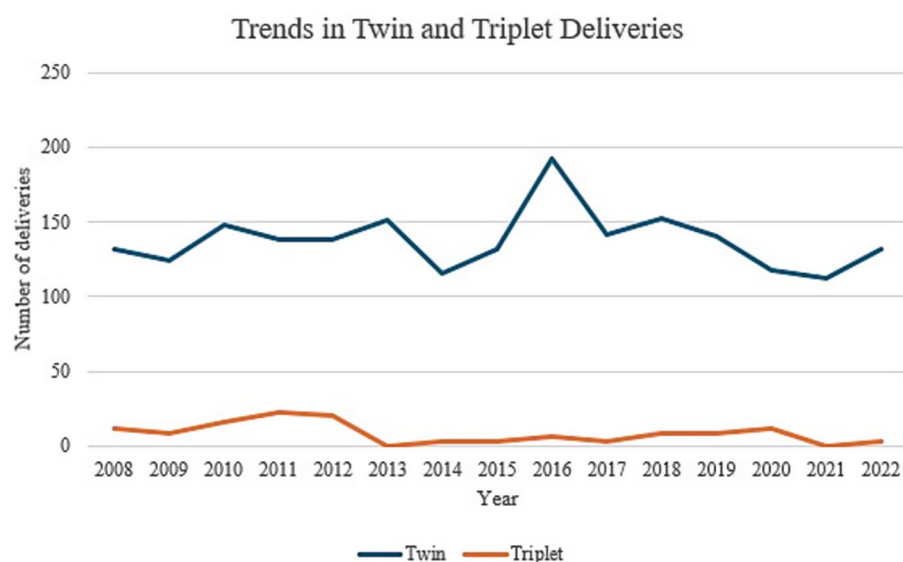


FIGURE 4
Trends in twin and triplet pregnancies from 2008 till 2022.

the rest of the gestation categories, with no significant increase in late preterm births across the 3 epochs (*p*-value 0.73).

Despite a decrease in the number of post-term births (beyond 42 weeks' gestation) over the past 5 years (48 babies 2008–2012, 31

babies 2013–2017, 3 babies 2018–2022), there was no statistical significance between the 3 epochs when comparing term: post-term ratio (*p* = 0.75) and proportion of post-term births out of total births (*p* = 0.087) (Table 7).

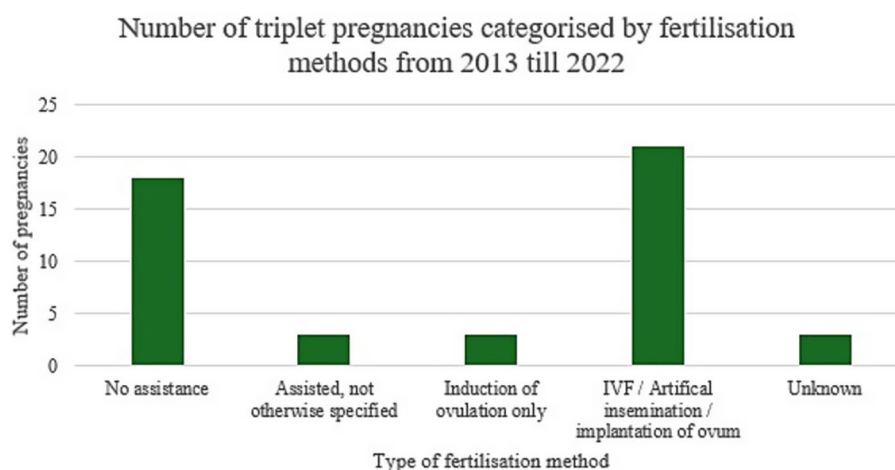


FIGURE 5
Triplet births categorized by fertilization method.

TABLE 4 ART pregnancies categorised by type for births from 2018 till 2022.

Type of art	2018 n (%)	2019 n (%)	2020 n (%)	2021 n (%)	2022 n (%)	Total births
Yes - type not specified	16 (8.79)	18 (12.41)	16 (10.32)	9 (6.82)	11 (5.85)	70
Induction of ovulation	31 (17.03)	33 (22.76)	40 (25.0)	27 (20.45)	22 (11.7)	153
Artificial insemination	8 (4.39)	4 (2.76)	5 (3.23)	5 (3.79)	12 (6.38)	34
IVF, ICSI	127 (69.80)	90 (62.07)	94 (60.64)	91 (68.94)	143 (76.06)	545
Total births	182	145	155	132	188	802

The highest number of early neonatal deaths were reported for the 22–23 weeks category with deaths amounting to 44.7% of the total births within this gestation. On the other hand, the highest number of late neonatal deaths was reported for the 24–27 weeks' gestation category, at 5.6% of the total births for this category (Table 11).

Trends in admission to the neonatal intensive care unit immediately after delivery

Data for this variable was only available from 2018 onwards. The rate of admissions varied from 6.88 to 9.06% of the total live births. Comparing the year 2019 (the highest proportion of admissions) with 2021 (the lowest proportion of admissions), the resulting difference in admissions is significant (z score 3.8, p -value of 0.0001) (Table 12).

Birthweight

A significant increase in neonates could be observed within the 2000–2999 g category ($p = 0.027$) and the 3,000–3999 g ($p = 0.007$) category over the 15 year period. No significant differences were noted for other birthweight categories throughout the three 5-year phases (Table 8).

Most of the 2000–2999 g consisted of newborns born beyond 37 weeks' gestation, although a significant proportion (14.9%) were newborns between 32 and 36⁺⁶ weeks' gestation. For the 3,000–3999 g birthweight category, 98.5% were within the 37⁺ weeks' category, whilst 1.5% were born between 32- and 36⁺⁶-weeks' gestation (Table 9).

Neonatal deaths

No statistically significant changes were noted for both early and late neonatal deaths throughout the 15 years studied, with a p -value of 0.35 (Table 10).

Therefore, whilst, the neonatal mortality rate appears to have a downward trend, with the lowest being reported for the 2018–2022 epoch at 3.92 per 1,000 live births, compared to 4.92 per 1,000 live births for the years 2008–2012, this was not statistically significant. (Figure 7).

Discussion

Neonatal and childhood mortality remains a significant global challenge up to this day, with an estimated death of 2.4 million newborns within their first month of life reported by UNICEF in 2023 alone, most of which were deemed preventable. This represents a significant loss of life and is a huge burden on communities, especially in the context of developing countries in which most of these deaths have been observed to occur (4, 5).

Testament to ongoing commitments of organizations, governments and healthcare professionals, the United Nations Inter-Agency Group for Child Mortality Estimation has reported in 2023 a global decline in the under-5-mortality rate by 51% since the year 2000 (6). Despite this, huge disparities in neonatal mortality still exist, ranging from <5 deaths per 1,000 live births in developed countries, to >35 deaths per 1,000 live births in low-income and developing countries. This emphasises the importance of having accessible high-quality healthcare, in both antenatal and postnatal settings; including the availability of services to care for the preterm and sickest newborns, to curtail preventable child deaths in every community (6–8).

TABLE 5 Changes in stillbirth outcomes from 2008 till 2022.

Outcome	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
Antepartum stillbirth	20	20	16	23	12	21	25	13	21	18	19	15	22	12	20
Intra partum stillbirth	4	1	1	2	4	1	2	2	1	0	4	0	1	1	1
Stillbirth, not otherwise specified	5	7	1	3	3	0	0	3	1	1	2	1	3	0	0
Total	29	28	18	28	19	22	27	18	23	19	25	16	26	13	21

Analysis of the total number of births over the past 15 years, revealed a significant increase in birth rate. Malta has experienced unprecedented changes in population size and structure, with an estimated 21% increase in resident population between 1998 and 2017, and a total foreign population of 115,449 inhabitants as of 2021, with foreigners between the years of 30 and 39 years of age comprising the biggest share (3, 9). Therefore, despite a decrease in deliveries to Maltese women, the resulting net immigration of foreigners could have been a significant factor in contributing toward an increase in the overall birth rate (9, 10). Within the European Union region, crude birth has been shown to overall decrease since 2021 to 9.1 live births per 1,000 persons (in contrast to 10.6 live births per 1,000 persons in 2008), although variations in this pattern were noted across countries, with sixteen country states reporting a decreasing trend and ten states reporting increasing trends. Malta fared the lowest total fertility rate as of 2022 at 1.15 live births per woman, in contrast to France with a reported 1.79 live births per woman. Moreover, 22% of children in the EU were reported to be born to foreign-born mothers. Malta was reported to have the highest increase in live births from foreign-born mothers at 33% (previously at 11% in 2013) from across EU member states, followed by Portugal (8 percentage points from 24 to 16%), and Spain, Cyprus and Slovenia for which increases of 7 percentage points were recorded; thus, explaining increasing trends in births for the Maltese population (11, 12). Analysis of gender revealed a stable male-to-female ratio of 1.08:1 throughout the period studied. Male:female ratio in the EU was reported to be at 1.055 in 2021 (13).

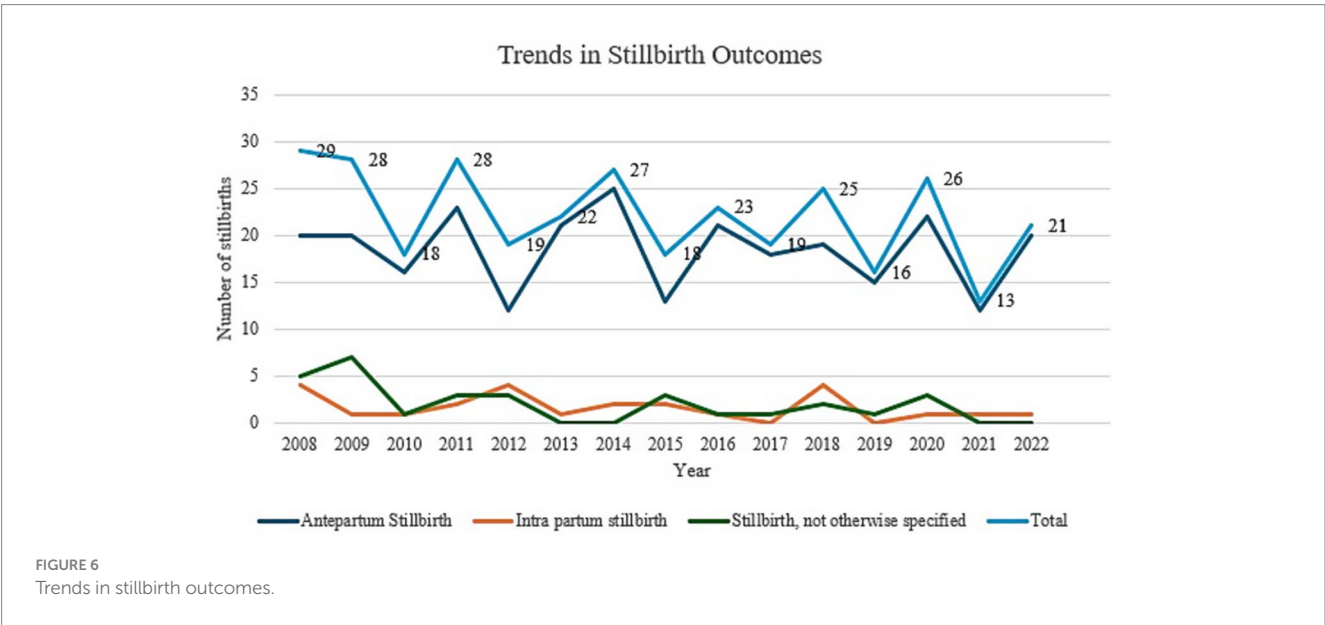
Multiple pregnancies pose a high risk of morbidity and mortality for both mothers and their newborns, requiring timely obstetric decisions and a balance of maternal and neonatal complications (14, 15). In our study, whilst the number of singleton neonates was noted to increase significantly throughout the 3 phases, no significant difference could be demonstrated for multiple births. Spontaneous triplet pregnancies are known to be relatively rare events occurring in 1/8000 pregnancies, though an upsurge was recorded worldwide secondary to the use of assisted reproductive techniques between the 1980s and 1990s. Its incidence was noted to thereafter decline as recommendations to minimize multiple embryo transfers were made (16, 17). These changes in trends have also been mirrored locally, as demonstrated in our study, as the implementation of the Embryo Protection Act came into force in 2012 with a legislative amendment regarding embryo freezing in 2018, with more couples having one embryo transferred rather than multiple. In our population, 56% of triplet births were a result of assisted pregnancies and deliveries compared with 38% occurring spontaneously in non-assisted pregnancies with successful delivery (18, 19).

A significant increase in absolute number of term births (37+ weeks) and in birthweight (2000-3999 g) was noted for the Malta population over the past 15 years, with no significant change in preterm and low birthweight births, reflecting preterm birth rates over the last decade at a global level. Interestingly, no increase in late preterm birth rates has been observed for Malta, as opposed to changes worldwide (20). Despite no statistical significance noted in the number of post-term babies over the years, a notable decrease in the number of babies being born beyond 42 weeks of gestation was observed for the past 5 years, which might suggest an increase in the number of labor induction practices. This reflects the increasing practice of labor induction over the past several decades in developed countries secondary to recommendations by various professional bodies outlining risks of spontaneous post-term labor vs. induction of labor (21–23). In developed countries, the proportion of infants delivered by induction is thought to be as high as

TABLE 6 Total births categorised into live vs. stillbirth.

Variable	Year	Total births	Mean	Standard deviation	p-value	Stillbirth rate (per 1,000 births)
Live	2008–2012	20,891	4178.20	101.812	0.008	
	2013–2017	21,781	4356.20	152.062		
	2018–2022	22,249	4449.80	72.234		
Stillbirths	2008–2012	122	24.40	5.413	0.427	5.80
	2013–2017	88	21.80	3.564		4.02
	2018–2022	80	20.20	5.630		3.58

Bold values indicate statistically significant p-values.



1 in 4 deliveries, quoted at up to 33% of total deliveries in some countries with considerable intercountry variations. Induction rates in Malta were quoted to be as high as 28.9% in 2015 (21–23).

Despite an overall worldwide decline in infant mortality rates of up to 52% over the past 22 years, the percentage of neonatal deaths has been reported to increase over time from 41% in the year 2000 to 47% in 2022, despite a decrease in the absolute number of neonatal deaths by 44% since 2000 (6). In our study, no significant changes in trends were noted for both early and late neonatal deaths throughout the 15 years. This stable trend in death rate can be attributed to various reasons including population change over the past few years, with high immigration patterns from conflict-zone countries (24). Various research has demonstrated immigration as an important determinant of health, with female immigrants being considered a vulnerable population, with limited healthcare access resulting in worse neonatal and perinatal outcomes compared to those of native-origin women in host countries (24–27). Differences in termination of pregnancy legislation between countries, especially within the context of pregnancies with congenital anomalies, might also play a role in affecting neonatal death rate. This argument is supported by a study published in 2023 by Tierny et al. (29), evaluating the effects of changes in abortion legislation in 2018 on admissions to paediatric intensive care in Ireland after its introduction, which demonstrated a modest reduction in live births with significant congenital anomalies since the introduction of the 2018 Termination of Pregnancy Act as

represented by the numbers of these infants presenting to paediatric intensive care unit. On the other hand, no statistically significant decline in perinatal and neonatal mortality rates was reported. Tierny et al. (29), go on to argue that major congenital anomalies remain the major cause of both early and late neonatal deaths, with a significantly reduced perinatal mortality rate when this is corrected for major congenital anomalies. This is interesting and warrants deeper investigation given that like Ireland, Malta has restrictive laws when it comes to non-medical termination of pregnancy (28, 29).

In our study, stillbirth rates showed a downward trend from 7 per 1,000 total births in 2008 to 5 per 1,000 total births in 2022. Despite this downward trend, statistical significance was not reached and the stillbirth rate reported in our study is still high when compared to other countries, with a reported stillbirth rate below 2.5 stillbirths per 1,000 total births for most European countries, and 4 stillbirths per 1,000 total births in England and Wales. Data on stillbirths and socioeconomic status from routine systems showed widespread and consistent socioeconomic inequalities in stillbirth rates in Europe, but further research is needed to better understand differences between countries in the magnitude of the socioeconomic gradient (30–33).

The rate of admissions to NICU from 2018 to 2022 for our population ranged from 6.88% in 2021 (68 per 1,000 live births) to 9.06% of the total live births in 2019 (91 per 1,000 live births). Comparing the year 2019 (the highest proportion of admissions) with 2021 (the lowest proportion of admissions), the resulting difference in admissions is significant (z score

TABLE 7 Total births categorised according to gestation.

Variable	Year	Number of babies	Mean	Standard deviation	<i>p</i> -value
22–27 ⁺⁶ weeks	2008–2012	118	23.60	6.025	0.914
	2013–2017	126	25.20	6.140	
	2018–2022	123	24.60	5.899	
28–31 ⁺⁶ weeks	2008–2012	168	33.60	7.021	0.761
	2013–2017	159	31.80	3.834	
	2018–2022	157	31.40	3.130	
32–36 ⁺⁶ weeks	2008–2012	1,301	260.20	15.073	0.677
	2013–2017	1,371	274.20	36.561	
	2018–2022	1,330	266.00	16.688	
37–40 ⁺⁶ weeks	2008–2012	19,378	3875.60	93.074	0.003
	2013–2017	20,203	4040.60	115.589	
	2018–2022	20,751	4150.20	80.014	
41 weeks +	2008–2012	48	9.60	9.915	0.087
	2013–2017	31	6.20	1.924	
	2018–2022	3	0.60	0.894	
Unspecified gestation	2008–2012	0	0.00	0.000	0.148
	2013–2017	0	0.00	0.000	
	2018–2022	3	0.60	0.894	

Bold values indicate statistically significant *p*-values.

TABLE 8 Total births categorised according to birthweight.

Variable	Year	Number of babies	Mean	Standard deviation	<i>p</i> -value
BW <500 g	2008–2012	29	5.80	3.347	0.618
	2013–2017	37	7.40	3.715	
	2018–2022	26	5.20	3.701	
BW 500–1499 g	2008–2012	235	47.00	8.515	0.860
	2013–2017	247	49.40	6.914	
	2018–2022	238	47.60	5.727	
1,500–1999 g	2008–2012	283	56.60	9.236	0.727
	2013–2017	276	55.20	15.271	
	2018–2022	305	61.00	10.050	
2000–2999 g	2008–2012	5,519	1103.80	21.076	0.027
	2013–2017	5,753	1150.60	62.488	
	2018–2022	5,932	1186.40	29.100	
3,000–3999 g	2008–2012	13,931	2786.20	88.793	0.007
	2013–2017	14,579	2915.80	72.040	
	2018–2022	14,859	2971.80	68.379	
4,000–4999 g	2008–2012	971	194.20	10.756	0.458
	2013–2017	1,018	203.60	16.211	
	2018–2022	957	191.40	18.849	
5,000 g+	2008–2012	12	2.40	1.517	0.679
	2013–2017	10	2.00	1.000	
	2018–2022	14	2.80	1.643	
Unspecified birthweight	2008–2012	33	6.60	8.444	0.778
	2013–2017	20	4.00	1.581	
	2018–2022	29	5.80	5.450	

Bold values indicate statistically significant *p*-values.

TABLE 9 Number of neonates stratified by birthweight and gestation categories.

Birthweight (grams)	22–23 ⁺⁶ weeks	24–27 ⁺⁶ weeks	28–31 ⁺⁶ weeks	32–36 ⁺⁶ weeks	37 ⁺ weeks	Unknown
0–499	51	42	6	0	1	0
500–999	34	183	72	8	3	1
1,000–1,499	0	46	225	139	9	0
1,500–1999	0	3	152	606	103	0
2000–2,499	0	2	14	1,260	1831	0
2,500–2,999	0	0	5	1,306	12,786	0
3,000–3,499	0	1	5	520	27,393	2
3,500–3,999	0	0	1	119	15,279	0
4,000–4,499	0	0	0	26	2,686	0
4,500–4,999	0	0	0	3	231	0
5,000+	0	5	4	9	98	1
Grand total	85	282	484	3,996	60,420	4

TABLE 10 Number of early and late neonatal deaths from 2008 till 2022.

Variable	Year	Number of live births	<i>n</i>	Standard deviation	<i>p</i> -value (comparison of means)	Neonatal mortality rate (per 1,000 live births)
Total Number of Neonatal Deaths	2008–2012	20,891	103	2.793	0.350	4.92
	2013–2017	21,781	98	4.980		4.63
	2018–2022	22,249	85	3.536		3.92
Early neonatal	2008–2012	20,891	103	2.702	0.134	
	2013–2017	21,781	98	4.207		
	2018–2022	22,249	85	2.387		
Late neonatal	2008–2012	20,891	16	1.000	0.659	
	2013–2017	21,781	19	1.924		
	2018–2022	22,249	19	1.643		

Bold values indicate statistically significant *p*-values.

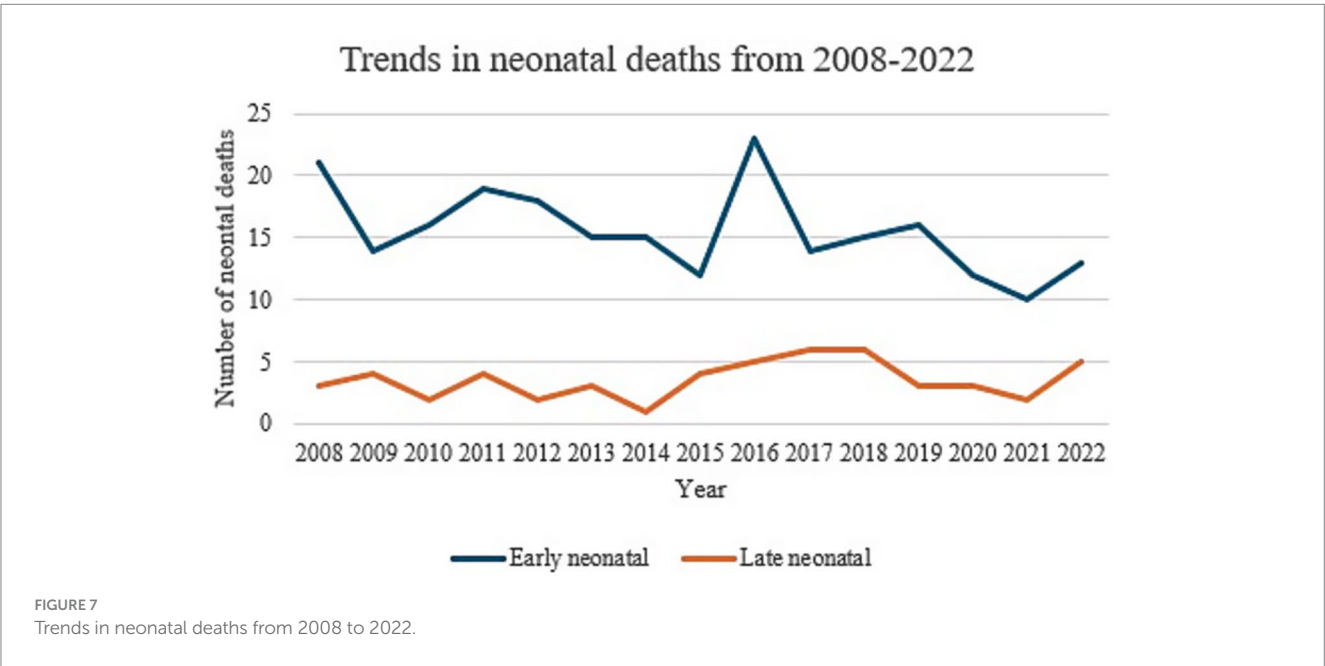


TABLE 11 All births by gestational age groups and outcome from 2008 till 2022.

GA group	Number of ENDs	% ENDs out of total births per GA group	Number of LNDs	% LNDs out of total births per GA group	Total number of births per GA group
22–23 weeks	38	44.7	3	3.53	85
24–27 weeks	63	22.3	16	5.6	282
28–31 weeks	36	7.4	7	1.4	484
32–36 weeks	40	1	13	0.3	3,996
37 + weeks	55	0.09	13	0.02	60,420
Unknown gestation	1	25	1	25	4
Total	233	0.36	53	0.08	65,271

GA, gestational age; END, early neonatal deaths; LND, late neonatal deaths.

TABLE 12 Number of admissions to NICU since 2018 expressed as a percentage out of total live births.

Year	Live births	Admitted to NICU	NICU admissions Z-score	% of total live births admitted
2018	4,491	360	0.36	8.02
2019	4,439	402	1.53	9.06
2020	4,522	335	−0.34	7.41
2021	4,464	307	−1.12	6.88
2022	4,333	332	−0.42	7.66

3.8, p -value of 0.0001). This was an interesting finding as overall NICU admissions seemed to remain stable, although no information was available as of pre-2018 to comment on whether assisted reproduction technologies have led to an increase in admission rates. Still, admission rates for term babies have been quoted to be less than 5.2% of total births in the year 2016 (34). The stable admission rates despite the COVID-19 pandemic in 2020 were an interesting finding, given that other countries and studies reported higher NICU admission numbers during the pandemic secondary to its profound negative maternal and neonatal impacts secondary to lockdown measures, maternal health complications and disruptions in prenatal care (35, 36). This observation in admission rates could possibly be a reflection of the recent modifications and implementation of stringent admission criteria during the period studied, such as increasing the cord pH thresholds for admission. Moreover, there has also been an improvement in obstetric diagnosis with some cases being transferred to tertiary centres abroad antenatally for delivery overseas.

Limitations

Data supplied for birthweight and gestation were already categorized independently of each other, thus it was not possible to categorize individual infants into small, appropriate, and large gestational age categories. Some data for birthweight (0.006%) and gestation (0.005%) was missing. Information on admissions to NICU and ART was only available as of 2018.

The data set lacked information maternal on country of origin and maternal education, which prevented us from analysing the implications of these factors on health outcomes. Factors such as socio-economic status, healthcare access, cultural practices, and language barriers can significantly impact these outcomes. Future research should prioritize comprehensive data collection from these particular groups.

The absence of long-term data on Assisted Reproductive Technology (ART) outcomes is a limitation of this study. The collection of ART-specific data and extended follow-up periods is vital for informing healthcare provision and best practice.

Conclusion

This study reports perinatal outcomes in Malta from 2008 to 2022, divided into three five-year epochs (2008–2012, 2013–2017, 2018–2022). The rate of stillbirth, preterm births and low birthweight deliveries did not show a statistically significant difference between these epochs. There has been an increase of 26.5 births per year (p 0.001) throughout the period studied. The underlying factors that have led to this increase, need further study. This increasing trend has important implications for access to care and for understanding the specific needs of pregnant women and their offspring.

Additionally, the use of Assisted Reproductive Technologies (ART) is increasing in Malta and other parts of the world, impacting perinatal care. This also requires specialized care for high-risk pregnancies. These developments are particularly relevant to policymakers and healthcare providers. Therefore, it is essential to thoroughly understand these implications when designing perinatal healthcare services and when organising data collection and monitoring systems.

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.

Author contributions

ND: Writing – original draft, Writing – review & editing, Methodology. MG: Writing – original draft, Writing – review & editing, Supervision. MK: Supervision, Writing – original draft, Writing – review & editing.

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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.

References

- Zeitlin J, Wildman K, Bréart G, Alexander S, Barros H, Blondel B, et al. PERISTAT: indicators for monitoring and evaluating perinatal health in Europe. *Eur J Pub Health*. (2003) 13:29–37. doi: 10.1093/eurpub/13.suppl_1.29
- European perinatal health report. (2010) [Internet]. Euro Peristat. (2013). Available online at: <https://www.europeristat.com/publications/european-perinatal-health-report-2010/>
- Malta National Statistics Office. Regional statistics malta 2023 Edition. (2023). Available online at: <https://nso.gov.mt/wp-content/uploads/Regional-Statistics-Malta-2023-Edition.pdf>
- United nations inter-Agency Group for Child Mortality Estimation (UN IGME). Levels and trends in child mortality: Report. New York: (2020).
- United Nations Inter-Agency Group for Child Mortality Estimation (UN IGME). A neglected tragedy: the global burden of stillbirths. Unicef.org Available online at: <https://www.unicef.org/reports/neglected-tragedy-global-burden-of-stillbirths-2020> (2020).
- Estimates developed by the UN Inter-agency Group for Child Mortality Estimation. (2023). Available online at: <https://childmortality.org/wp-content/uploads/2024/03/UNIGME-2023-Child-Mortality-Report.pdf>
- Arora A. Levels and trends in child mortality, Unicef.org Available online at: <https://data.unicef.org/resources/levels-and-trends-in-child-mortality-2024/> (2024)
- UN Children's Fund, WHO, World Bank Group, UN Department of Economic and Social Affairs Population Division, UN Economic Commission for Latin America and the Caribbean Population Division. (2021). Available online at: <https://www.who.int/publications/m/item/levels-and-trends-in-child-mortality-report-2021>
- Prevalence charts and tables Europa. eu. Available online at: https://eu-rd-platform.jrc.ec.europa.eu/eurocat/eurocat-data/prevalence_en (2018)
- England K, Buttigieg S. The impact of demographic changes in Malta on health and the health system over the past two decades. *Centres for Disease Control and Prevention*. (2019) Available online at: <https://www.um.edu.mt/library/oar/handle/123456789/49262>
- Demography of Europe – 2023 edition - Interactive publications - Eurostat [Internet]. Europa.eu. Available online at: <https://ec.europa.eu/eurostat/web/interactive-publications/demography-2023>
- Statistics explained [Internet]. Europa.eu. (2023). Available online at: https://ec.europa.eu/eurostat/statistics-explained/index.php?title=Fertility_statistics
- TRADING ECONOMICS. European Union - Sex ratio at birth (male births per female births). 20250427T06: 36: 00.00Z. (2023). Available online at: <https://tradingeconomics.com/european-union/sex-ratio-at-birth-male-births-per-female-births-wb-data.html>
- Bernal Claverol M, Aracil Moreno I, Ruiz Minaya M, Fernández Muñoz M, Reyes Angullo ZR, González Navarro P, et al. Maternal, perinatal and neonatal outcomes of triplet pregnancies according to chorionicity: a systematic review of the literature and meta-analysis. *J Clin Med*. (2022) 11:1871. doi: 10.3390/jcm13061793
- Hayata E, Nakata M, Morita M. Time trend analysis of perinatal mortality, stillbirth, and early neonatal mortality of multiple pregnancies for each gestational week from the year 2000 to 2019: A population-based study in Japan (2022) 17. doi: 10.1371/journal.pone.0272075
- Martin JA, Osterman MJ, Thoma ME. Declines in triplet and higher-order multiple births in the United States, 1998–2014. *NCHS Data Brief*. (2016) 243:1–8. Available online at: <https://www.cdc.gov/nchs/products/databriefs/db243.htm>
- Benirschke K, Kim CK. Multiple pregnancy. *N Engl J Med*. (1973) 288:1329–36. doi: 10.1056/NEJM197306212882505
- Vella S. Widened access and scope of in vitro fertilisation laws, amid controversy European Social Policy Network (2022) ESPN Flash Report 2022/44. European Commission.
- Grech V, Gatt M. Assisted reproductive technology and multiple pregnancies in Malta — a population-based study. *Early Hum Dev*. (2021) 157:105378. doi: 10.1016/j.earlhumdev.2021.105378
- Karnati S, Kollikonda S, Abu-Shaweeh J. Late preterm infants - changing trends and continuing challenges. *Int J Pediatr Adolesc Med*. (2020) 7:36–44. doi: 10.1016/j.ijpam.2020.02.006
- Caruana M, Giacchino T, Borg M, Baron YOM. Induction of labour at mater Dei hospital Malta. *Eur J Obstetrics Gynaecol Reproductive Biol*. (2016) 206:e23. doi: 10.1016/j.ejogrb.2016.07.087
- Caughey AB, Sundaram V, Kaimal AJ, Cheng YW, Gienger A, Little SE, et al. Maternal and neonatal outcomes of elective induction of labour. Evidence Report/Technology Assessment No. 176. Agency for Healthcare Research and Quality (2009). Available online at: <https://pubmed.ncbi.nlm.nih.gov/19408970/>
- Seijmonsbergen-Schermer AE, van den Akker T, Rydahl E, Beeckman K, Bogaerts A, Binfal L, et al. Variations in the use of childbirth interventions in 13 high-income countries: a multinational cross-sectional study. *PLoS Med*. (2020) 17:e1003103. doi: 10.1371/journal.pmed.1003103
- Behboudi-Gandevani S, Bidhendi-Yarandi R, Panahi MH, Mardani A, Prinds C, Vaismoradi M. Perinatal and neonatal outcomes in immigrants from conflict-zone countries: a systematic review and Meta-analysis of observational studies. *Front Public Health*. (2022) 10, 766943. doi: 10.3389/fpubh.2022.766943
- Hili C, Savona-Ventura C, Xuereb RB. The perinatal outcomes of Maltese and sub-Saharan African migrant women: a comparative. *Retrospective Study Creative Nursing*. (2023) 13:IJC-2022-0012.R1. doi: 10.1891/IJC-2022-0012
- Savona-Ventura C, Buttigieg GG, Gatt M. Obstetric outcomes in immigrants of African nationality. *Int J Risk Safety Med*. (2009) 21:147–52. doi: 10.3233/JRS-2009-0473
- World Health Organization (WHO). Trends in maternal mortality 2000–2017. Geneva: World Health Organization (2019).
- San Lazaro Campillo I, Manning E, Corcoran P, Keane J, McKernan J, Escanuela Sanchez T, et al. On behalf of the Perinatal Mortality National Clinical Audit Governance Committee. Perinatal Mortality National Clinical Audit in Ireland Annual Report 2021. Cork: National Perinatal Epidemiology Centre (2023).

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29. Tierney N, Healy M, Lyons B. Changes in abortion legislation and admissions to paediatric intensive care in Ireland. *Clin Ethics*. (2024) 19:47–53. doi: 10.1177/14777509231196700
30. WHO. Indicator Metadata Registry Details. (2023). Available online at: <https://www.who.int/data/gho/indicator-metadata-registry/imr-details/2444#:~:text=Definit ion%3A>
31. UNICEF. Stillbirths and stillbirth rates. UNICEF DATA. (2023). Available online at: <https://data.unicef.org/topic/child-survival/stillbirths/> (Accessed on August 8, 2024).
32. Stillbirth statistics. [Internet]. Tommys.org. [cited 2024 Aug 8]. Available online at: <https://www.tommys.org/baby-loss-support/stillbirth-information-and-support/stillbirth-statistics>. (2022).
33. Zeitlin J, Mortensen L, Prunet C, Macfarlane A, Hindori-Mohangoo AD, Gissler M, et al. Socioeconomic inequalities in stillbirth rates in Europe: measuring the gap using routine data from the euro-Peristat project. *BMC Pregnancy Childbirth*. (2016) 16:15. doi: 10.1186/s12884-016-0804-4
34. Borg R, Dimech MA, Xuereb S, Muscat Baron Y. Term admissions to neonatal intensive care a Maltese observational study. *Malta Medical School Gazette*. (2018) 2, 4–9. Available online at: <https://www.um.edu.mt/library/oar/handle/123456789/37415>
35. Harrison W, Goodman D. Epidemiologic trends in neonatal intensive care, 2007–2012. *JAMA Pediatr*. (2015) 169:855–62. doi: 10.1001/jamapediatrics.2015.1305
36. Jegatheesan P, Narasimhan SR, Huang A, Nudelman M, Song D. Higher NICU admissions in infants born at ≥ 35 weeks gestational age during the COVID-19 pandemic. *Front Paediatrics*. (2023) 11:1206036. doi: 10.3389/fped.2023.1206036

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