PHYSICAL FITNESS AND CARDIOVASCULAR HEALTH IN SPECIFIC POPULATIONS

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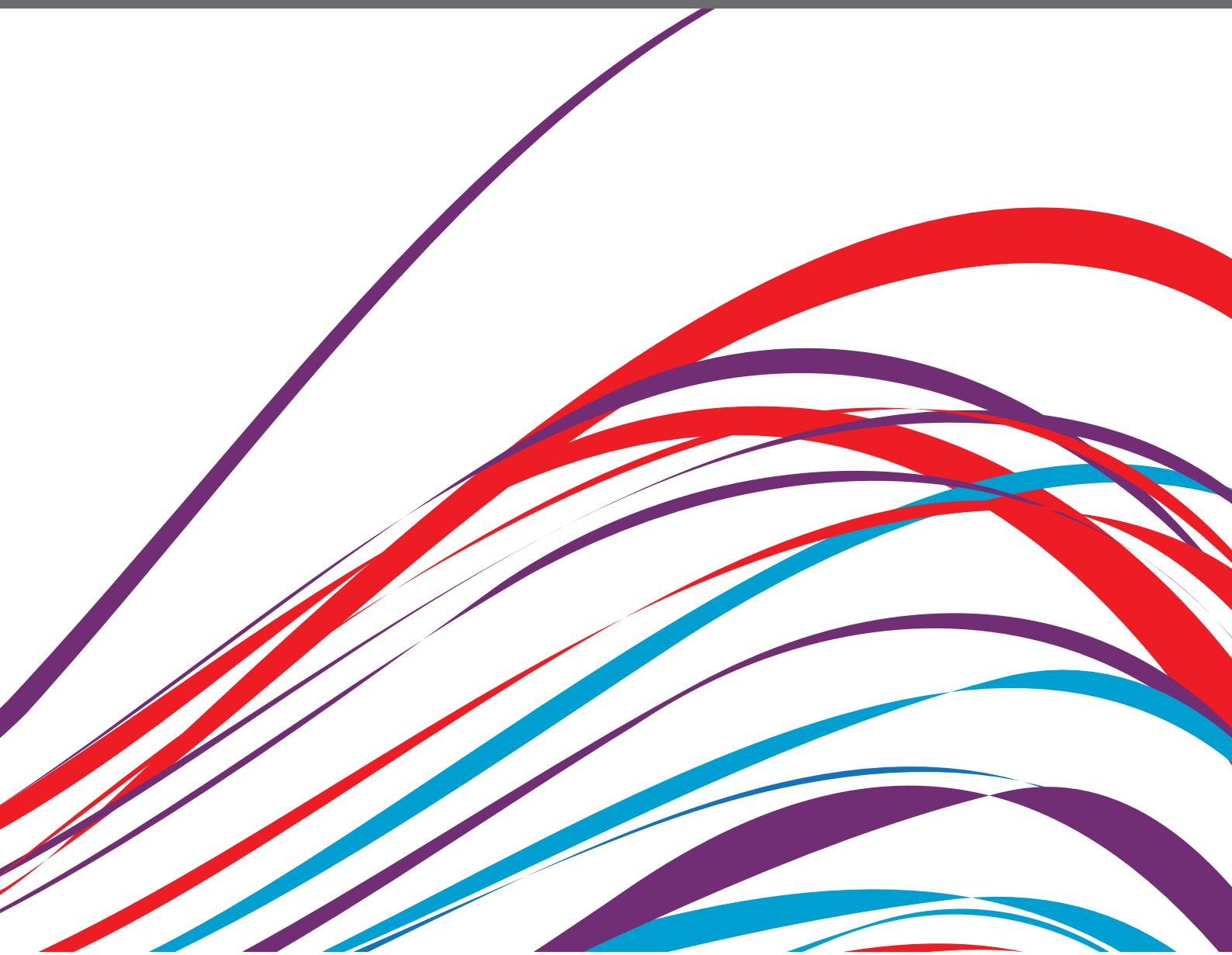

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PHYSICAL FITNESS AND CARDIOVASCULAR HEALTH IN SPECIFIC POPULATIONS

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EDITORIAL
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Editorial: Physical Fitness and Cardiovascular Health in Specific Populations

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Keywords: athlete's heart, physical activity, physical fitness, predictive models, specific populations, sex difference, myocarditis

Editorial of the Research Topic

Physical Fitness and Cardiovascular Health in Specific Populations

Athlete's heart has been regarded as a benign phenotype of cardiac remodeling related to physical training. Several electrocardiographic changes such as first-degree atrioventricular block and left ventricular hypertrophy are prevalent in athletes (1). In cardiac imaging studies, athletes have greater chamber sizes and more effective diastolic function than sedentary individuals (2). Previous studies have revealed racial differences in the cardiac adaptions to exercise and to left ventricular pressure overload. For given levels of training, athletes of African/Afro-Caribbean descent demonstrate more marked morphologic changes than Caucasian athletes, which is likely due in part to genetic factors (3, 4). In addition, the cardiac remodeling in male athletes is greater than that in female athletes Wooten et al.. However, there have only a few studies investigating cardiovascular health in Asian athletes and in some specific subgroups such like military individuals who have to receive regular training but are at high risk of psychological stress and metabolic abnormalities. In the current Topic Research, we have collected 9 high quality studies for investigating cardiovascular health and prognosis in athletes and specific populations.

From an Asian population of physically active military personnel in Taiwan (5–7), Liu et al. demonstrated that cardiac structural and functional characteristics differ between endurance and strength elite male athletes. While greater left ventricular mass index predicts elite status in both groups of male athletes, consistent with findings from Western elite athletes, greater diastolic function and right ventricular systolic pressure characterize strength elite athletes, while lower heart rate at rest predicts endurance elite athletic status. Lin et al. further found a sex difference that only greater right ventricular chamber size could characterize elite female strength athletes. For the electrocardiographic (ECG) changes in physically active obese military males, Lin et al. uncovered that obesity which was defined as body mass index $\geq$27.0 kg/m^2 was associated with higher risk of ECG based left atrial enlargement and T wave inversion in inferior leads, whereas the risk between obesity and ECG based left ventricular hypertrophy might vary by the ECG criteria, possibly due to a high prevalence of exercise induced-left ventricular hypertrophy in military and greater chest wall thickness in obesity. This study highlighted that the cardiac prognosis for various ECG criteria defined left ventricular hypertrophy in physically active obese adults requires further investigation.

In a Korean population of 68,223 individuals older than 65 years of age, Kim et al. displayed that compared with the sedentary group, the physically active groups with and without cardiovascular diseases (CVD) had a lower risk of all-cause death with a median follow-up of 42 months. A 500 metabolic equivalent task-minute per week increase in physical activity resulted in an 11% and 16%

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reduction in the mortality risk in the non-CVD and CVD groups, respectively. Kim et al. found that in the elderly, the benefits of physically activity in patients with CVD, especially stroke or heart failure, were greater than those without. In another Chinese population of 2,830 individuals older than 65 years of age, Lyu et al. showed that after adjusting for CVD risk factors, there was a negative association of weekly walking activity with vascular hypertensive mediated organ damage (HMOD), objectively evaluated by carotid-femoral pulse wave velocity, carotid intima–media thickness, and ankle-brachial index. Increased daily walking duration $\geq$1 h, but not walking frequency, was significantly associated with improved vascular HMOD in the elderly Chinese. In a British population of 5,300 individuals without CVD who had an average of 68 years of age, Liu et al. demonstrated that the low grip strength trajectory pattern was associated with higher risk of incident CVD for a median of 6.1-year follow-up. This study emphasized that continuous measurement of grip strength values could help identify the elderly individuals at risk of CVD.

For snorers with uncontrolled hypertension, Wang et al. developed a predictive model for the occurrence of coronary heart disease within 8 years in which the area under the receiver operating characteristic curve was 0.71. A total of more than 134 points in the nomogram can be used in the identification of high-risk patients for coronary heart disease in snorers with uncontrolled hypertension. In another paper developing a novel machine learning model to predict cardio-respiratory fitness level based on the anthropometric parameters and workload and steady-state heart rate of a submaximal exercise test, Xiang et al. found that the accuracy was 75%, and R^2 in the groups of age 21–40 years and above age 40 years were 0.85 and 0.75, respectively, when the support vector machine was used. Finally, Wang et al. analyzed the statistics regarding the global, regional, and national burden of myocarditis from 1990 to 2017, which could provide a platform for further investigation into the myocarditis burden in the COVID-19 pandemic era.

Taken together, the present Research Topic represents an important source of up-to-date information, covering many aspects of physical activity, fitness and cardiovascular health in specific populations. More comprehensive knowledge according to these discoveries may bring about new perspectives.

AUTHOR CONTRIBUTIONS

All authors listed have made an equal, substantial, direct, and intellectual contribution to the work and approved it for publication.

REFERENCES

1. Chao WH, Su FY, Lin F, Yu YS, Lin GM. Association of electrocardiographic left and right ventricular hypertrophy with physical fitness of military males: the CHIEF study. *Eur J Sport Sci.* (2019) 19:1214–20. doi: 10.1080/17461391.2019.1595741
2. Pluim BM, Zwinderman AH, van der Laarse A, van der Wall EE. The athlete's heart. A meta-analysis of cardiac structure and function. *Circulation.* (2000) 101:336–44. doi: 10.1161/01.CIR.101.3.336
3. Sheikh N, Sharma S. Impact of ethnicity on cardiac adaptation to exercise. *Nat Rev Cardiol.* (2014) 11:198–217. doi: 10.1038/nrcardio.2014.15
4. Papadakis M, Wilson MG, Ghani S, Kervio G, Carre F, Sharma S. Impact of ethnicity upon cardiovascular adaptation in competitive athletes: relevance to preparticipation screening. *Br J Sports Med.* (2012) 46:i22–8. doi: 10.1136/bjsports-2012-091127
5. Lin GM Li YH, Lee CJ, Shiang JC, Lin KH, Chen KW, Chen YJ, et al. Rationale and design of the cardiorespiratory fitness and hospitalization events in armed forces study in Eastern Taiwan. *World J Cardiol.* (2016) 8:464–71. doi: 10.4330/wjc.v8.i8.464
6. Lin GM, Liu K. An electrocardiographic system with anthropometrics via machine learning to screen left ventricular hypertrophy among young adults. *IEEE J Transl Eng Health Med.* (2020) 8:1800111. doi: 10.1109/JTEHM.2020.2990073
7. Lin GM, Lu HH, A. 12-Lead ECG-based system with physiological parameters and machine learning to identify right ventricular hypertrophy in young adults. *IEEE J Transl Eng Health Med.* (2020) 8:1900510. doi: 10.1109/JTEHM.2020.2996370

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ORIGINAL RESEARCH
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Global, Regional, and National Burden of Myocarditis From 1990 to 2017: A Systematic Analysis Based on the Global Burden of Disease Study 2017

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Objective: The global trends in myocarditis burden over the past two decades remain poorly understood and might be increasing during the coronavirus disease 2019 (COVID-19) worldwide pandemic. This study aimed to provide comprehensive estimates of the incidence, mortality, and disability-adjusted life years (DALYs) for myocarditis globally from 1990 to 2017.

Methods: Data regarding the incidence, mortality, DALY, and estimated annual percentage change (EAPC) between 1990 and 2017 for myocarditis worldwide were collected and calculated from the 2017 Global Burden of Disease study. We additionally calculated the myocarditis burden distribution based on the Socio-Demographic Index (SDI) quintile and Human Development Index (HDI).

Results: The incidence cases of myocarditis in 2017 was 3,071,000, with a 59.6% increase from 1990, while the age-standardized incidence rate (ASIR) was slightly decreased. The number of deaths due to myocarditis increased gradually from 27,120 in 1990 to 46,490 in 2017. The middle SDI quintile showed the highest number of myocarditis-related deaths. On the contrary, the global age-standardized death rate (ASDR) decreased with an overall EAPC of −1.4 [95% uncertainty interval (UI) = −1.8 to −1.0]. Similar to ASDR, the global age-standardized DALY rate also declined, with an EAPC of −1.50 (95% UI = −2.30 to −0.8) from 1990 to 2017. However, there was a 12.1% increase in the number of DALYs in the past 28 years; the middle SDI and low-middle SDI quintiles contributed the most to the DALY number in 2017. We also observed significant positive correlations between the EPAC of age-standardized rate and HDI for both death and DALY in 2017.

Conclusions: Globally, the ASIR, ASDR, and age-standardized DALY rate of myocarditis decreased slightly from 1990 to 2017. The middle SDI quintile had the highest level of

ASIR, ASDR, and age-standardized DALY rate, indicating that targeted control should be developed to reduce the myocarditis burden especially based on the regional socioeconomic status. Our findings also provide a platform for further investigation into the myocarditis burden in the era of COVID-19.

Keywords: myocarditis, Global Burden of Disease, incidence, death, disability-adjusted life years

INTRODUCTION

Cardiovascular disease is a major contributor to disease burden and death globally (1). Myocarditis is a cause of cardiovascular disease that primarily manifests as chest pain, sudden death, and heart failure. There were 353,700 [95% uncertainty index (UI): 339,500 to 370,600] deaths globally due to myocarditis and cardiomyopathy in 2015, representing a considerable public health problem (2, 3). It was also ranked as the third leading cause of sudden cardiac death in competitive athletes reported by the American Heart Association and the American College of Cardiology, and it was considered the most common known cause of dilated cardiomyopathy in children <18 years of age (4).

However, the actual burden of myocarditis is challenging to determine and is likely under-reported, and the burden of myocarditis is either limited to the local scope or does not include an analysis of regional and temporal variations (5, 6). The fundamental knowledge of the incidence, mortality, or disability-adjusted life years (DALYs) for myocarditis, which is used to appropriately guide efforts in improving cardiovascular health at national levels, remains inadequate across the world. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection can induce myocardial injury and myocarditis (7–9). In the current worldwide pandemic of coronavirus disease 2019 (COVID-19), the number, incidence, and/or mortality of myocarditis might be increasing. Therefore, fundamental data on the burden of myocarditis before the COVID-19 pandemic is valuable to investigate the impact of COVID-19 on the prospective myocarditis burden.

The remaining knowledge gap can be filled by a systematic evaluation of available data from the Global Burden of Disease (GBD) database that can provide an opportunity for timely and transparent estimates of disease incidence, mortality, DALY, and other metrics to describe the disease burden at the geographic scales of global, regional, and national levels. So far, a large number of articles using the GBD database have been published and serve to improve health policies (10–12).

In the present study, we used the GBD 2017 database to describe the incidence, mortality, and DALY burden of myocarditis by region, age, and sex in 2017 and to evaluate their temporal trends from 1990 to 2017 across the world. Furthermore, we calculated the myocarditis burden distribution based on the Socio-Demographic Index (SDI) quintile and Human Development Index (HDI). The results of this study will help to facilitate the development of global responses that can support the health care system in improving cardiovascular health globally.

METHODS

Study Data

Detailed data on the incidence, mortality, DALY, and the age-standardized rate (ASR) for myocarditis from 1990 to 2017 were extracted from the Global Health Data Exchange (GHDx) query tool (http://ghdx.healthdata.org/gbd-results-tool) (13). The overall burden of disease was assessed using the DALY, a time-based measure that combines years of life lost due to premature mortality and years of life lost due to time lived in a state of less than full health or years of healthy life lost due to disability (14). The general methods for the GBD study and the methods for estimating myocarditis disease burden have been detailed in a previous study (15). **Supplementary Table 1** delineates the International Classification of Diseases 10 (ICD-10) codes and subgroups that embody the GBD myocarditis cause code (B.2.6.1).

Information regarding the sex and age was also retrieved to evaluate their influence on the global burden of myocarditis. To further characterize the global burden of myocarditis, these detailed data were reanalyzed on three levels based on the SDI (16) quintiles, 21 GBD regions, and 195 countries and territories. The five SDI quintiles (high, high-middle, middle, low-middle, and low levels) are based on the SDI, a summary measurement of a region's socio-demographic development status based on total fertility rate, per capita income, and educational level (17). A detailed methodology regarding the calculation of SDI cutoff points is reported elsewhere (1, 18). We then characterized the distribution of the global burden of myocarditis according to the 21 GBD regions. Finally, the annual changes in the incidence rates, mortality rates, and DALY rates in 195 countries and territories over the same time period were described using tables and world maps. HDI (19) is a statistic composite index of life expectancy, education, and per capita income indicators, which is used to rank countries into four tiers of human development. The HDI data in 2017 provided by the World Bank (20) were also extracted by our group to evaluate the relationship between myocarditis disease burden and national development status.

Statistical Analysis

To compare the myocarditis disease burden of the population between the different demographic structures or within same population in which age profiles changed between different time points, the parameters of age-standardized incidence rate (ASIR), age-standardized death rate (ASDR), and age-standardized DALY rate were used in this study. ASR (per 100,000 population) is equal to the sum of the product of the specific age ratio (a_i) in age group i and

TABLE 1 | The incidence cases and age-standardized incidence rate of myocarditis between 1990 and 2017 and its temporal trends from 1990 to 2017.

Characteristics	1990		2017		1990–2017
	Incidence cases No. $\times 10^4$ (95% UI)	ASIR per 100,000 No. (95% UI)	Incident cases No. $\times 10^4$ (95% UI)	ASIR per 100,000 No. (95% UI)	EAPC No. (95% CI)
Global	192.5 (171.4–216.4)	41.0 (36.1–46.1)	307.1 (274.5–307.1)	39.21 (35.1–39.2)	0.0 (−0.6–0.5)
Sex					
Female	94.0 (83.7–105.6)	39.0 (34.8–43.9)	151.8 (135.7–171.3)	37.5 (33.5–42.1)	−0.2 (−0.7–0.2)
Male	98.5 (87.6–110.5)	43.0 (38.5–48.4)	155.3 (138.7–175.0)	41.0 (36.8–46.1)	−0.1 (−0.6–0.4)
Andean Latin America	1.1 (1.0–1.2)	38.00 (33.98–42.99)	2.3 (2.1–2.6)	40.01 (35.72–45.12)	0.2 (−0.3–0.8)
Australasia	0.8 (0.7–0.9)	33.78 (30.34–38.09)	1.3 (1.1–1.4)	32.76 (29.38–36.72)	0.1 (−0.4–0.7)
Caribbean	1.3 (1.2–1.5)	43.58 (38.92–49.05)	2.3 (2.0–2.5)	45.87 (41.01–51.64)	0.1 (0.1–0.2)
Central Asia	2.0 (1.8–2.2)	34.28 (30.74–38.72)	2.7 (2.4–3.1)	33.49 (30.02–37.66)	0.0 (−0.8–0.8)
Central Europe	6.1 (5.4–6.8)	44.87 (40.2–50.45)	7.1 (6.3–8.0)	44.22 (39.71–49.48)	−0.1 (−1.0–0.8)
Central Latin America	5.2 (4.6–5.8)	42.65 (38.18–48.04)	10.5 (9.3–11.8)	42.73 (38.3–48.1)	0.0 (−0.2–0.3)
Central Sub-Saharan Africa	1.4 (1.2–1.6)	38.46 (34.4–43.37)	3.1 (2.7–3.5)	40.4 (36.0–45.59)	0.1 (−0.6–0.8)
East Asia	53.9 (47.9–60.3)	49.8 (44.63–55.85)	79.2 (70.6–89.6)	46.72 (41.81–52.39)	−0.1 (−1.2–1.0)
Eastern Europe	14.4 (12.9–16.2)	56.9 (51.12–63.76)	13.7 (12.2–15.4)	49.8 (44.51–55.82)	−1.0 (−2.2–0.1)
Eastern Sub-Saharan Africa	4.7 (4.1–5.3)	38.11 (33.94–43.02)	10.1 (8.9–11.5)	39.1 (34.9–44.04)	0.1 (−0.4–0.7)
High-income Asia Pacific	8.4 (7.5–9.5)	44.35 (39.69–49.69)	12.0 (10.7–13.6)	42.18 (37.81–47.26)	−0.1 (−1.6–1.4)
High-income North America	5.8 (5.1–6.6)	17.82 (15.76–20.25)	7.8 (7.1–8.6)	16.18 (14.86–17.68)	−0.1 (−2.8–2.6)
North Africa and Middle East	9.1 (8.1–10.2)	37.2 (33.19–41.79)	19.5 (17.3–22.0)	38.29 (34.22–43.13)	0.1 (−0.6–0.8)
Oceania	0.2 (0.2–0.2)	42.58 (38.14–48.22)	0.4 (0.4–0.5)	43.45 (38.83–49.05)	0.0 (−0.7–0.8)
South Asia	29.8 (26.4–33.6)	36.69 (32.76–41.24)	55.5 (49.4–62.8)	35.82 (32.04–40.48)	0.1 (0.0–0.1)
Southeast Asia	16.5 (14.6–18.6)	45.8 (41.07–51.62)	29.5 (26.3–33.4)	47.57 (42.58–53.69)	0.1 (−0.8–1.0)
Southern Latin America	1.1 (1.0–1.2)	23.01 (20.48–25.95)	1.7 (1.5–1.9)	22.65 (20.13–25.57)	0.0 (−1.9–1.9)
Southern Sub-Saharan Africa	1.6 (1.4–1.7)	39.88 (35.66–44.85)	2.7 (2.4–3.0)	40.4 (36.00–45.59)	0.0 (−0.5–0.5)
Tropical Latin America	5.6 (5.0–6.3)	46.25 (41.40–52.00)	10.7 (9.5–12.0)	46.64 (41.75–52.55)	0.0 (−0.2–0.2)
Western Europe	19.0 (17.0–21.4)	56.9 (51.12–63.76)	24.1 (21.5–27.2)	36.99 (33.2–41.48)	0.0 (−0.5–0.4)
Western Sub-Saharan Africa	4.9 (4.4–5.5)	37.51 (33.49–42.45)	11.1 (9.8–12.5)	38.31 (34.22–43.26)	0.1 (−0.4–0.6)

the number [or weight (w_i)] of the selected reference standard population group i divided by the sum of the number (or weight) of the standard population, i.e., $\mathrm{ASR} = \frac{\sum_{i=1}^{A} a_i\, w_i}{\sum_{i=1}^{A} w_i} \times 100,000$.

More importantly, the trend of the ASR can be used as a good surrogate for the rate of incidence, deaths, and DALYs with a shifting pattern in a certain population, and the estimated annual percentage change (EAPC) can serve as a measurement change of ASR trend in a time interval (21). Consequently, a regression line was fitted into the natural logarithm of the rates: $y = \alpha + \beta x + \epsilon$, where y represents ln ASR and x refers to the calendar year. EAPC $= 100 \times \left(\exp\left(\beta\right) - 1\right)$ and its 95% uncertainty interval (UI) can also be obtained from the regression model (21). If the EAPC estimation and its lower limit of 95% UI are both positive, the ASR is considered to be in an increasing trend. Conversely, if the EAPC estimation and its upper limit of 95% UI are both negative, the ASR is in a downward trend. If the above conditions are not met or the estimated UI overlap, the ASR is deemed to be stable. The R program (version 3.6.3, R Core Team) was used to perform the statistical analysis and draft the graphs. Differences were considered significant at a p-value of <0.05.

RESULTS

The Incidence Burden of Myocarditis

Trends of Myocarditis Incidence From 1990 to 2017

Globally, the incidence number of myocarditis was 3,071,000 (95% UI = 2,745,000–3,071,000) in 2017, with a 59.6% increase from 1,925,000 (95% UI = 1,741,000–2,164,000) in 1990 (**Table 1**, **Supplementary Table 2**, and **Figure 1A**). In addition, the ASIR decreased globally from 1990 to 2017 globally (41.0 per 100,000 persons in 1990 vs. 39.2 per 100,000 persons in 2017) (**Table 1** and **Figures 1B,C**).

The incidence of myocarditis increased across all the five SDI regions from 1990 to 2017, especially in the middle SDI (**Table 1** and **Figure 2A**). The middle SDI quintile had the highest number of myocarditis incidences cases (945,000, 95%UI = 842,000–1,065,000) (**Table 1**). However, the ASIR decreased in the middle SDI, high-middle SDI, and high SDI regions with the EAPC of 0.0 (95% UI = −0.7 to 0.6), −0.3 (95% UI = −0.8 to −0.2) and −0.1 (95% UI = −1.2 to 1.0), respectively. The ASIR in the low SDI and low-middle SDI remained stable during the study period (**Figure 3A** and **Table 1**).

As shown in **Figure 4**, we found no significant correlation between the EAPC and the ASIR in 1990 ($\rho = -0.093$, $p =$

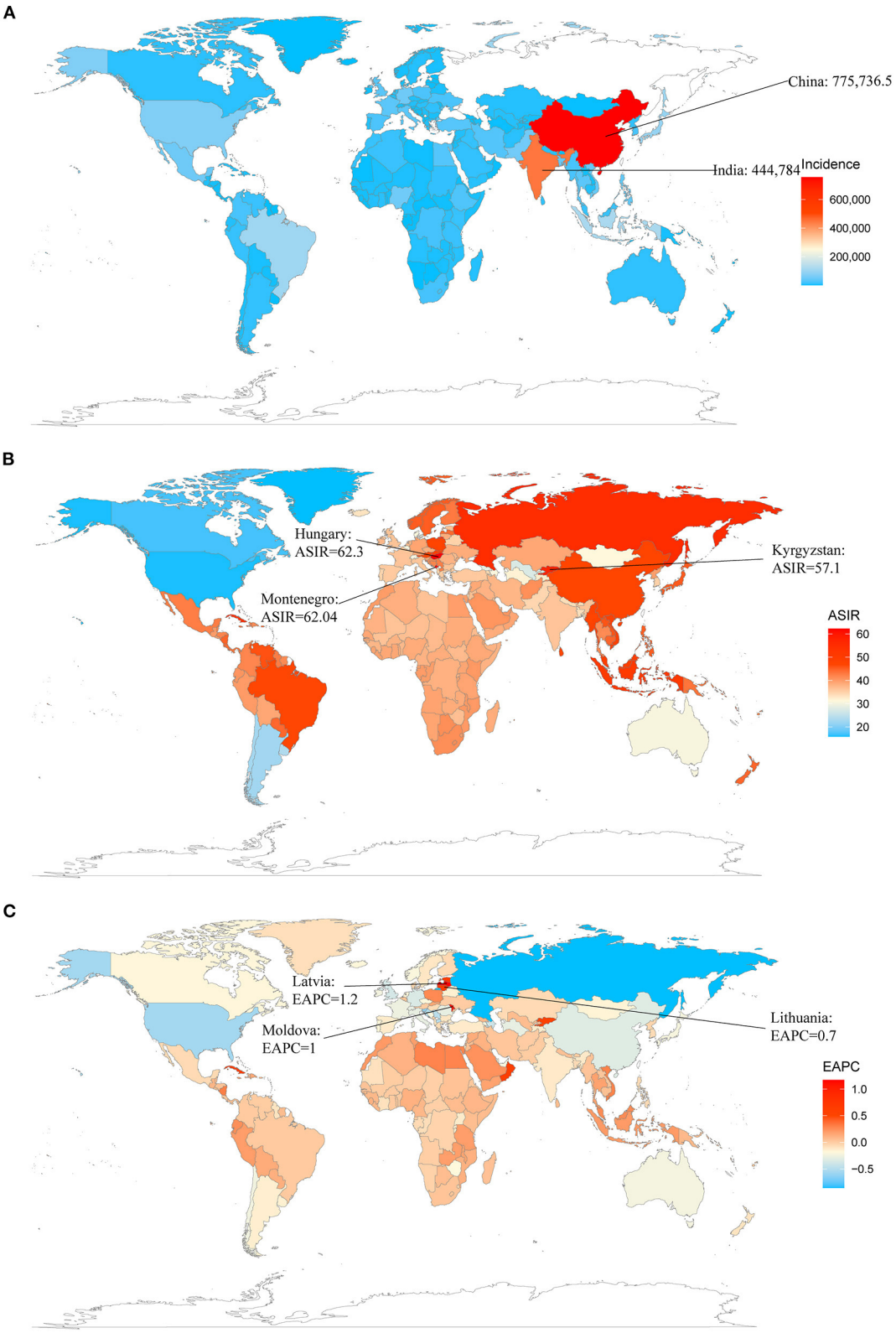

FIGURE 1 | The global incidence burden of myocarditis in 195 countries and territories. **(A)** The absolute number of myocarditis incidence cases in 2017. **(B)** The ASIR of myocarditis in 2017. **(C)** The EAPC of myocarditis ASIRs between 1990 and 2017. ASIR, age-standardized incidence rate; EAPC, estimated annual percentage change.

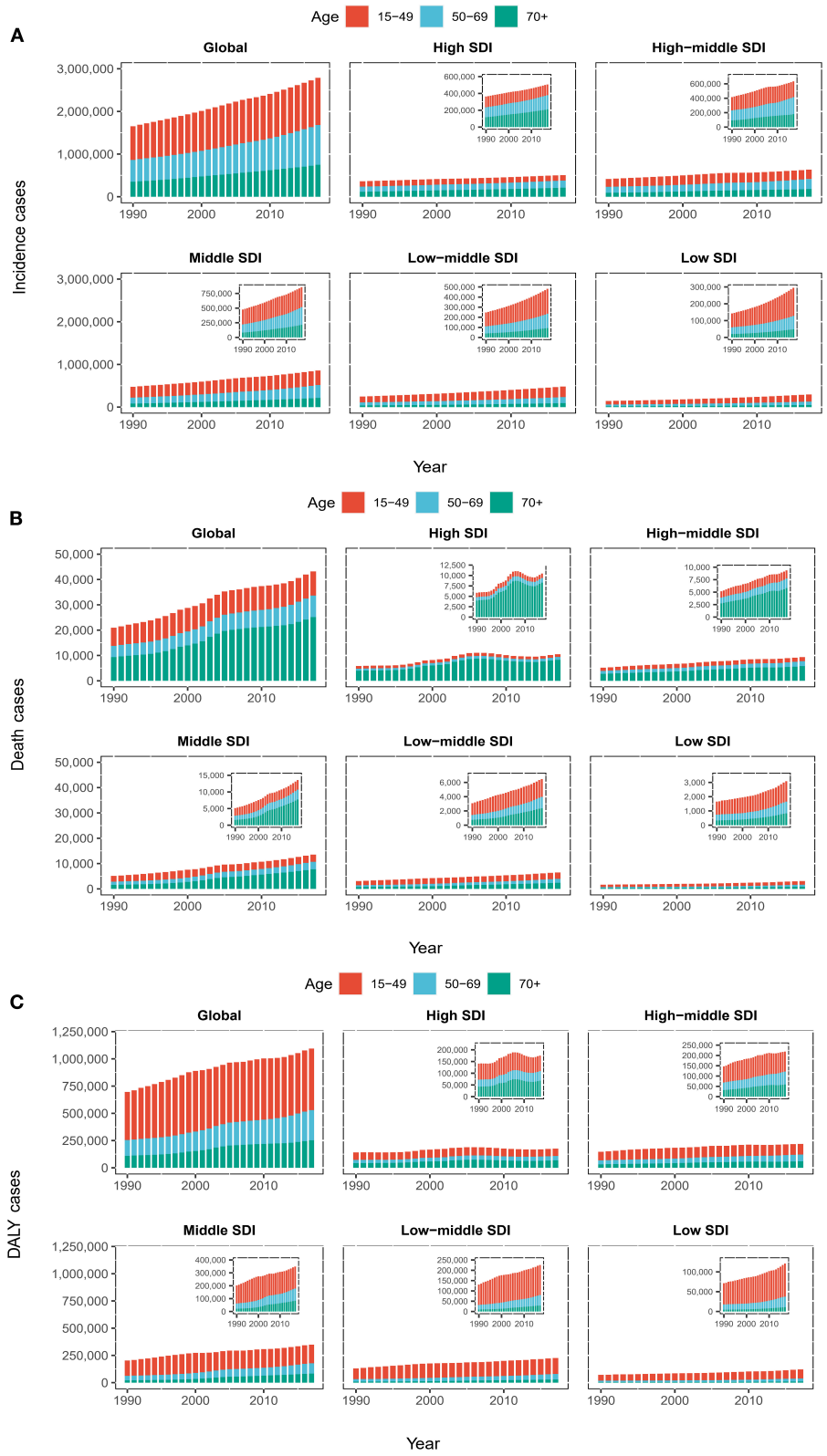

FIGURE 2 | The proportion of the three age groups (15–49 years, 50–69 years and 70+ years) for myocarditis incidences **(A)**, deaths **(B)**, and DALY **(C)** cases globally and in five SDI quintiles between 1990 and 2017. SDI, Socio-Demographic Index; DALY, disability-adjusted life year.

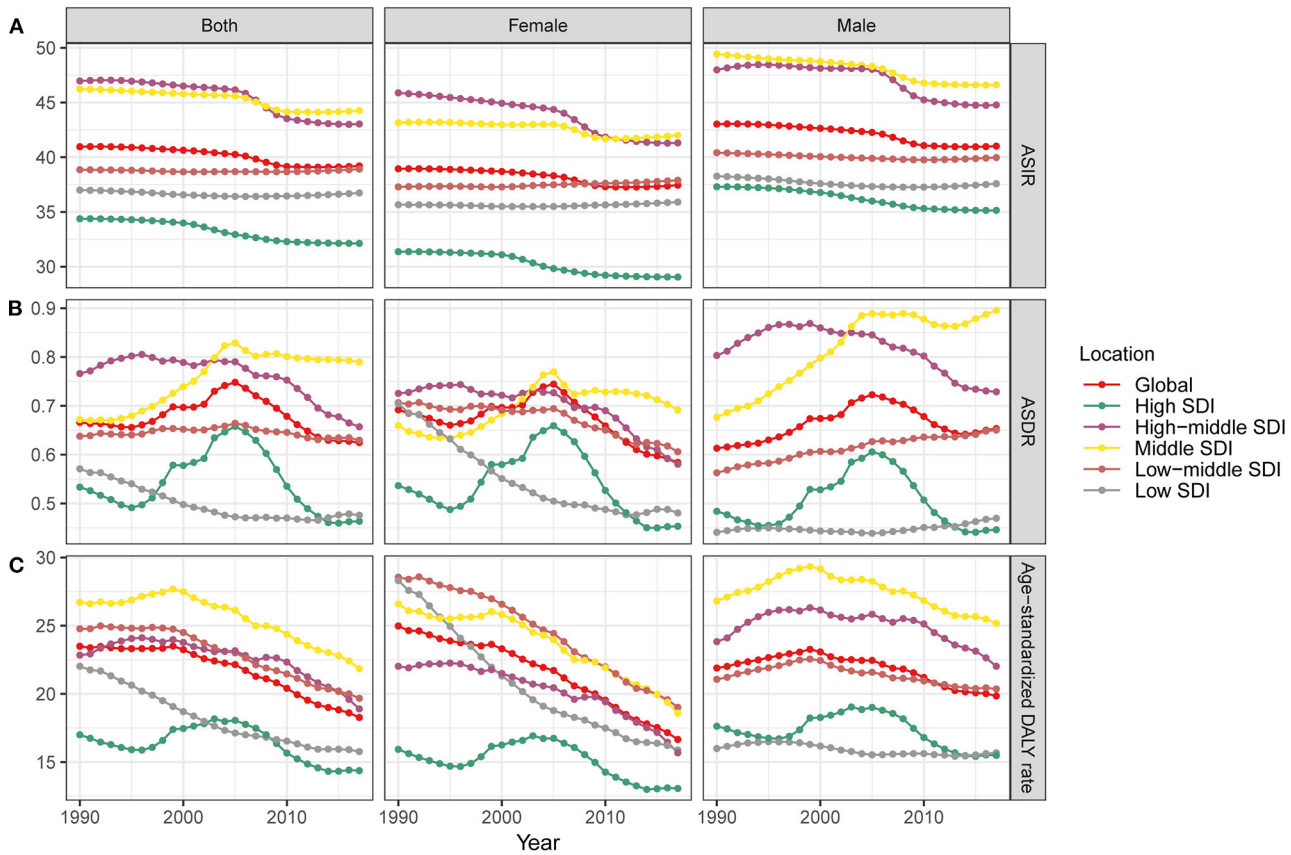

FIGURE 3 | The trends of ASIR change **(A)**, ASDR **(B)**, and age-standardized DALY rate **(C)** (per 100,000 persons) globally and among different SDI quintiles between 1990 and 2017. ASIR, age-standardized incidence rate; ASDR, age-standardized death rate; DALY, disability-adjusted life year; SDI, Socio-Demographic Index.

0.19, **Figure 4A**), and a negative correlation between the EAPC of ASIR and the HDI in 2017 ($\rho = -0.24$, $p = 0.001$, **Figure 4B**). These results illustrate that countries with a higher HDI have experienced a more rapid decrease in the ASIR of myocarditis from 1990 to 2017.

With respect to 21 GBD regions, the highest incidence in 2017 was observed in East Asia (792,000, 95% UI = 706,000–896,000), followed by South Asia (555,000, 95% UI = 494,000–628,000) (**Table 1**). The highest ASIR of 49.8/100,000 persons (95% UI = 44.51–55.82) was observed in Eastern Europe, and the lowest ASIR of 16.18/100,000 persons (95% UI = 14.86–17.68) was observed in high-income North America (**Table 1**). The greatest increase was observed in Western Sub-Saharan Africa (126.5%) followed by Central Sub-Saharan Africa (121.4%) (**Table 1** and **Supplementary Figure 1A**). In 2017, Hungary, Montenegro, and Kyrgyzstan, had the highest myocarditis ASIRs for myocarditis, while Greenland and the United States were the top two countries with the lowest ASIRs (**Supplementary Table 2** and **Figures 1A,B**).

Trends of Myocarditis Incidence Across Ages and Genders

Globally, the male and female genders experienced a similar increase in incidence from 1990 to 2017, while the ASIR of both genders remained relatively stable with an EAPC of −0.2 [95% confidence interval (CI) = −0.7–0.2], −0.1 (95% CI = −0.6–0.4), respectively (**Table 1** and **Figure 3A**). Males achieved higher ASIR than females in five regions (**Figures 3B,C**). The incidence of myocarditis increased across all three age groups (15–49, 50–69, and 70+ years) from 1990 to 2017, and the 15–49 age group had the highest increase in incidence in all regions with low and high-middle SDIs. Regarding high SDI quintile, the 70+ years age group accounted for a larger proportion of the incidence (**Figure 2A**).

Regionally, the incidence of myocarditis in East Asia and Western Europe grew rapidly, especially among elderly people (over 70 years old) (**Figure 5A**). In South Asia, the incidence of myocarditis in the young age group (15–49 years old) in 2017 increased sharply compared to that in 1990 (**Figures 5A,D**). Overall, the incidence of myocarditis varied largely between age groups and gender type, and the highest incidence was clearly observed in the group of people under the age of 20 for both males and females (**Figure 6A**).

The Death Burden of Myocarditis

Trends of Myocarditis Death From 1990 to 2017

Globally, the annual death due to myocarditis increased gradually from 27,120 (95% UI = 21,810–110,574) in 1990 to 46,490

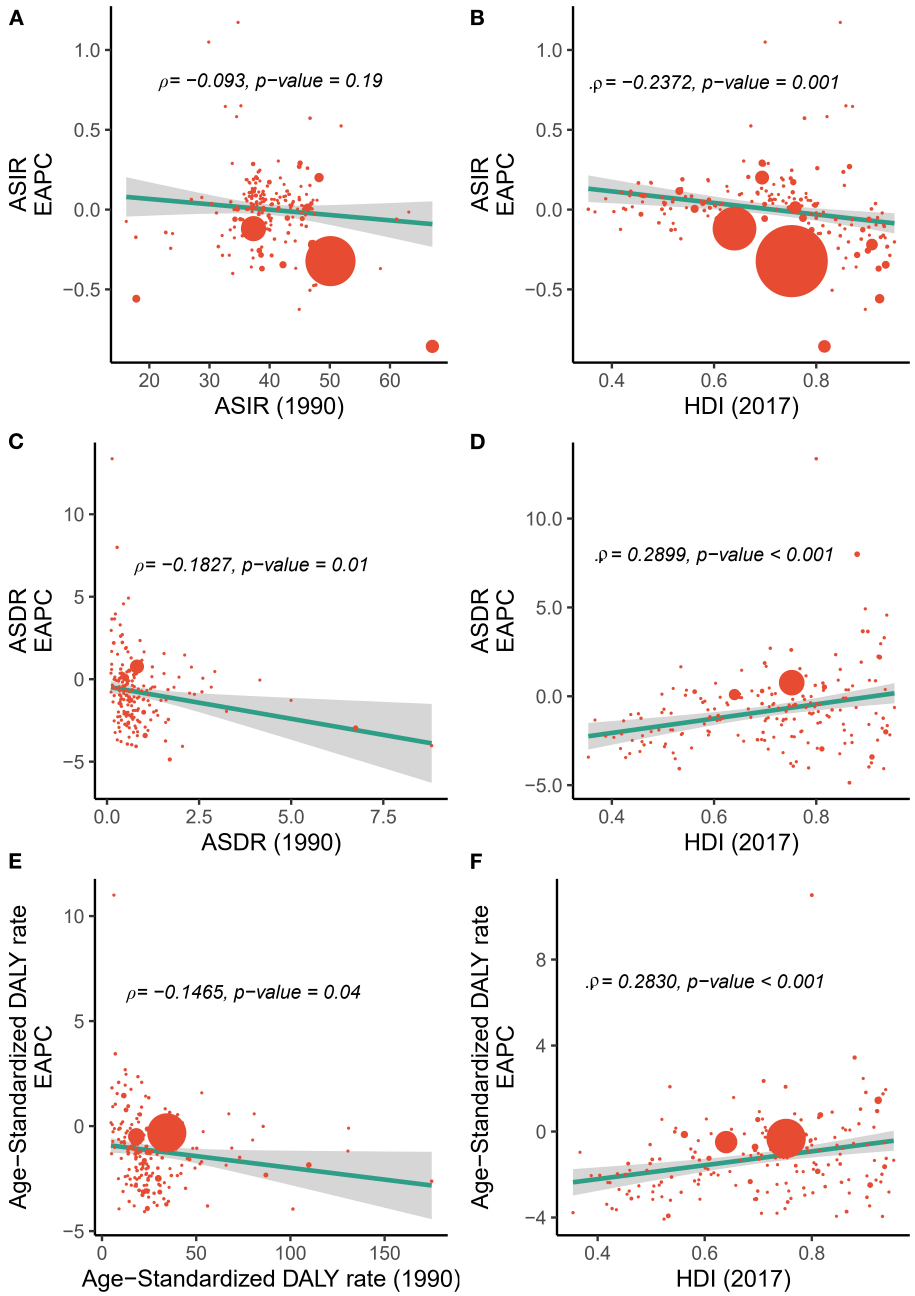

FIGURE 4 | Correlation between the EAPC of incidences/deaths/DALYs and **(A,C,E)** the corresponding ASRs in 1990 and **(B,D,F)** HDI in 2017. The size of the circle is increased with the number of incidence, death, and DALY cases of myocarditis. ASR, age-standardized rate; ASIR, age-standardized incidence rate; ASDR, age-standardized death rate; DALY, disability-adjusted life year; EAPC, estimated annual percentage change; HDI, Human Development Index.

(95% UI = 39,710–51,820) in 2017. However, the global ASDR increased at the beginning of 1990 and then decreased over time (**Table 1**).

Regarding SDI level analysis, the number of myocarditis-related deaths increased across all five SDI quintiles from 1990 to 2017; it precipitously increased in the middle SDI (0.97-fold) and less obviously in the low SDI quintile (0.28-fold) (**Table 2** and **Figure 2B**). Generally, the ASDR in the five SDI quintiles declined, and the middle SDI quintile had the highest ASDR (0.79, 95% UI = 0.64–0.79), which was higher than the world average (**Table 2** and **Figures 2B**, **3B**).

We also found a significant negative relationship between the EAPC and the ASDR in1990 ($\rho = -0.1827$, $p = 0.01$, Pearson correlation analysis), suggesting that those countries with lower disease reservoirs at baseline experienced a more rapid decrease in ASDR (**Figure 4C**). A positive correlation was found between

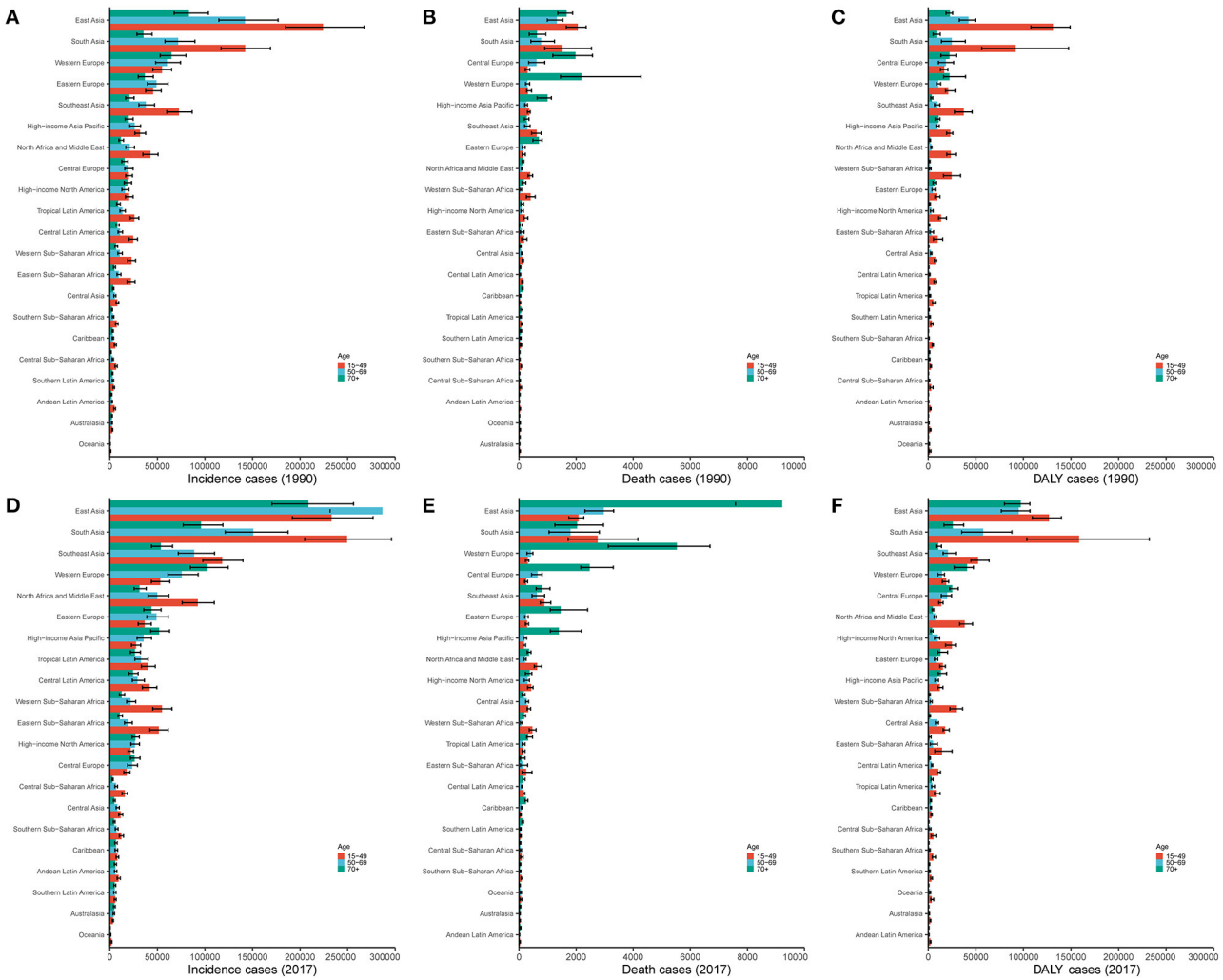

FIGURE 5 | The proportion of the three age groups (15–49, 50–69, and 70+ years) for myocarditis incidence **(A,D)**, deaths **(B,E)**, and DALYs **(C,F)** in 21 GBD regions between 1990 and 2017. DALY, disability-adjusted life year; GBD, Global Burden of Disease.

the EAPC of ASDR and the HDI in 2017 ($\rho = 0.2899$, $p < 0.01$, Pearson correlation analysis) (**Figure 4D**).

With respect to 21 GBD regions, the highest number of deaths in 2017 were observed in East Asia (15,370, 95% UI = 12,710–16,760), followed by South Asia (7,030, 95% UI = 4,460–10,450) (**Table 2** and **Supplementary Figure 2A**). Regionally, the absolute number of myocarditis-related deaths increased in almost all GBD regions between 1990 and 2017, except for Central Europe, and the most pronounced increase was observed in East Asia (**Supplementary Figure 1B**). In 2017, China and India were found to have the highest reported number of myocarditis-related deaths, which may be a result of their larger population numbers or underlying risk factors. Bahrain and Latvia were the top two countries with the lowest number of myocarditis-related deaths (**Supplementary Table 3**, **Supplementary Figures 2A,B**).

Trends of Myocarditis Death Across Ages and Genders

Globally, deaths were more frequent among men (85%) than women (60%). The ASDR of males increased while the ASDR of females decreased from 1990 to 2017 (**Table 2** and **Figure 3**). The myocarditis-related death cases increased across all three age groups (15–49, 50–69, and 70+ years) from 1990 to 2017, and the 70+ years age group had the highest number of deaths in all regions with low to high-middle SDIs (**Figures 5B,E**). Distinctly, the proportion of myocarditis-related deaths among elderly people was much larger in the high SDI, high-middle SDI, and middle SDI quintile, but in the low-middle SDI and low SDI quintile, the most pronounced number of deaths was observed in the young age group (15–49 years) (**Figure 2B**).

Regionally, the number of myocarditis-related deaths among the young age group (15–49 years old) in 2017 decreased

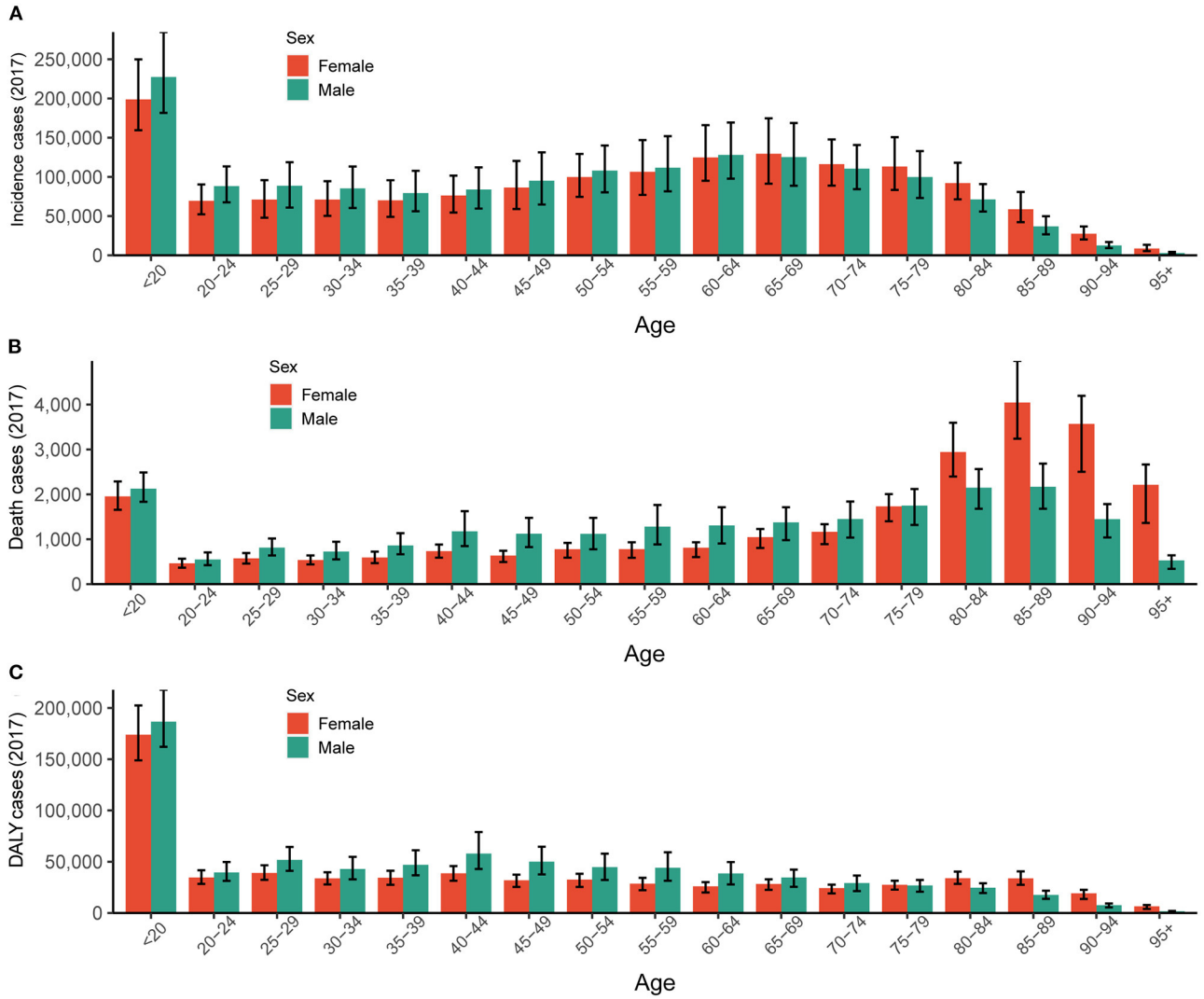

FIGURE 6 | The global burden of myocarditis in both genders and different age groups in 2017. **(A)** The absolute number of incidence cases. **(B)** The absolute number of death cases. **(C)** The absolute number of DALYs. DALY, disability-adjusted life year.

compared to 1990. In contrast, the incidence of myocarditis-related deaths in East Asia and Western Europe grew rapidly, especially among elderly people (over 70 years old) (**Figures 5B,E**). Myocarditis-related deaths varied between age and sex groups. However, it is worth emphasizing that the group of people under the age of 20 for both males and females accounted for a large portion of overall number of deaths in 2017 (**Figure 6B**).

The DALY Burden of Myocarditis

Trends of Myocarditis DALY From 1990 to 2017

Globally, the myocarditis-related DALY number in 2017 was 1,390,700 (95% UI = 1,224,200–1,470,400), and a 12.1% increase was noted for DALYs over the past 28 years. In contrast, the global age-standardized DALY rate decreased from 23.5/100,000 persons (95% UI = 19.3–27.7) in 1990 to 18.27/100,000 persons (95% UI = 16.1–20.4) in 2017, with an overall EAPC of −1.50 (95% UI = −2.30 to −0.8) (**Table 3** and **Figure 3C**).

The global myocarditis-related DALY number in 2017 was 1,390,700 (95% UI = 1,224,200–1,470,400), while the middle SDI and low-middle SDI quintile accounted for the majority of the DALY number (**Table 3** and **Figure 2C**). The middle SDI quintile had the highest age-standardized DALY rate (21.9/100,000 persons, 95% UI = 18.8–25.4), while the high SDI quintile had the lowest age-standardized DALY rate (14.4/100,000 persons, 95% UI = 12.2–15.7) (**Table 3** and **Figure 3C**). The age-standardized DALY rate declined most seriously in the high-middle SDI quintile with an EAPC of −2.0 (95% UI = −3.7 to −0.4) (**Table 3** and **Figure 3C**).

The results also revealed a significant negative relationship between EAPC and the age-standardized DALY rate in 1990 (ρ = −0.1465, p = 0.04) (**Figure 4E**), contrary to a positive pattern

TABLE 2 | The death cases and age-standardized death rate of myocarditis between 1990 and 2017 and its temporal trends from 1990 to 2017.

Characteristics	1990		2017		1990–2017
	Death cases No. ×102 (95% UI)	ASDR per 100,000 No. (95% UI)	Death cases No. ×102 (95% UI)	ASDR per 100,000 No. (95% UI)	EAPC No. (95% CI)
Global	271.2 (218.1–314.0)	0.7 (0.5–0.8)	464.9 (397.1–518.2)	0.6 (0.5–0.7)	−1.4 (−1.8 to −1.0)
Sex					
Female	153.1 (114.7–182.4)	0.7 (0.5–0.8)	245.6 (201.2–270.9)	0.6 (0.5–0.7)	−1.5 (−1.8 to −1.2)
Male	118.0 (93.7–138.9)	0.6 (0.5–0.7)	219.3 (178.3–265.9)	0.7 (0.5–0.8)	0.7 (0.4–1.1)
Andean Latin America	1.1 (0.8–1.4)	0.4 (0.3–0.5)	1.2 (1.0–1.4)	0.21 (0.18–0.24)	−2.5 (−2.8 to −2.1)
Australasia	0.9 (0.7–1.3)	0.4 (0.4–0.6)	1.2 (1.0–1.5)	0.31 (0.27–0.39)	−2.0 (−3.9–0.0)
Caribbean	2.7 (2.2–3.3)	1.0 (0.8–1.2)	4.2 (3.6–5.0)	0.84 (0.72–0.99)	−0.8 (−7.5–6.3)
Central Asia	3.0 (2.6–3.6)	0.6 (0.5–0.6)	7.9 (7.0–9.1)	1.01 (0.85–1.14)	−1.8 (−3.7–0.2)
Central Europe	29.6 (18.2–38.0)	2.4 (1.5–3.0)	20.1 (15.9–30.2)	0.56 (0.37–0.66)	−2.1 (−4.1 to −0.1)
Central Latin America	3.1 (2.5–3.5)	0.3 (0.2–0.3)	5.0 (4.5–6.2)	0.21 (0.15–0.26)	−0.3 (−3.4–2.8)
Central Sub-Saharan Africa	1.8 (1.1–2.7)	0.5 (0.3–0.7)	2.6 (1.5–4.2)	0.37 (0.20–0.59)	−0.6 (−1.7–0.6)
East Asia	74.6 (84.9)	0.8 (0.7–0.9)	153.7 (127.1)	1.0 (0.84–1.09)	−1.4 (−2.3 to −0.5)
Eastern Europe	10.3 (7.8–12.0)	0.5 (0.4–0.6)	20.1 (15.9–30.2)	0.64 (0.52–0.94)	0.1 (−1.1–1.3)
Eastern Sub-Saharan Africa	6.7 (4.2–10.9)	0.5 (0.3–0.8)	7.0 (3.4–12.7)	0.30 (0.12–0.60)	−1.0 (−5.5–3.7)
High-income Asia Pacific	16.8 (12.0–18.6)	1.0 (0.7–1.1)	17.8 (14.4–26.8)	0.39 (0.32–0.56)	−1.7 (−2.8 to −0.5)
High-income North America	5.1 (4.1–7.9)	0.2 (0.1–0.3)	12.4 (8.3–14.4)	0.29 (0.20–0.33)	−0.2 (−1.6–1.1)
North Africa and Middle East	14.7 (11.0–18.2)	0.5 (0.4–0.6)	16.9 (14.5–19.8)	0.34 (0.25–0.39)	−2.1 (−2.3 to −1.8)
Oceania	0.9 (0.7–1.4)	2.9 (2.2–4.0)	1.9 (1.4–2.6)	2.61 (1.98–3.39)	−0.6 (−1.8–0.6)
South Asia	37.5 (23.1–59.4)	0.5 (0.3–0.8)	70.3 (44.6–104.5)	0.55 (0.35–0.81)	1.0 (0.9–1.2)
Southeast Asia	17.3 (13.0–20.8)	0.5 (0.4–0.6)	26.1 (21.1–33.5)	0.47 (0.37–0.60)	−0.8 (−3.3–1.9)
Southern Latin America	2.2 (1.7–2.7)	0.5 (0.4–0.6)	2.5 (2.1–3.1)	0.32 (0.27–0.40)	−2.6 (−5.1–0.1)
Southern Sub-Saharan Africa	1.7 (1.5–2.1)	0.4 (0.4–0.5)	2.0 (1.6–3.0)	0.31 (0.25–0.47)	−3.4 (−6.6 to −0.1)
Tropical Latin America	3.6 (3.0–5.4)	0.3 (0.3–0.5)	6.6 (5.5–9.8)	0.31 (0.26–0.45)	−1.1 (−3.4–1.2)
Western Europe	28.6 (20.7–51.2)	0.5 (0.4–0.9)	62.9 (37.9–75.2)	0.56 (0.37–0.66)	−3.8 (−4.7 to −3.0)
Western Sub-Saharan Africa	8.6 (5.5–11.8)	0.8 (0.5–1.1)	8.7 (7.0–10.6)	0.4 (0.60–0.79)	−1.0 (−1.2 to −0.7)

of EAPC of DALYs and the HDI in 2017 ($\rho = 0.2830$, $p < 0.01$) (**Figure 4F**).

With respect to 21 GBD regions, the highest DALY number in 2017 was observed in East Asia (415,800, 95% UI = 353,900–451,300), followed by South Asia (282,300, 95% UI = 190,200–401,100) (**Table 3**). South Asia displayed the largest increase in myocarditis DALY numbers between 1990 and 2017 (**Table 3**). However, the myocarditis DALY number in the high-income Asia Pacific region and Southern Latin America decreased from 1990 to 2017 (**Table 3** and **Figures 5C,F**).

Trends of Myocarditis DALY Across Ages and Genders

Globally, the age-standardized DALY rate decreased for both genders, while a more pronounced decline was noted for women from 1990 to 2017 (**Table 3** and **Figure 3C**). The proportion of the three age groups (15–49, 50–69, and 70+ years) in myocarditis DALY number remained relatively stable between 1990 and 2017. Myocarditis-related DALY number in the 15–49 years age group remained the highest across all of the SDI quintiles (**Figure 2C**).

The age-standardized DALY rate in women was higher than that in men subjects in 1990, while in 2017, the age-standardized DALY rate was higher in men than women (**Table 3** and **Figure 3C**). The myocarditis DALY number at a young age in 2017 (15–49 years old group) remained stable when compared to the data in 1990. In East Asia, the 15–49 years group accounted for most of the DALY number in 1990, while in 2017, the 70+ years group experienced a sharp increase compared to 1990. In South Asia, people aged 15–49 years accounted for the largest proportion (**Figures 5C,F**). Overall, the myocarditis DALY cases varied across different age groups and genders, and the largest number of DALY was clearly observed in the group of people under the age of 20 for both males and females (**Figure 6C**).

DISCUSSION

The current study systematically evaluated the global epidemiological data of myocarditis and demonstrated that myocarditis has been confirmed as a constantly developing condition due to its progressive and significant effects on mortality and disability. Some specific differences were identified based on age, gender, nation, SDI quintiles, and GBD regions, and these heterogeneities were likely to have significant implications for global public health and health policymaking related to myocarditis.

TABLE 3 | The DALY and age-standardized DALY rate of myocarditis between 1990 and 2017 and its temporal trends from 1990 to 2017.

Characteristics	1990		2017		1990–2017
	DALY no. $\times 10^3$ (95% UI)	Age-standardized DALY rate per 100,000 no. (95% UI)	DALY no. $\times 10^3$ (95% UI)	Age-standardized DALY rate per 100,000 no. (95% UI)	EAPC No. (95% CI)
Global	1,240.2 (1,010.2–1,470.4)	23.5 (19.3–27.7)	1,390.7 (1,224.2–1,470.4)	18.27 (16.1–20.4)	−1.5 (−2.3 to −0.8)
Sex					
Female	670.5 (519.5–829.5)	25.0 (19.6–30.7)	646.1 (561.1–723.2)	16.7 (14.5–18.7)	−1.5 (−2.0 to −1.1)
Male	569.7 (437.9–670.6)	21.9 (17.5–25.7)	744.6 (624.8–893.8)	19.9 (16.8–23.7)	−0.3 (−0.6–0.0)
Andean Latin America	5.8 (4.2–7.2)	15.5 (11.4–19.0)	4.3 (3.7–5.2)	7.3 (6.3–8.6)	−2.8 (−3.3 to −2.3)
Australasia	4.1 (3.5–5.7)	20.9 (17.7–29.1)	4.5 (3.8–5.4)	14.9 (12.8–18.2)	−2.0 (−3.4 to −0.5)
Caribbean	10.6 (8.2–13.6)	31.3 (24.7–39.2)	11.4 (9.7–13.5)	24.4 (20.6–29.3)	−1.1 (−4.6–2.4)
Central Asia	14.1 (12.3–16.5)	22.2 (19.3–26.1)	31.2 (28.1–36.9)	34.7 (31.5–40.5)	−1.5 (−3.6–0.6)
Central Europe	64.4 (43.4–81.3)	49.1 (33.8–60.5)	60.4 (50.5–67.2)	35.4 (30.0–39.0)	−1.2 (−4.2–2.0)
Central Latin America	18.3 (14.2–20.5)	11.3 (8.9–12.6)	22.8 (20.5–27.4)	9.0 (8.1–10.9)	−0.2 (−2.9–2.5)
Central Sub-Saharan Africa	11.6 (6.9–17.9)	19.6 (12.3–28.2)	14.3 (8.7–24.4)	13.3 (8.1–20.8)	−1.3 (−2.0 to −0.6)
East Asia	408.2 (327.9–472.1)	33.9 (27.4–39.0)	415.8 (353.9–451.3)	29.2 (25.2–31.5)	−2.9 (−4.1 to −1.8)
Eastern Europe	25.1 (20.9–31.3)	11.2 (9.3–13.7)	38.6 (32.6–48.9)	15.2 (13.0–18.5)	0.4 (−2.7–3.7)
Eastern Sub-Saharan Africa	44.2 (27.6–70.9)	20.3 (12.9–31.9)	40.2 (22.7–68.2)	11.7 (6.0–20.3)	−1.0 (−5.2–3.4)
High-income Asia Pacific	51.0 (40.9–56.6)	29.3 (22.9–32.5)	36.0 (29.8–46.7)	14.5 (12.3–18.1)	−1.7 (−2.6 to −0.8)
High-income North America	29.5 (24.0–42.2)	11.2 (9.2–16.2)	51.5 (37.6–58.9)	15.5 (11.5–17.5)	−0.7 (−1.6–0.3)
North Africa and Middle East	102.5 (72.3–128.0)	25.4 (19.0–31.2)	93.4 (79.4–110.3)	15.9 (13.5–18.6)	−2.4 (−3.6 to −1.2)
Oceania	4.3 (3.1–6.3)	85.9 (63.8–125.6)	8.1 (6.0–11.2)	78.8 (59.7–106.1)	−0.7 (−3.4–2.0)
South Asia	196.7 (130.0–306.4)	19.2 (12.2–29.9)	282.3 (190.2–401.1)	17.3 (11.6–24.7)	0.1 (−0.4–0.6)
Southeast Asia	99.6 (74.4–126.1)	21.8 (16.7–26.4)	109.7 (94.8–132.3)	17.4 (15.0–20.8)	−0.9 (−2.8–0.9)
Southern Latin America	9.3 (7.5–11.3)	19.2 (15.4–23.2)	7.6 (6.4–9.7)	11.1 (9.3–14.6)	−2.8 (−5.1 to −0.3)
Southern Sub-Saharan Africa	9.6 (8.2–11.3)	18.7 (16.3–22.0)	10.2 (7.8–15.4)	13.5 (10.4–20.1)	−3.6 (−6.8 to −0.3)
Tropical Latin America	21.3 (17.6–30.6)	14.0 (11.8–20.2)	22.5 (18.6–32.7)	11.0 (9.0–15.9)	−1.5 (−3.8–1.0)
Western Europe	61.1 (51.4–87.9)	13.9 (11.8–19.3)	78.5 (59.0–89.4)	12.0 (9.2–13.6)	−2.7 (−3.8 to −1.6)
Western Sub-Saharan Africa	48.7 (30.8–67.0)	25.3 (16.4–34.3)	47.4 (38.3–56.9)	12.4 (10.1–14.8)	−1.0 (−2.3–0.4)

In general, myocarditis increased in incidence, death, and DALY cases, while the global ASR for these three metrics decreased between 1990 and 2017. Population growth and aging in many regions increased the myocarditis disease burden worldwide (22, 23), and the change in diagnostic method from clinical ± bx to MRI (non-invasive) may have also led to an increase in the incidence, mortality, and DALY cases of myocarditis. Regarding the different age stratifications and SDI quintiles, the group under the age of 20 had a higher myocarditis burden compared with other age groups, and middle SDI quintiles had higher ASR for the incidence, death, and DALY. Another finding was that the ASDR trend for myocarditis has plateaued since 2007 and has shown no decline in middle SDI quintile, indicating that a targeted control and prevention strategy should be developed to reduce the myocarditis burden in these regions.

Understanding the temporal trends of the myocarditis disease burden facilitates the initiation of more targeted public health strategies. Although a 59.6% increase in incidence cases, 71.4% increase in deaths cases, and 12.1% increase in DALY cases were observed over the past 28 years across the world, the global ASIR, ASDR, and age-standardized DALY rate showed a declining trend with negative EAPC values. As for the analysis of SDI levels, the incidence, death, and DALY cases of myocarditis increased in all SDI quintiles between 1990 and 2017, increasing sharply in the middle SDI and high-middle SDI quintiles and gently increasing in low SDI quintile. Correspondingly, the ASIR, ASDR, and age-standardized DALY rates in five SDI quintiles declined or remained stable during the same period. From a regional perspective, the most pronounced increase in myocarditis disease burden was observed in Virgin Islands, United States, Czech Republic, Andorra, Qatar, and Uzbekistan, while Libya, Poland, Singapore, Austria, and Rwanda had made substantial strides in decreasing incidence numbers. Our study adds to the accumulating evidence that myocarditis is another component of the recognized epidemiological transition. This phenomenon must be considered for policymakers to allocate limited resources and formulate relevant policies more rationally.

From 1990 to 2017, the global ASIR trend of myocarditis varied considerably between men and women, and the ASIR in males was higher than that in females during the same period, both globally and in the five SDI quintiles. In addition to the higher incidence of myocarditis in males (24, 25), previous studies also demonstrated that males have a higher risk of myocarditis compared to females (26–28). Some clinical trials also displayed a slight male preponderance in the incidence of

myocarditis, with the women/men ratio ranging from 1:1.5 to 1:1.7 (24, 25). Little is known about the mechanism of this apparent male preponderance in myocarditis, but some studies have shown that sex hormones and additional genetic variations may be responsible for the differences in left ventricular recovery, epidemiology, and survival between men and women (29). With respect to age, elderly people may be more likely to be infected by myocarditis due to frailty (30).

In 2017, the incidence and death cases displayed a bimodal distribution as age increased, and the population under the age of 20 accounted for a large proportion of incidence, death, and DALY cases. People aged 65–69 and 85–89 years also had high rates of incidence and death, respectively. These data demonstrated that younger people and older people accounted for a major global burden of myocarditis in 2017. Consistent with our data, previous reports demonstrated that both the incidence of myocarditis and sudden cardiovascular death (SCD) attributed to myocarditis in children and young adults were significantly higher than those in middle-aged and older adults (26, 31, 32). As for the different ages and genders, Kytö et al. found that myocarditis occurred in all ages, and young men were more susceptible compared to their age-matched female counterparts. The distribution of myocarditis in female patients was significantly more stable across all age groups and showed no increase in young adults (32). However, our data showed that people under the age of 20 years had the highest incidence, number of deaths, and DALY cases both in men and women. Testosterone may account for the development of myocarditis in different ages and genders. Previous experimental data showed that increased virus binding to myocytes (33), commitment to T helper type 1 immune response (34), inhibition of anti-inflammatory cell populations (35), and upregulation of cardiac fibrotic remodeling genes (29) were the possible mechanisms of testosterone action in myocarditis.

Moreover, our results indicated a significantly negative association between the EAPC of ASR and the baseline ASR (in 1990), and a significantly positive association between the EAPC of ASR and HDI (in 2017) for both death and DALY. The ASIR of myocarditis in 1990 reflected the disease reservoir at baseline, and the HDI in 2017 can serve as a surrogate for the level and availability of health care in each country. The results could be explained by the fact that countries with higher ASDR and age-standardized DALY rates were more likely to consider myocarditis as a priority in prevention programs in terms of public health considerations. The decline in ASIR was more pronounced in countries with high HDI, possibly because of the better healthcare systems in these countries.

To allocate limited resources more reasonably in the health care system and evaluate the impact of myocarditis control and benchmark progress in their nations, policymakers need the country-specific information about myocarditis disease burden. Considering the fact that most of the existing data are of low quality, sparse, or with limited scope, the GBD study aimed to provide up-to-data estimates of disease incidence, mortality, and DALY, which can be used by stakeholders to gain knowledge of the trend of myocarditis in their local area.

Although the GBD study can be used to fill the remaining knowledge gap, there are still several limitations. First, the quality of the globally included information might be confounded by a multitude of factors, such as the differences in data collecting and the quality of data sources, which remains inevitable in this type of analysis using the ICD-10 codes. Second, the classifications of myocarditis are not available in this study, and it is well-known that the clinical course varies depending on the type of myocarditis. This should be investigated in future studies. Third, the identification of myocarditis has improved remarkably over the last decade with the introduction of high-sensitivity troponins and cardiac magnetic resonance imaging. However, it is difficult to measure the influence of diagnostic methods, and further studies are needed to confirm these results.

CONCLUSION

In general, there was a huge increase in total cases of myocarditis and a slight decrease in ASR in terms of the incidence, death, and DALY, worldwide between 1990 and 2017. The ASIR, ASDR, and age-standardized DALY rate in the middle SDI quintile were higher than in the low and high SDI regions, suggesting that a larger investment was needed to reduce the myocarditis burden in middle SDI regions. Notably, this changing pattern was also heterogeneous among the gender and age groups. The total myocarditis burden was higher in the group of people under the age of 20, and the cases and ASR of the incidence, death, and DALY in the male population were always higher than those in the female population, globally or regionally. Increased awareness regarding myocarditis and timely treatment are important for these young people in clinical practice. These results highlight the need for policies to strengthen the screening, prevention, and treatment of myocarditis in children and young adults, especially in men. The heterogeneities of myocarditis disease burden illustrated by our study should be considered by policymakers to rationalize limited resources and formulate relevant policies.

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS

XW conceived the study, analyzed the data, and wrote the manuscript. XB analyzed the data and revised the manuscript. LW, JL, and DY revised the manuscript and reviewed the results. DM and AM revised the manuscript and provided comments of this research. TH revised the manuscript and provided guidance for this study. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2021.692990/full#supplementary-material

Supplementary Figure 1 | The global disease burden of myocarditis for both genders in 195 countries and territories. **(A)** The relative change in incident cases of myocarditis between 1990 and 2017. **(B)** The relative change in myocarditis-related deaths between 1990 and 2017. **(C)** The relative change in DALY cases of myocarditis between 1990 and 2017. ASIR, age-standardized incidence rate; ASDR, age-standardized death rate; DALY, disability-adjusted life year; EAPC, estimated annual percentage change.

Supplementary Figure 2 | The global death burden of myocarditis in 195 countries and territories. **(A)** The absolute number of myocarditis incidence cases in 2017. **(B)** The ASDR (per 100,000 persons) of myocarditis in 2017. **(C)** The EAPC of myocarditis ASDRs between 1990 and 2017. ASDR, age-standardized death rate; EAPC, estimated annual percentage change.

Supplementary Figure 3 | The global DALY burden of myocarditis in 195 countries and territories. **(A)** The absolute number of myocarditis DALY cases in 2017. **(B)** The age-standard DALY rate (per 100,000 persons) of myocarditis in 2017. **(C)** The EAPC of myocarditis age-standardized DALY rate between 1990 and 2017. DALY, disability-adjusted life year; EAPC, estimated annual percentage change.

REFERENCES

1. GBD 2016 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990-2016: a systematic analysis for the global burden of disease study 2016. *Lancet*. (2017) 390:1211–59. doi: 10.1016/S0140-6736(17)32154-2
2. Cooper LT Jr. Myocarditis. *N Engl J Med*. (2009) 360:1526–38. doi: 10.1056/NEJMra0800028
3. Mason JW. Myocarditis and dilated cardiomyopathy: an inflammatory link. *Cardiovasc Res*. (2003) 60:5–10. doi: 10.1016/S0008-6363(03)00437-1
4. Towbin JA, Lowe AM, Colan SD, Sleeper LA, Orav EJ, Clunie S, et al. Incidence, causes, and outcomes of dilated cardiomyopathy in children. *JAMA*. (2006) 296:1867–76. doi: 10.1001/jama.296.15.1867
5. Lynge TH, Nielsen TS, Gregers Winkel B, Tfelt-Hansen J, Banner J. Sudden cardiac death caused by myocarditis in persons aged 1-49 years: a nationwide study of 14 294 deaths in Denmark. *Forensic Sci Res*. (2019) 4:247–56. doi: 10.1080/20961790.2019.1595352
6. Arola A, Pikkarainen E, Sipilä JO, Pykäri J, Rautava P, Kytö V. Occurrence and features of childhood myocarditis: a nationwide study in Finland. *J Am Heart Assoc*. (2017) 6:e005306. doi: 10.1161/JAHA.116.005306
7. Starekova J, Bluemke DA, Bradham WS, Eckhardt LL, Grist TM, Kusmirek JE, et al. Evaluation for myocarditis in competitive student athletes recovering from coronavirus disease 2019 with cardiac magnetic resonance imaging. *JAMA Cardiol*. (2021) e207444. doi: 10.1001/jamacardio.2020.7444. [Epub ahead of print].
8. Bajaj R, Sinclair HC, Patel K, Low B, Pericao A, Manisty C, et al. Delayed-onset myocarditis following COVID-19. *Lancet Respir Med*. (2021) 9:e32–4. doi: 10.1016/S2213-2600(21)00085-0
9. Imazio M, Klingel K, Kindermann I, Brucato A, De Rosa FG, Adler Y, et al. COVID-19 pandemic and troponin: indirect myocardial injury, myocardial inflammation or myocarditis? *Heart*. (2020) 106:1127–31. doi: 10.1136/heartjnl-2020-317186
10. Hashemi SY, Momenabadi V, Faramarzi A, Kiani A. Trends in burden of chronic obstructive pulmonary disease in Iran, 1995-2015: findings from the global burden of disease study. *Arch Public Health*. (2020) 78:45. doi: 10.1186/s13690-020-00426-x
11. Rahmani H, Sarabi Asiabar A, Niakan S, Hashemi SY, Faramarzi A, Manuchehri S, et al. Burden of esophageal cancer in Iran during 1995–2015: review of findings from the global burden of disease studies. *Med J Islam Repub Iran*. (2018) 32:55. doi: 10.14196/mjiri.32.55
12. Nahvijou A, Arab M, Faramarzi A, Hashemi SY, Javan-Noughabi J. Burden of esophageal cancer according to world health organization regions: review of findings from the global burden of disease study 2015. *Health Scope*. (2019) 8:e64984. doi: 10.5812/jhealthscope.64984
13. *Global Health Data Exchange (GHDx) Query Tool*. (2020). Available online at: http://ghdx.healthdata.org/gbd-results-tool (accessed June 15, 2021).
14. *Disability-Adjusted Life Years (DALYs)*. Available online at: https://www.who.int/data/gho/indicator-metadata-registry/imr-details/158 (accessed June 15, 2021).
15. Cooper LT Jr, Keren A, Sliwa K, Matsumori A, Mensah GA. The global burden of myocarditis: part 1: a systematic literature review for the global burden of diseases, injuries, and risk factors 2010 study. *Glob Heart*. (2014) 9:121–9. doi: 10.1016/j.gheart.2014.01.007
16. McKee S. *Rethinking Development and Health: Findings From the GLOBAL Burden of Disease Study*. Seattle, WA: Institute for Health Metrics and Evaluation (2016). p. 14.
17. IHME. *Global Burden of Disease Collaborative Network. Global Burden of Disease Study 2017 (GBD 2017) Socio-Demographic Index (SDI) 1950-2017*. Available online at: http://ghdx.healthdata.org/record/ihme-data/gbd-2017-socio-demographic-index-sdi-1950%E2%80%932017 (accessed June 15, 2021).
18. Khan MAB, Grivna M, Nauman J. Global incidence and mortality patterns of pedestrian road traffic injuries by sociodemographic index, with forecasting: findings from the global burden of diseases, injuries, and risk factors 2017. *Study*. (2020) 17:2135. doi: 10.3390/ijerph17062135
19. Human Development Index. Available online at: http://hdr.undp.org/en/content/human-development-index-hdi (accessed June 15, 2021).
20. Mathers CD, Salomon JA, Ezzati M, Begg S, Hoorn SV, Lopez AD. Sensitivity and uncertainty analyses for burden of disease and risk factor estimates. In: Lopez AD, Mathers CD, Ezzati M, Jamison DT, Murray CJL, editors. *Global Burden of Disease and Risk Factors*. Washington, DC; New York, NY: The International Bank for Reconstruction and Development/The World Bank Oxford University Press Copyright© 2006, The International Bank for Reconstruction and Development/The World Bank Group (2006).
21. Liu Z, Jiang Y, Yuan H, Fang Q, Cai N, Suo C, et al. The trends in incidence of primary liver cancer caused by specific etiologies: results from the global burden of disease study 2016 and implications for liver cancer prevention. *J Hepatol*. (2019) 70:674–83. doi: 10.1016/j.jhep.2018.12.001
22. Roth GA, Huffman MD, Moran AE, Feigin V, Mensah GA, Naghavi M, et al. Global and regional patterns in cardiovascular mortality from 1990 to 2013. *Circulation*. (2015) 132:1667–78. doi: 10.1161/CIRCULATIONAHA.114.008720
23. Moran AE, Forouzanfar MH, Roth GA, Mensah GA, Ezzati M, Flaxman A, et al. The global burden of ischemic heart disease in 1990 and 2010: the global burden of disease 2010 study. *Circulation*. (2014) 129:1493–501. doi: 10.1161/CIRCULATIONAHA.113.004046
24. Magnani JW, Danik HJ, Dec GW Jr, DiSalvo TG. Survival in biopsy-proven myocarditis: a long-term retrospective analysis of the histopathologic, clinical, and hemodynamic predictors. *Am Heart J*. (2006) 151:463–70. doi: 10.1016/j.ahj.2005.03.037
25. Caforio AL, Calabrese F, Angelini A, Tona F, Vinci A, Bottaro S, et al. A prospective study of biopsy-proven myocarditis: prognostic relevance of

clinical and aetiopathogenetic features at diagnosis. *Eur Heart J.* (2007) 28:1326–33. doi: 10.1093/eurheartj/ehm076
26. Kytö V, Saraste A, Voipio-Pulkki LM, Saukko P. Incidence of fatal myocarditis: a population-based study in Finland. *Am J Epidemiol.* (2007) 165:570–4. doi: 10.1093/aje/kwk076
27. Wang H, Yao Q, Zhu S, Zhang G, Wang Z, Li Z, et al. The autopsy study of 553 cases of sudden cardiac death in Chinese adults. *Heart Vessels.* (2014) 29:486–95. doi: 10.1007/s00380-013-0388-0
28. Mason JW, O'Connell JB, Herskowitz A, Rose NR, McManus BM, Billingham ME, et al. A clinical trial of immunosuppressive therapy for myocarditis. The myocarditis treatment trial investigators. *N Engl J Med.* (1995) 333:269–75. doi: 10.1056/NEJM199508033330501
29. Fairweather D, Cooper LT, Jr., Blauwet LA. Sex and gender differences in myocarditis and dilated cardiomyopathy. *Curr Probl Cardiol.* (2013) 38:7–46. doi: 10.1016/j.cpcardiol.2012.07.003
30. Headley C, Turner J, Rajaram MV. Aging heart and infection. *Aging.* (2019) 11:4781–82. doi: 10.18632/aging.102128
31. Li L, Zhang Y, Burke A, Xue A, Zhao Z, Fowler D, et al. Demographic, clinical and pathological features of sudden deaths due to myocarditis: results from a state-wide population-based autopsy study. *Forensic Sci Int.* (2017) 272:81–6. doi: 10.1016/j.forsciint.2016.12.037
32. Kytö V, Sipilä J, Rautava P. The effects of gender and age on occurrence of clinically suspected myocarditis in adulthood. *Heart.* (2013) 99:1681–4. doi: 10.1136/heartjnl-2013-304449
33. Lyden DC, Olszewski J, Feran M, Job LP, Huber SA. Coxsackievirus b-3-induced myocarditis. Effect of sex steroids on viremia and infectivity of cardiocytes. *Am J Pathol.* (1987) 126:432–8.
34. Huber SA, Pfaeffle B. Differential Th1 and Th2 cell responses in male and female BALB/c mice infected with coxsackievirus group B type 3. *J Virol.* (1994) 68:5126–32. doi: 10.1128/jvi.68.8.5126-5132.1994
35. Frisancho-Kiss S, Coronado MJ, Frisancho JA, Lau VM, Rose NR, Klein SL, et al. Gonadectomy of male BALB/c mice increases Tim-3(+) alternatively activated M2 macrophages, Tim-3(+) T cells, Th2 cells and Treg in the heart during acute coxsackievirus-induced myocarditis. *Brain Behav Immun.* (2009) 23:649–57. doi: 10.1016/j.bbi.2008.12.002

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A Prospective Study of Grip Strength Trajectories and Incident Cardiovascular Disease

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Background: A single measurement of grip strength (GS) could predict the incidence of cardiovascular disease (CVD). However, the long-term pattern of GS and its association with incident CVD are rarely studied. We aimed to characterize the GS trajectory and determine its association with the incidence of CVD (myocardial infarction, angina, stroke, and heart failure).

Methods: This study included 5,300 individuals without CVD from a British community-based cohort in 2012 (the baseline). GS was repeatedly measured in 2004, 2008, and 2012. Long-term GS patterns were identified by the group-based trajectory model. Cox proportional hazard models were used to examine the associations between GS trajectories and incident CVD. We identified three GS trajectories separately for men and women based on the 2012 GS measurement and change patterns during 2004–2012.

Results: After a median follow-up of 6.1 years (during 2012–2019), 392 participants developed major CVD, including 114 myocardial infarction, 119 angina, 169 stroke, and 44 heart failure. Compared with the high stable group, participants with low stable GS was associated with a higher incidence of CVD incidence [hazards ratio (HR): 2.17; 95% confidence interval (CI): 1.52–3.09; $P < 0.001$], myocardial infarction (HR: 2.01; 95% CI: 1.05–3.83; $P = 0.035$), stroke (HR: 1.96; 95% CI: 1.11–3.46; $P = 0.020$), and heart failure (HR: 6.91; 95% CI: 2.01–23.79; $P = 0.002$) in the fully adjusted models.

Conclusions: The low GS trajectory pattern was associated with a higher risk of CVD. Continuous monitoring of GS values could help identify people at risk of CVD.

Keywords: muscle function, trajectory, myocardial infarction, stroke, heart failure

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INTRODUCTION

Muscle dysfunction reduces the quality of life and increases healthcare budgets. Many studies suggest that muscle dysfunction predisposes to the development of diabetes (1), hypertension (2), and cardiovascular disease (CVD) (3, 4). Therefore, monitoring muscle function is essential to improve quality of life. However, the exact measurement of muscle content requires consuming

and costly techniques, such as magnetic resonance imaging or dual-energy X-ray absorptiometry techniques (5–7); meanwhile, muscle content might not fully reflect muscle function (8). Muscle strength, as measured by grip strength (GS), has been shown to be a simple, inexpensive indicator of CVD in population studies (9).

CVDs are known as the leading causes of non-communicable disease-related deaths and one of the most serious health problems worldwide (10), which caused nearly one-third of all deaths worldwide (11). Universally, CVD can refer to a kind of disease that involves the blood vessels or heart (12). This disease consists of myocardial infarction (MI), stroke, heart failure, and many other vascular and cardiac problems (12). In the past few decades, the adverse impacts of CVD have been improved. However, CVD is still responsible for a huge reduction in quality of life and imposes remarkable expenditures on health systems in different countries (13).

Previous cohort (9, 14, 15) and Mendelian randomization (16) studies have consistently shown that muscle strength was a risk factor for CVD incidence. Data from the Prospective Urban Rural Epidemiology (PURE) study of nearly 140,000 participants from 613 communities in 17 countries showed that lower GS is associated with a higher risk of CVD incidence (9). Another study (17) conducted in the UK investigated the changes in GS to be associated with mortality, but GS has only been measured twice in 4 years, and that study did not investigate whether changes in GS are associated with CVD. So far, there is a lack of research on the GS trajectory and its relationship with CVD. Besides, few studies have simultaneously reported the association between GS and MI, angina, stroke, and heart failure. This might be partly due to the different goals of diverse studies, but it could also be due to data-driven emphasis about which outcome to report.

In view of these knowledge gaps, this study aimed to identify GS trajectories over 8 years among 5,300 English participants and to explore the relationship between long-term GS patterns and the subsequent CVD risk. We further investigated the association of GS trajectories with the components of the CVD events, including MI, angina, stroke, and heart failure. We hypothesized that (a) people have different GS patterns and (b) people with different GS patterns would be at different levels of risk for the incidence of CVD.

METHODS

Study Design and Participants

Data were obtained from the English Longitudinal Study of Ageing (ELSA). ELSA is a nationally representative, biannual, ongoing, longitudinal cohort study based on community-dwelling adults living in England (18). The detailed descriptions of the study design, sampling procedure, and data collection were published previously (18, 19).

The current study used data from wave 2 (2004/2005) to wave 9 (2018/2019). Every 4 years from 2004 (wave 2) through 2012 (wave 6), GS was measured by trained nurses. Participants were excluded if they did not have valid GS measurements between 2004 and 2008 (wave 2 or wave 4, $n = 1{,}522$) or if they already had a doctor-diagnosed CVD (i.e., MI, angina, stroke, and heart failure, $n = 766$) at the baseline (i.e., 2012). In addition, we excluded participants who were lost to follow-up from wave 7 to wave 9 ($n = 466$). Finally, a total of 5,300 participants were included in 2012 (the baseline), with at least two repeat GS measures and at least one follow-up reassessment (during 2012–2019) for the current analysis of CVD risk. The participant selection flowchart is shown in **Figure 1**.

All waves of the ELSA received ethical approval from the London Multicenter Research Ethics Committee (MREC/01/2/91), and all participants provided informed consents.

Objective Measurement of Grip Strength

The Smedley handheld dynamometer (Stoelting Co., Wood Dale, IL, USA) was used to measure GS (kg) three times on each hand. The participant was asked to squeeze the device for a couple of seconds and to rest at least 30 s between each measurement. The overall GS value was computed as the average of maximum GS of the non-dominant and dominant hands.

Assessment of Covariates

Covariates shown by previous studies to be associated with both CVD and GS were selected for our study, including age, sex, body mass index (BMI), education, current smoking, physical activity, sleep quality, depression, hypertension, and diabetes. BMI (kg/m^2) was calculated based on body weight and height measured in light clothing without shoes. Education level was classified as (1) equivalent or less than the general certificate of education (GCE) O-level, (2) equivalent or GCE O-level, and (3) higher than GCE A-level or equivalent. Smoking status was categorized as non-smokers (never smoked or ex-smokers) and current smokers. Physical activity was divided into two levels based on whether once or more times moderate or vigorous exercises a week. Sleep quality was grouped as good (score $\leq$2) or bad (score $>$2) using the Jenkins sleep scale. The level of depression was evaluated by the Centre for Epidemiological Studies Depression scale (CES-D). A score $\geq$4 denoted a higher level of depression. The BPs were measured three times using an electronic sphygmomanometer (Omron HEM-907, Omron Corporation, Kyoto, Japan) after resting for more than 5 min, and the average value of the three consecutive readings was used in the analyses. Hypertension was diagnosed as individuals with a mean SBP $\geq$140 mmHg and/or mean DBP $\geq$90 mmHg, or individuals who reported hypertension or received antihypertensive treatment. Diabetes was defined as individuals who reported diabetes or use insulin/antidiabetic medications.

Outcomes

The primary outcome of the current study was the incidence of CVD, defined as the composite outcome of self-reported physician-diagnosed MI, angina, stroke, and heart failure. The secondary outcomes were the components of the primary composite outcome. The incidence of CVD was defined as the report of physician-diagnosed from wave 7 to wave 9. The date of diagnosis of the CVD event is recorded between the date of the last interview and the date of the interview reporting the CVD event. The researchers of ELSA had collected further information

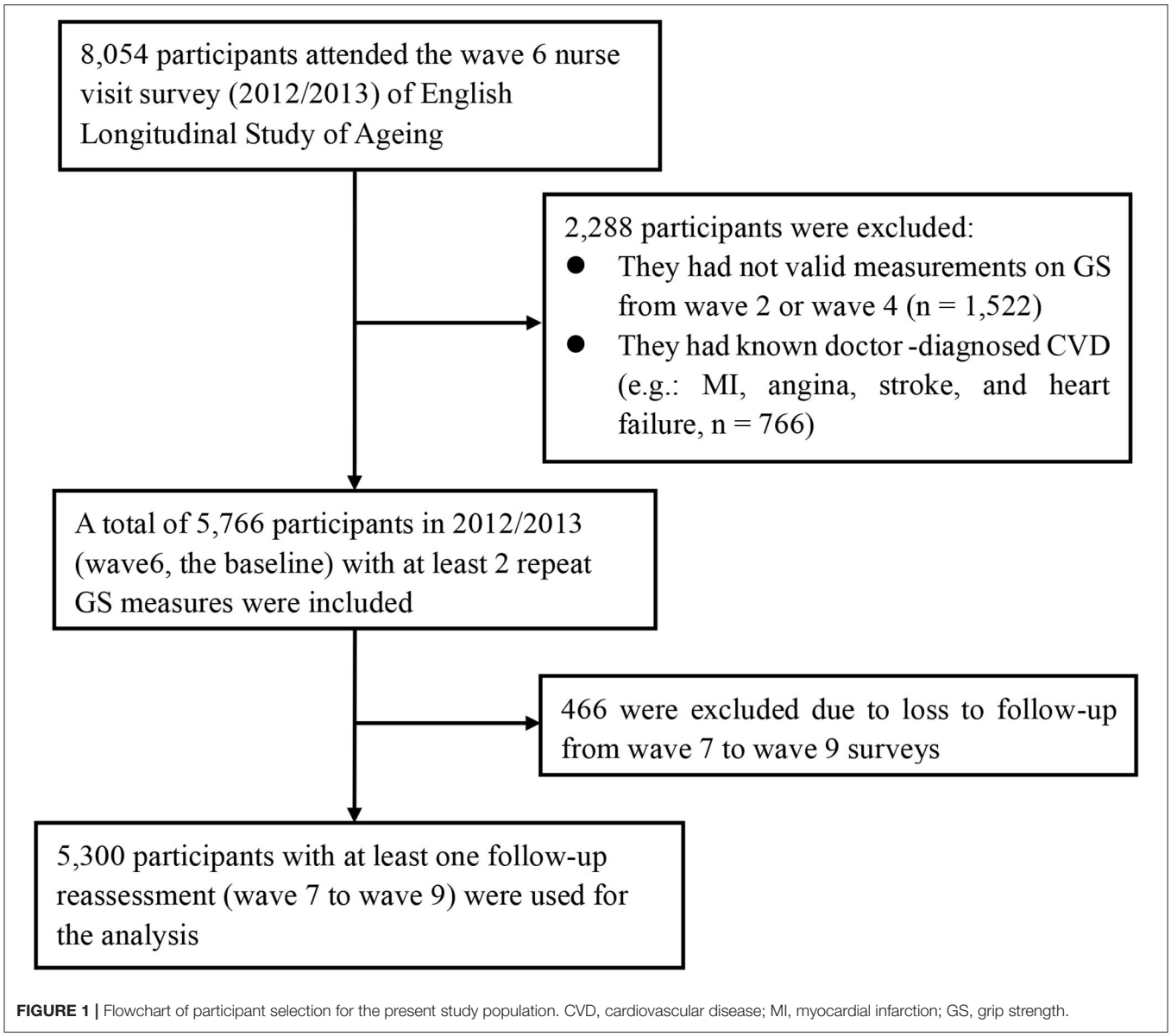

FIGURE 1 | Flowchart of participant selection for the present study population. CVD, cardiovascular disease; MI, myocardial infarction; GS, grip strength.

of incident CVD events from the medical records to confirm the diagnosis.

Statistical Analysis

To distinguish the heterogeneity of CVD by investigating the trajectory of the GS pattern before the CVD event, we applied the group-based trajectory model (GBTM) analysis (20–22) to categorize participants with similar GS change patterns through the TRAJ procedure in SAS. The GBTM could classify the participants with a similar GS pattern into a group automatically and fit the GS measurements in each group according to a generalized linear mixed model. Considering GS values change with time, the GBTM used in our study is useful because it simulates the group-specific trajectories of GS. In our study, GS patterns from 2004 to 2012 were modeled by the latent class method. As GS varies largely according to gender and age, GS was modeled separately for men and women as well as adjusting for age. Up to five trajectory groups were set in advance. We fitted the model from one group trajectory to five group trajectories, and visit wave (years) was used as the time scale. The censored normal model was used appropriately for continuous outcomes. To identify the model with optimal functional forms of distinct GS trajectories, starting from the highest polynomial, the cubic, quadratic, and linear terms were considered and assessed according to the significance level. Model fit was compared using the Bayesian information criterion (BIC) and Akaike's information criterion (AIC) value, with the smallest negative number indicating the best fit model. We described GS from 2004 to 2012 by mean [standard deviation (SD)].

Multivariable Cox proportional hazard models were used to analyze the association between GS patterns from 2004 to 2012 and the risk of CVD. The proportionality of hazards was checked

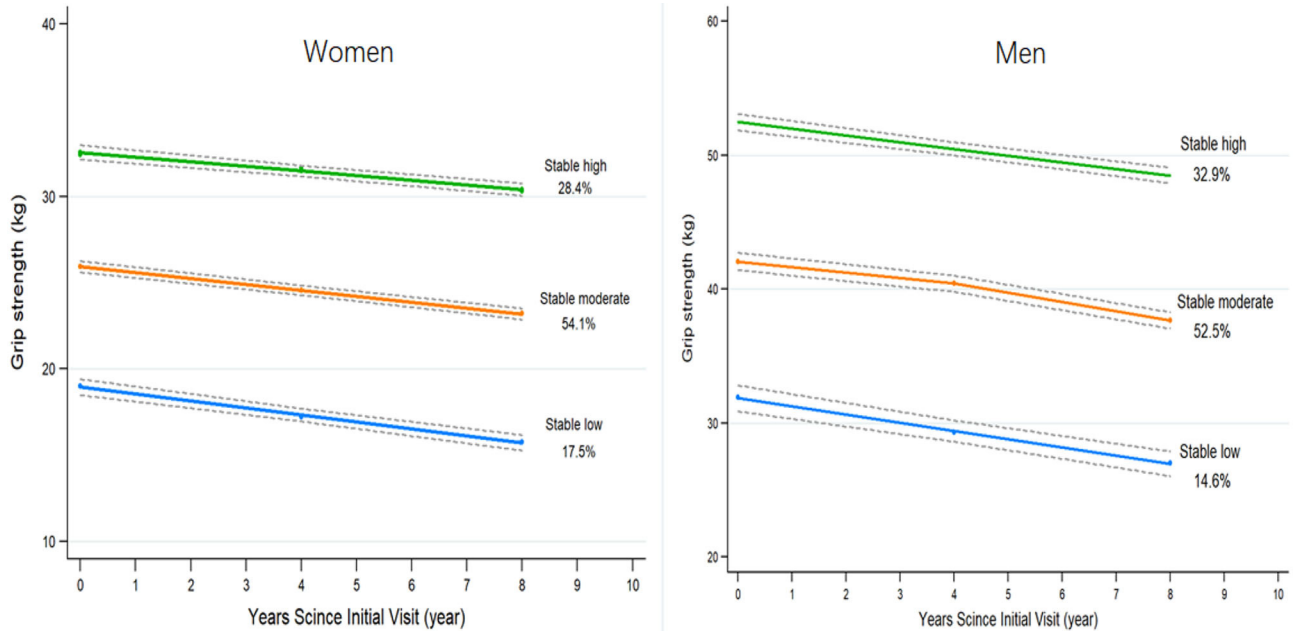

FIGURE 2 | The trajectories of grip strength by sex predicted with 95% confidence intervals. Three groups are indicated by stable high (green), stable moderate (orange), and stable low (blue). Percentages represent the proportion of the cohort with the corresponding group number as the highest predicted posterior probability.

by the Schoenfeld residuals method. Results of Cox models were presented as hazard ratios [HRs; 95% confidence intervals (CIs) and *P*-values]. All analyses are presented as the two models with adjustment of confounding factors in 2012. These confounders shown by previous studies to be associated with both CVD and GS were selected for our analyses. More specifically, the minimally adjusted model was adjusted for age and sex. The fully adjusted model was further adjusted for education, BMI, systolic blood pressure, smoking, physical activity, depression, and quality of sleep.

For the effects of sex or age, likelihood ratio tests were performed to explore statistical interactions between GS patterns and age ($\leq$65 vs. >65) and GS patterns and sex of primary outcome, respectively, by comparison of the −2 logarithmic likelihood chi-square between the nested model with and without a product term. Stratified models by sex and age ($\leq$65 vs. >65) were utilized to explore the associations between trajectories and CVD risks. We conducted all analyses with SAS version 9.4 (Cary, NC, USA).

RESULTS

The model with three trajectories according to the change patterns of GS from 2004 to 2012 was identified as the fit by comparing the BIC and the proportion of the participants within each trajectory group (**Figure 2**). For women, 507 participants were classified as low stable GS (15.8–19.0 kg), 1,656 as moderate stable GS (23.2–26.0 kg), and 820 as high stable GS (30.3–32.4 kg). For men, 325 participants were classified as low stable GS (27.0–31.9 kg), 1,241 as moderate stable GS (37.7–42.1 kg), and 751 as high stable GS (48.4–52.3 kg) (**Supplementary Tables 1–3**).

Table 1 shows the baseline characteristics of participants in each GS trajectory group. Compared with the low stable GS group, participants with high and moderate stable patterns of GS tend to be younger, have lower systolic BP and higher BMI and diastolic BP, and have a higher prevalence of levels of education above the GCE A-level or equivalent, moderate–vigorous activity, and good sleep quality. The proportion of participants who reported current use of tobacco, non-diabetes, and non-hypertension was the highest in the stable high GS group, followed by the moderate stable GS and low stable GS groups.

During a median follow-up of 6.1 years (interquartile range: 5.8–6.3 years), we recorded 392 CVD events, with 114 MI, 119 angina, 169 stroke, and 44 heart failure. In comparing high vs. low, low stable GS was associated with a higher risk of CVD incidence during 2012–2019. **Table 2** shows the HR for CVD incidence (HR: 2.29; 95% CI: 1.64–3.20; $P < 0.001$) was greater in individuals with low stable GS compared with the high stable GS in age/sex-adjusted models. The association remained significant (HR: 2.17; 95% CI: 1.52–3.09; $P < 0.001$) after adjustment for further confounding factors. Compared with the stable high group, participants in the stable low GS group had a double significantly higher risk of CVD incidence.

Results stratified by age and sex are shown in **Table 2**. Associations between GS trajectories and CVD risk were generally consistent in the subgroup analysis, as no significant interactions were observed in terms of age (*P*-interaction = 0.572) and gender (*P*-interaction = 0.462).

TABLE 1 | Baseline characteristics of the participants based on trajectories of grip strength.

Variables	Total (*N* = 5,300)	Stable low grip strength (*N* = 832)	Stable moderate grip strength (*N* = 2,897)	Stable high grip strength (*N* = 1,571)	*P*
Age (years)	68.0 ± 8.3	76.3 ± 9.6	68.2 ± 7.2	63.2 ± 5.4	<0.0001
Women	2,983 (56.3)	507 (60.9)	1,656 (57.2)	820 (52.2)	<0.0001
Education					<0.0001
Less than GCE O-level	2,039 (38.6)	437 (52.9)	1,121 (38.8)	481 (30.8)	
GCE O-level	1,490 (28.2)	205 (24.8)	829 (28.7)	456 (29.2)	
Higher than GCE A-level	1,750 (33.2)	184 (22.3)	939 (32.5)	627 (40.1)	
Body mass index (kg/m^2)	27.2 ± 7.2	25.6 ± 8.8	27.3 ± 7.0	28.1 ± 6.4	<0.0001
Systolic blood pressure (mmHg)	132.7 ± 17.1	134.1 ± 18.7	132.9 ± 17.2	131.6 ± 16.2	0.0090
Diastolic blood pressure (mmHg)	73.8 ± 10.3	70.0 ± 10.8	73.8 ± 10.2	76.0 ± 9.7	<0.0001
Current smoking	516 (9.7)	62 (7.5)	284 (9.8)	170 (10.8)	0.0293
Moderate-vigorous activity	3,470 (65.5)	370 (44.5)	1,960 (67.7)	1,140 (72.6)	<0.0001
Good sleep quality	4,204 (79.4)	617 (74.2)	2,301 (79.6)	1,286 (81.9)	<0.0001
Depressive symptoms	344 (6.5)	46 (5.5)	182 (6.3)	116 (7.4)	0.1712
Hypertension	1,733 (32.7)	355 (42.7)	963 (33.2)	415 (26.4)	<0.0001
Diabetes	420 (7.9)	100 (12.0)	231 (8.0)	89 (5.7)	<0.0001

Data are expressed as number (%) or mean (standard deviation).

Besides, for individuals with older age (>65 years), low and moderate GS was associated with a more substantial increment of CVD risk (**Table 2**), as compared with younger participants (age ≤65 years). Furthermore, low GS was associated with significantly higher CVD risk in individuals aged >65 years, but lost its statistical significance ($P = 0.572$) in individuals aged ≤65 years.

Table 3 examines the associations of GS trajectories with the components of the CVD events. In the age/sex-adjusted model, low stable GS was positively associated with MI, angina, stroke, and heart failure incidence, respectively. The results remained similar after adjusting for additional covariates, except for the incidence of angina (fully adjusted HR: 1.73; 95% CI: 0.93, 3.19; $P = 0.083$). Compared with the high stable GS group, individuals with stable low GS had a higher risk of MI (fully adjusted HR: 2.01; 95% CI: 1.05, 3.83; $P = 0.035$), stroke (fully adjusted HR: 1.96; 95% CI: 1.11, 3.46; $P = 0.020$), and heart failure (fully adjusted HR: 6.91; 95% CI: 2.01, 23.79; $P = 0.002$), respectively.

In addition, we have also added relevant data on the association between baseline grip strength and CVD risk in **Supplementary Table 4**.

DISCUSSION

Muscles, as the main sites for protein storage and glucose processing, play an important role in maintaining the health of people (23, 24). GS was chosen as a biomarker of muscular fitness given its sensitivity to physiological change and its use as a valid marker of muscle function (25). In this English cohort study from 2004 to 2019, we explored the different GS patterns (2004–2012) before the diagnosis of CVD. By using GBTM, we identified three GS groups. The incidence of CVD was highest in the low stable GS group (14.1%), followed by the moderate stable (6.7%) and high stable (5.2%) groups. As far as we know, this is the first prospective cohort study regarding the impacts of longitudinal GS patterns on the incidence of CVD.

The main finding of our study was that stable low GS was strongly associated with a wide range of CVD outcomes. Several studies (9, 14, 26–28) have documented the associations between GS and risk of CVD, where GS was only measured once at baseline. Our results showed that people with the low GS trajectory pattern had a double higher risk of CVD compared with those in the stable high GS group in the fully adjusted model. The associations observed were consistent between the sexes. Interpretations could be multiple regarding how muscle function decline could lead to the incidence of CVD. Musculoskeletal dysfunction may lead to a reduction in muscular contraction-inducing factors (also known as myokines) with anti-inflammatory effects (29), which increases the risk of developing CVD and relevant complications. Besides, endothelial dysfunction, autonomic imbalance, and arterial stiffness might mediate the relationship between CVD and muscle strength (28). Our data suggest that long-term GS patterns might be used to screen patients during physical examination, which has remarkable implications for primary healthcare practice. The general practitioners could stratify individuals given the values of GS change and prescribe physical activities to enhance the general muscular fitness of people with stable low GS, which may serve as an essential part in the management and prevention of CVD. Therefore, there is a demand for increasing recognition that the long-term GS value can be used as a useful clinical biomarker in a health monitoring system.

In the analysis by age subgroup, the association between GS patterns and CVD incidence was more obvious among participants aged >65 years compared with those aged ≤65 years. However, the interaction between age and GS trajectories for CVD was not statistically significant. Previously, few studies have investigated whether the associations between CVD and GS are

TABLE 2 | Cox regression analyses for CVD incidence per trajectory of grip strength (2004–2012).

	Trajectories of grip strength			*P* for interaction
	Stable high	**Stable moderate**	**Stable low**	
Total population				
No. of events (%)	81/1,571 (5.2)	194/2,897 (6.7)	117/832 (14.1)	
HR (95% CI)				
Age/sex adjusted	1 (ref)	1.17 (0.89–1.53)	2.29 (1.64–3.20)	
Fully adjusted[a]	1 (ref)	1.13 (0.85–1.51)	2.17 (1.52–3.09)	
Stratified by sex				0.462
Women				
No. of events (%)	34/820 (4.2)	81/1,656 (4.9)	67/507 (13.2)	
HR (95% CI)				
Age/sex adjusted	1 (ref)	1.04 (0.69–1.56)	2.23 (1.37–3.63)	
Fully adjusted	1 (ref)	0.99 (0.64–1.52)	2.05 (1.22–3.43)	
Men				
No. of events (%)	47/751 (6.3)	113/1,241 (9.1)	50/325 (15.4)	
HR (95% CI)				
Age/sex adjusted	1 (ref)	1.30 (0.91–1.86)	2.33 (1.47–3.69)	
Fully adjusted	1 (ref)	1.26 (0.86–1.85)	2.23 (1.37–3.63)	
Stratified by age				0.572
≤65 years				
No. of events (%)	56/1,114 (5.0)	60/1,171 (5.1)	10/112 (8.9)	
HR (95% CI)				
Age/sex adjusted	1 (ref)	1.10 (0.76–1.59)	1.95 (0.99–3.83)	
Fully adjusted	1 (ref)	1.08 (0.73–1.59)	1.90 (0.95–3.81)	
>65 years				
No. of events (%)	25/457 (5.5)	134/1,726 (7.8)	107/720 (14.9)	
HR (95% CI)				
Age/sex adjusted	1 (ref)	1.56 (1.02–2.39)	3.66 (2.37–5.67)	
Fully adjusted	1 (ref)	1.49 (0.96–2.34)	3.47 (2.18–5.52)	

Data are expressed as n (%) or hazard ratio (95% CI). For this analysis, the group with stable high trajectories of grip strength was used as the reference (ref) and compared with all the other groups.

CVD, cardiovascular disease; NA, not available; HR, hazard ratio; CI, confidence interval.

[a]*Fully adjusted = adjusted for age, sex, education level, body mass index, systolic blood pressure, smoking, physical activity, depression, and sleep quality.*

consistent across age groups. A systematic review (30) including 53,476 individuals from 14 studies showed that the relationship between GS and mortality appeared to be weaker in people under 60 years, but the interaction with age was not formally verified due to the low number of available studies. Our results showed that in the elderly, the risk of CVD in the stable low GS population is 3.5 times that of the stable high GS population. Our findings are important for CVD prevention in the elderly, especially for the elderly with stable low GS. A future study is warranted to investigate whether improved muscle strength could directly lower the risk of CVD.

Furthermore, we examined the association of GS trajectories with the components of the CVD events. The predicted 6-year risk of MI and stroke increased substantially in the group of stable low GS. In the PURE study (9), a large longitudinal population study, baseline GS was more predictive of adverse health outcomes than SBP. It has also been shown that every 5 kg decline in GS was associated with a 7% increase in the risk of MI and a 9% higher increase in stroke. In addition, our research also suggested that stable low GS people were associated with a higher risk of heart failure. However, the accuracy of the estimation of HR value could be less accurate due to the rare incidence of heart failure and the wide confidence interval. Collectively, these data indicate that long-term GS testing should be used as a first-line screening for identifying people at high risk of a wide range of CVD events.

To our knowledge, the current study was the first to investigate the association between GS trajectory and the risk of CVD among a nationally representative English population. The prospective design and high follow-up rate minimized the possibility of recall bias and follow-up loss, allowing the capture of a considerable number of CVD events. Our study design involved repeated GS measurements, which enabled us to create the trajectory of GS change and obtain the GS performance of participants in the years before CVD diagnosis. Because we excluded participants with diagnosed CVD at baseline and used longitudinal GS changes instead of one measurement of GS, reverse causality bias is unlikely in our study.

TABLE 3 | Cox regression analyses for the components of the CVD events per trajectory of grip strength (2004–2012).

	Trajectories of grip strength		
	Stable high	**Stable moderate**	**Stable low**
Myocardial infarction			
No. of events (%)	28/1,571 (1.8)	56/2,897 (1.9)	30/832 (3.6)
HR (95% CI)			
Age/sex adjusted	1 (ref)	1.07 (0.67–1.72)	2.01 (1.14–3.83)
Fully adjusted[a]	1 (ref)	1.10 (0.67–1.80)	2.01 (1.05–3.83)
Angina			
No. of events (%)	32/1,571 (2.0)	56/2,897 (1.9)	31/832 (3.7)
HR (95% CI)			
Age/sex adjusted	1 (ref)	0.96 (0.61–1.50)	1.94 (1.08–3.47)
Fully adjusted	1 (ref)	0.80 (0.49–1.29)	1.73 (0.93–3.19)
Stroke			
No. of events (%)	30/1,571 (1.9)	85/2,897 (2.9)	54/832 (6.5)
HR (95% CI)			
Age/sex adjusted	1 (ref)	1.24 (0.80–1.90)	2.12 (1.25–3.60)
Fully adjusted	1 (ref)	1.32 (0.83–2.10)	1.96 (1.11–3.46)
Heart failure			
No. of events (%)	4/1,571 (0.3)	24/2,897 (0.8)	14/832 (1.7)
HR (95% CI)			
Age/sex adjusted	1 (ref)	3.18 (1.08–9.34)	3.90 (0.97–8.65)
Fully adjusted	1 (ref)	6.58 (1.95–22.20)	6.91 (2.01–23.79)

Data are expressed as n (%) or hazard ratio (95% CI). For this analysis, the group with stable high trajectories of grip strength was used as the reference (ref) and compared with all the other groups.

CVD, cardiovascular disease; NA, not available; HR, hazard ratio; CI, confidence interval.

[a]*Fully adjusted = adjusted for age, sex, education level, body mass index, systolic blood pressure, smoking, physical activity, depression, and sleep quality.*

Despite the strengths mentioned above, our study still has several limitations. First, the use of self-reported physician-diagnosed CVD could cause misclassifications of CVD events and might influence the results to a lesser extent. However, most CVD cases identified in our study were confirmed by ELSA researchers based on medical records. Second, the number of GS measurements is relatively less and the study may not acquire sufficient power to depict the full trajectories of GS. Defining the trajectory of GS changes based on three measurements within 8 years does not seem optimal. However, the systematic measurement of longitudinal GS data is already precious. Third, the use of data from the responders might have influenced our results, as non-responders might have a higher incidence of CVD and an accelerated rate of GS change compared with responders. Finally, although we have attempted to minimize potential confounding in the analyses, the findings might still be affected by the residual confounders from unknown and unmeasured factors (such as inflammation markers, lipid levels, and diet).

CONCLUSION

In summary, the long-term GS pattern was associated with the altered risk of CVD. People with stable low GS had twice the risk of developing CVD as those with stable high GS. When stratifying by age, the association was more pronounced in the older population. These results suggest that continuous GS values could be utilized to identifying people at risk of CVD, especially in the elderly. Furthermore, our research indicates that high stable muscle function may reduce the risk of CVD, which provides the potential to prevent and treat the condition.

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS

WL carried out the concepts, design, data analysis, and manuscript. RC, CY, and CW reviewed and polished the drafts. JH and CS provided assistance for data acquisition. The final manuscript was approved by all authors.

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SUPPLEMENTARY MATERIAL

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REFERENCES

1. Celis-Morales CA, Petermann F, Hui L, Lyall DM, Iliodromiti S, McLaren J, et al. Associations between diabetes and both cardiovascular disease and all-cause mortality are modified by grip strength: evidence from UK Biobank, a prospective population-based cohort study. *Diabetes Care*. (2017) 40:1710–8. doi: 10.2337/dc17-0921
2. Liu W, Leong DP, Hu B, AhTse L, Rangarajan S, Wang Y, et al. The association of grip strength with cardiovascular diseases and all-cause mortality in people with hypertension: findings from the prospective urban rural epidemiology China study. *J Sport Health Sci*. (2020). S2095-2546(20)30144-7. doi: 10.1016/j.jshs.2020.10.005
3. Artero EG, Lee DC, Lavie CJ, EspaÑa-Romero V, Sui X, Church TS, et al. Effects of muscular strength on cardiovascular risk factors and prognosis. *J Cardiopulm Rehabil Prev*. (2012) 32:351–8. doi: 10.1097/HCR.0b013e3182642688
4. Ozemek C, Laddu DR, Lavie CJ, Claeys H, Kaminsky LA, Ross R, et al. An update on the role of cardiorespiratory fitness, structured exercise and lifestyle physical activity in preventing cardiovascular disease and health risk. *Prog Cardiovasc Dis*. (2018) 61:484–90. doi: 10.1016/j.pcad.2018.11.005
5. Greene KA, Withers SS, Lenchik L, Tooze JA, Weaver AA. Trunk skeletal muscle changes on CT with long-duration spaceflight. *Ann Biomed Eng*. (2021) 49:1257–66. doi: 10.1007/s10439-021-02745-8
6. Yamaguchi S, Watanabe M, Hattori Y. Statistical parametric mapping of three-dimensional local activity distribution of skeletal muscle using magnetic resonance imaging (MRI). *Sci Rep*. (2021) 11:4808. doi: 10.1038/s41598-021-84247-0
7. Buckinx F, Landi F, Cesari M, Fielding RA, Visser M, Engelke K, et al. Pitfalls in the measurement of muscle mass: a need for a reference standard. *J Cachexia Sarcopenia Muscle*. (2018) 9:269–78. doi: 10.1002/jcsm.12268
8. Roberts HC, Denison HJ, Martin HJ, Patel HP, Syddall H, Cooper C, et al. A review of the measurement of grip strength in clinical and epidemiological studies: towards a standardised approach. *Age Ageing*. (2011) 40:423–9. doi: 10.1093/ageing/afr051
9. Leong DP, Teo KK, Rangarajan S, Lopez-Jaramillo P, Avezum A Jr, Orlandini A, et al. Prognostic value of grip strength: findings from the Prospective Urban Rural Epidemiology (PURE) study. *Lancet*. (2015) 386:266–73. doi: 10.1016/S0140-6736(14)62000-6
10. Mensah GA, Roth GA, Fuster V. The global burden of cardiovascular diseases and risk factors: 2020 and beyond. *J Am Coll Cardiol*. (2019) 74:2529–32. doi: 10.1016/j.jacc.2019.10.009
11. Global, regional, and national age-sex specific mortality for 264 causes of death, 1980–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet*. (2017) 390:1151–210. doi: 10.1016/S0140-6736(17)32152-9
12. Amini M, Zayeri F, Salehi M. Trend analysis of cardiovascular disease mortality, incidence, and mortality-to-incidence ratio: results from global burden of disease study 2017. *BMC Public Health*. (2021) 21:401. doi: 10.1186/s12889-021-10429-0
13. GBD 2017 DALYs and HALE Collaborators. Global, regional, and national disability-adjusted life-years (DALYs) for 359 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet*. (2018) 392:1859–922. doi: 10.1016/S0140-6736(18)32335-3
14. Celis-Morales CA, Welsh P, Lyall DM, Steell L, Petermann F, Anderson J, et al. Associations of grip strength with cardiovascular, respiratory, and cancer outcomes and all cause mortality: prospective cohort study of half a million UK Biobank participants. *BMJ*. (2018) 361:k1651. doi: 10.1136/bmj.k1651
15. Celis-Morales CA, Lyall DM, Anderson J, Iliodromiti S, Fan Y, Ntuk UE, et al. The association between physical activity and risk of mortality is modulated by grip strength and cardiorespiratory fitness: evidence from 498 135 UK-Biobank participants. *Eur Heart J*. (2017) 38:116–22. doi: 10.1093/eurheartj/ehw249
16. Xu L, Hao YT. Effect of handgrip on coronary artery disease and myocardial infarction: a Mendelian randomization study. *Sci Rep*. (2017) 7:954. doi: 10.1038/s41598-017-01073-z
17. Hamer M, O'Donovan G. Sarcopenic obesity, weight loss, and mortality: the English Longitudinal study of ageing. *Am J Clin Nutr*. (2017) 106:125–9. doi: 10.3945/ajcn.117.152488
18. Steptoe A, Breeze E, Banks J, Nazroo J. Cohort profile: the English longitudinal study of ageing. *Int J Epidemiol*. (2013) 42:1640–8. doi: 10.1093/ije/dys168
19. Xie W, Zheng F, Yan L, Zhong B. Cognitive decline before and after incident coronary events. *J Am Coll Cardiol*. (2019) 73:3041–50. doi: 10.1016/j.jacc.2019.04.019
20. Nagin DS, Odgers CL. Group-based trajectory modeling in clinical research. *Ann Rev Clin Psychol*. (2010) 6:109–38. doi: 10.1146/annurev.clinpsy.121208.131413
21. Wang M, Bodner TE. Growth mixture modeling: identifying and predicting unobserved subpopulations with longitudinal data. *Organ Res Methods*. (2015) 10:635–56. doi: 10.1177/1094428106289397
22. Nagin DS, Jones BL, Passos VL, Tremblay RE. Group-based multi-trajectory modeling. *Stat Methods Med Res*. (2018) 27:2015–23. doi: 10.1177/0962280216673085
23. Sayer AA, Syddall HE, Dennison EM, Martin HJ, Phillips DI, Cooper C, et al. Grip strength and the metabolic syndrome: findings from the Hertfordshire Cohort Study. *QJM*. (2007) 100:707–13. doi: 10.1093/qjmed/hcm095
24. Suetta C, Haddock B, Alcazar J, Noerst T, Hansen OM, Ludvig H, et al. The copenhagen sarcopenia study: lean mass, strength, power, and physical function in a Danish cohort aged 20–93 years. *J Cachexia Sarcopenia Muscle*. (2019) 10:1316–29. doi: 10.1002/jcsm.12477
25. Sayer AA, Kirkwood TB. Grip strength and mortality: a biomarker of ageing? *Lancet*. (2015) 386:226–7. doi: 10.1016/S0140-6736(14)62349-7
26. Lindgren M, Aberg M, Schaufelberger M, Aberg D, Schioler L, Toren K, et al. Cardiorespiratory fitness and muscle strength in late adolescence and long-term risk of early heart failure in Swedish men. *Eur J Prev Cardiol*. (2017) 24:876–84. doi: 10.1177/2047487317689974
27. Sillars A, Celis-Morales CA, Ho FK, Petermann F, Welsh P, Iliodromiti S, et al. Association of fitness and grip strength with heart failure: findings from the UK Biobank Population-Based Study. *Mayo Clin Proc*. (2019) 94:2230–40. doi: 10.1016/j.mayocp.2019.04.041
28. Pavasini R, Serenelli M, Celis-Morales CA, Gray SR, Izawa KP, Watanabe S, et al. Grip strength predicts cardiac adverse events in patients with cardiac disorders: an individual patient pooled meta-analysis. *Heart*. (2019) 105:834–41. doi: 10.1136/heartjnl-2018-313816
29. Walsh K. Adipokines, myokines and cardiovascular disease. *Circ J*. (2009) 73:13–8. doi: 10.1253/circj.CJ-08-0961

30. Cooper R, Kuh D, Hardy R. Objectively measured physical capability levels and mortality: systematic review and meta-analysis. *BMJ*. (2010) 341:c4467. doi: 10.1136/bmj.c4467

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Athlete's Heart in Asian Military Males: The CHIEF Heart Study

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Background: Elite athlete's heart is characterized by a greater left ventricular mass indexed by body surface area (LVMI) and diastolic function; however previous studies are mainly conducted in non-Asian athletes compared to sedentary controls.

Methods: This study included 1,388 male adults, aged 18–34 years, enrolled in the same unified 6-month physical training program in Taiwan. During the midterm exams of 2020, all trainees completed a 3-km run (endurance) test, and 577 were randomly selected to attend a 2-min push-up (muscular strength) test. Elite athletes were defined as the performance of each exercise falling one standard deviation above the mean (16%). Cardiac structure and function were measured by echocardiography and compared between elite and non-elite athletes. Multiple logistic regression analysis was used to determine the independent predictors of elite athlete status at each exercise modality.

Results: As compared to non-elite controls, elite endurance athletes had greater LVMI (84.4 ± 13.6 vs. 80.5 ± 12.9 g/m^2, $p < 0.001$) and lateral mitral E'/A' ratio (2.37 ± 0.73 vs. 2.22 ± 0.76, $p < 0.01$) with lower late diastolic A' (7.77 ± 2.16 vs. 8.30 ± 3.69 cm/s, $p = 0.03$). Elite strength athletes had greater LVMI (81.8 ± 11.4 vs. 77.5 ± 12.1, $p = 0.004$) and lateral mitral E'/A' ratio (2.36 ± 0.70 vs. 2.11 ± 0.71, $p < 0.01$) with a greater early diastolic E' (19.30 ± 4.06 vs. 18.18 ± 4.05 cm/s, $p = 0.02$). Greater LVMI and lower heart rate were independent predictors of elite endurance athletes [odds ratio (OR) and 95% confidence intervals: 1.03 (1.02, 1.04) and 0.96 (0.95, 0.98), respectively]. Greater LVMI, lateral mitral E'/A' ratio and right ventricular systolic pressure were independent predictors of elite strength athletes [OR: 1.03 (1.01, 1.05), 1.50 (1.06, 2.12), and 1.12 (1.05, 1.19), respectively].

Conclusions: Cardiac structural and functional characteristics differ between endurance and strength elite athletes. While greater LVMI predicts elite status in both groups of Asian athletes, consistent with findings from Western elite athletes, greater diastolic function, and right ventricular systolic pressure characterize strength elite athletes, while lower heart rate at rest predicts endurance elite athletic status.

Keywords: Asian athletes, cardiac remodeling, endurance exercise performance, muscular strength exercise, left ventricular diastolic function

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INTRODUCTION

Aerobic and anaerobic fitness have been associated with cardiovascular (CV) health and mortality in the general population (1, 2). The performance in endurance and muscular strength exercises correlated well with aerobic and anaerobic fitness can modulate cardiac structure remodeling and diastolic left ventricular (LV) function. Prior studies have shown that elite athletes, such as Olympic athletes and US football players, had greater LV mass index (LVMI) and diastolic function measured by transthoracic echocardiography (3–5). In summary, elite athletes who expertise endurance exercise, or muscular strength exercise, or both had a greater LVMI than sedentary individuals or the reference values according to age suggested by the U.S. and European echocardiographic societies (6). With regard to the LV diastolic function, the E/A ratio evaluated by mitral inflow Doppler is slightly enhanced or normal in athletes compared to sedentary controls (5–7). As the LV diastolic function is assessed by tissue Doppler imaging of septal or lateral wall motion, the E'/A' ratio is significantly greater in athletes for an enhanced peak early E' or a reduced late atrial A' tissue velocity than controls (6–8). Currently, these findings for athlete's heart are mainly from the Western Countries.

Previous reports have revealed racial differences in the physiologically cardiac adaptions to regular exercise and to LV pressure overload (9–11). For given levels of physical training, athletes of African/Afro-Caribbean descent display more marked cardiac structure changes than do Caucasian athletes (10, 11), possibly due in part to genetic variations. However, there have been rare studies investigating CV health in Asian athletes. Moreover, prior studies compared elite athletes to sedentary controls but rarely to those in a similar training program whether the marked cardiac adaptations in elite athletes are also observed in physically active individuals are unknown (12). Therefore the aim of this study is to investigate the cardiac structure and function of elite athletes from a military population of physically active males in Taiwan.

METHODS

Study Population

The cardiorespiratory fitness and hospitalization events in armed forces study (CHIEF Heart Study) included 1,388 military males, aged 18–34 years, from the ROC Army Huadong Defense Command Base, in Taiwan in January 2020 (13–17). All participants underwent the annual health examination, and self-reported a questionnaire for their habits of toxic substance use including tobacco smoking and alcohol consumption (active vs. former and never) in the Hualien Armed Forces General Hospital of Eastern Taiwan. In the Base, all military males have to receive a unified physical training program for two 3-km runs at 6:00 a.m. and at 16:00 p.m., respectively, along with their Company members led by the Captain within 20 min daily. In addition, all military males perform at least 20 successive push-ups and 20 successive sit-ups in order after each run in unlimited time. In July, 2020, all participants attended the midterm exams for an evaluation of their physical fitness. Of these, 1,388 participants received a 3-km run for examining their endurance capacity, and 577 participants randomly selected from the overall subjects by the Commander for a 2-min push-up test 1 week later to examine their muscular strength capacity. After exams, all participants carried out a 12-lead electrocardiography (ECG) and transthoracic echocardiography (TTE) for assessing their cardiac structure and function before August 31, 2020.

Anthropometric Measurements

Measurements of body height and body weight of each study participant were performed in a standing position. Body mass index was defined as body weight (kg) divided by body height squared (m^2). Mean blood pressure (BP) of each participant at rest was defined as (2 × diastolic BP + 1 × systolic BP) divided by 3. Body surface area was calculated as 0.20247 × body height $(m)^{0.725}$ × body weight $(kg)^{0.425}$ according to the Dubois formula (18).

Physical Fitness Measurements

The endurance capacity of each study participant was evaluated by time for a 3-km run. All examinees did not carry any heavy objects and the test was performed on a flat playground at the Military Physical Training and Testing Center in Hualien, Taiwan. The aerobic exercise test was held outdoor at 16:00 p.m. only when the product of outdoor temperature (°C) and relative humidity (%) × 0.1 was <40 and the weather was not raining.

The muscular strength capacity of each participant was investigated by the 2-min push-up performance (2, 19). The upward and downward movements of push-ups of each examinee were performed on a sponge pad, and were scored only if the examinee's back and buttock line got the baseline peak and bottom levels set by the infrared sensors of a computerized scoring system during the priming period. However, the push-up test was aborted when any parts of the examinee's body except the hands and foot touched the pad before the time ran out (2 min).

TTE Measurements

The TTE using a 1–5 MHz transducer (iE33; Philips Medical Systems, Andover, MA, USA) was performed by the same experienced technician under the supervision by the certificated cardiologist at the Hualien-Armed Forces General Hospital. Measurements of cardiac structure such as LV wall thickness and chamber dimensions were based on the recommendations of the American Society of Echocardiography (20). LV mass was calculated at end diastole according to the corrected formula proposed by Fernandes et al. (21). LV mass = 0.8 × {1.04 × [(LV internal diameter (LVIDd) + posterior wall thickness + interventricular septal thickness]^3 – LVIDd^3} + 0.6. LV hypertrophy for males was defined as the LV mass indexed by body surface area (LVMI) ≥88 g/m^2 based on the Dubois formula (16, 22). Right ventricular (RV) hypertrophy for males was defined as the anterior RV wall thickness in parasternal long-axis window >5.2 mm (17). LV diastolic function was assessed by mitral inflow power Doppler for the early diastolic E wave, the late diastolic A wave related to atrial contraction and the E/A ratio, and assessed by tissue Doppler imaging for the lateral mitral annulus velocity of early diastolic E', the late diastolic A'

TABLE 1 | Clinical characteristics of elite endurance and strength athletes and non-elite controls.

Clinical characteristics	Participants attending a 3-KM run test (*N* = 1,388)			Participants attending a 2-min push-up test (*N* = 577)		
	Elite endurance athletes (≤780 s) (*N* = 233)	Controls (>780 s) (*N* = 1,155)	*P*-value	Elite strength athletes (≥54 times) (*N* = 78)	Controls (<54 times) (*N* = 499)	*P*-value
Age (years)	25.04 ± 3.64	25.21 ± 3.68	0.52	25.04 ± 3.75	25.22 ± 3.73	0.69
(Range: min–max)	(19–34)	(18–34)		(19–33)	(19–34)	
Height (cm)	171.65 ± 5.61	172.21 ± 5.76	0.17	171.32 ± 5.53	172.18 ± 5.62	0.21
Weight (kg)	68.43 ± 9.23	73.58 ± 12.08	<0.001	70.00 ± 9.61	72.70 ± 11.52	0.05
Body mass index (kg/m^2)	23.20 ± 2.75	24.77 ± 3.62	<0.001	23.83 ± 3.07	24.49 ± 3.50	0.12
Body surface area (m^2)	1.80 ± 0.13	1.87 ± 0.16	<0.001	1.82 ± 0.13	1.85 ± 0.16	0.04
Waist circumference (cm)	78.51 ± 6.97	83.10 ± 9.41	<0.001	79.76 ± 7.73	82.30 ± 8.90	0.01
Systolic blood pressure (mmHg)	116.07 ± 11.18	118.46 ± 12.30	0.006	116.36 ± 11.80	117.26 ± 11.85	0.53
Diastolic blood pressure (mmHg)	67.94 ± 8.41	69.15 ± 9.40	0.07	66.25 ± 8.69	68.24 ± 8.73	0.06
Blood test						
Creatinine (mg/dL)	0.94 ± 0.10	0.94 ± 0.11	0.96	0.96 ± 0.12	0.94 ± 0.10	0.11
Total cholesterol (mg/dL)	167.14 ± 31.83	167.68 ± 32.10	0.81	171.49 ± 34.32	167.93 ± 33.12	0.38
HDL-C (mg/dL)	52.55 ± 10.69	48.40 ± 9.72	<0.001	52.63 ± 11.24	48.92 ± 9.19	0.001
LDL-C (mg/dL)	98.40 ± 26.46	103.20 ± 28.77	0.01	103.90 ± 29.10	104.00 ± 30.38	0.97
Triglycerides (mg/dL)	86.51 ± 71.72	100.63 ± 76.39	0.009	93.35 ± 71.81	97.60 ± 67.10	0.60
Fasting glucose (mg/dL)	91.36 ± 8.32	92.95 ± 10.02	0.02	93.42 ± 10.09	93.09 ± 8.84	0.76
Current tobacco smoking	87 [37.3]	522 [45.2]	0.02	37 [48.7]	215 [43.1]	0.35
Exercise performance						
3-KM running (seconds)	748.08 ± 31.71	880.12 ± 74.30	<0.001	833.15 ± 82.75	869.84 ± 81.58	<0.001
2-min push-ups (numbers)*	49.95 ± 12.28	45.54 ± 10.04	<0.001	61.14 ± 10.92	43.88 ± 8.33	<0.001

Continuous variables are expressed as mean ± SD (standard deviation), and categorical variables as n [%].
HDL-C, high-density lipoprotein cholesterol; KM, kilometer; LDL-C, low-density lipoprotein cholesterol.
**N = 577.*

and the E'/A' ratio. RV systolic pressure (RVSP) was assessed by the continuous wave Doppler in the four-chamber window.

Statistical Analysis

Elite athletes were defined as the score of each exercise falling one standard deviation above the mean (16%), and the controls were the other physically active males not getting to the level of elite athletes in each exercise (84%). Demographic, anthropometric, ECG and TTE characteristics of the elite athletes and the non-elite controls were expressed as mean ± standard deviation for continuous variables and numbers (%) for categorical variables, respectively. Continuous variables were compared by analysis of variance (ANOVA) and categorical variables were compared by chi-square or Fisher's exact test. Dimensions of cardiac chambers and wall thickness were compared utilizing analysis of covariance (ANCOVA) with adjustment for body surface area. Multiple logistic regressions were used to determine the odds ratio (OR) of the TTE characteristics with the elite athletes to non-elite controls. In model 1, age, smoking, LVMI, RVSP, and lateral mitral E'/A' ratio were adjusted. In model 2, BMI was additionally adjusted. In model 3, mean BP was additionally adjusted. In model 4, heart rate was further adjusted. A two-tailed value of $P < 0.05$ was considered significant. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA). This study was approved by the Institutional Review Board of the Mennonite Christian Hospital (No. 16-05-008) in Taiwan, and written informed consent was obtained from all participants.

RESULTS

Clinical Features and Laboratory Findings

There were 233 males (16.8%) classified as elite endurance athletes who spent <780 s for a 3-km run and the other 1,155 physically active males (93.2%) were classified as non-elite controls (**Table 1**). In addition, there were 78 males (13.5%) classified as elite strength athletes who performed more than 54 push-ups within 2 min and the other 499 physically active males (86.5%) were classified as non-elite controls. Elite endurance athletes had lower levels of body weight related anthropometrics, such as BMI and waist circumference (WC), systolic BP, fasting plasma glucose and low-density lipoprotein, a higher level of high-density lipoprotein, and a relatively better 2-min push-ups score (49.9 ± 12.3 vs. 45.5 ± 10.0). Elite strength athletes had a lower WC and a higher high-density lipoprotein, and a relatively better 3-km run score (833.2 ± 82.2 vs. 869.8 ± 81.6 s).

ECG Features

In **Table 2**, elite endurance athletes had significantly slower heart rate (sinus bradycardia), greater QRS duration and axis, and a higher prevalence of ECG-based LV hypertrophy (70.8 vs. 54.8%,

TABLE 2 | Electrocardiographic characteristics of elite endurance and strength athletes and non-elite controls.

ECG characteristics	Participants attending a 3-KM run test (*N* = 1,388)			Participants attending a 2-min push-up test (*N* = 577)		
	Elite endurance athletes (≤780 s) (*N* = 233)	Controls (>780 s) (*N* = 1,155)	*P*-value	Elite strength athletes (≥54 times) (*N* = 78)	Controls (<54 times) (*N* = 499)	*P*-value
Heart rate (beats/min)	61.93 ± 10.02	66.68 ± 10.58	<0.001	65.37 ± 12.05	66.03 ± 10.62	0.61
P duration (ms)	106.36 ± 11.78	105.90 ± 14.05	0.64	108.35 ± 11.75	105.56 ± 14.57	0.10
PR interval (ms)	156.77 ± 16.56	155.62 ± 18.81	0.38	156.41 ± 16.78	154.71 ± 19.93	0.47
QRS duration (ms)	99.95 ± 11.23	97.90 ± 10.95	0.03	98.62 ± 10.21	97.25 ± 10.02	0.26
QTc interval (ms)	387.02 ± 21.95	388.67 ± 22.81	0.30	392.23 ± 26.56	387.75 ± 21.73	0.10
QRS axis (degree)	71.06 ± 22.00	62.89 ± 31.61	<0.001	64.69 ± 25.05	65.00 ± 28.22	0.92
ECG based LVH (%)	165 [70.8]	633 [54.8]	<0.001	51 [65.4]	293 [58.7]	0.26
ECG based RVH (%)	35 [15.1]	177 [15.3]	0.92	13 [16.7]	81 [16.2]	0.92
Sinus bradycardia (%)	102 [43.8]	295 [25.5]	<0.001	28 [35.9]	137 [27.5]	0.12
Ectopic P rhythm (%)	19 [8.2]	108 [9.4]	0.56	5 [6.4]	55 [11.0]	0.21
Left atrial enlargement (%)	36 [15.5]	199 [17.2]	0.50	11 [14.1]	81 [16.2]	0.63
First degree atrioventricular block (%)	3 [1.3]	25 [2.2]	0.38	2 [2.6]	9 [1.8]	0.64
Left axis deviation (%)	0 [0.0]	18 [1.6]	0.05	2 [2.6]	3 [0.6]	0.08
Right axis deviation (%)	30 [12.9]	123 [10.6]	0.32	5 [6.4]	50 [10.0]	0.31
Complete right bundle branch block (%)	12 [5.1]	42 [3.6]	0.27	2 [2.6]	14 [2.8]	0.90
Incomplete right bundle branch block (%)	23 [9.9]	79 [6.8]	0.10	8 [10.3]	30 [6.0]	0.16
QTc prolongation > 480 ms (%)	1 [0.4]	7 [0.6]	0.74	2 [2.6]	2 [0.4]	0.03
T wave inversion (%)	6 [2.6]	37 [3.2]	0.61	2 [2.6]	15 [3.0]	0.83

Categorical variables are expressed as N [%].
ECG, electrocardiography; LVH, left ventricular hypertrophy; KM, kilometer; RVH, right ventricular hypertrophy.

$p < 0.001$) according to the Soklow-Lyon voltage criterion (23). Elite strength athletes merely had a higher prevalence of the corrected QT interval prolongation >480 ms on the basis of the Bazett's formula (2.6 vs. 0.4%, $p = 0.03$) (24).

TTE Findings

In **Table 3**, elite athletes and non-elite controls had similar chamber dimensions of left atrium, LV and RV in diastole, and similar LVM and RV wall thickness, except that elite endurance athletes had greater LV diastolic dimension with adjustment for body surface area. As compared to non-elite controls, elite endurance athletes had greater LVMI (84.4 ± 13.6 vs. 80.5 ± 12.9 g/m^2, $p < 0.001$) and lateral mitral annulus E'/A' ratio (2.37 ± 0.73 vs. 2.22 ± 0.76, $p < 0.01$) with lower late diastolic A' (7.77 ± 2.16 vs. 8.30 ± 3.69 cm/s, $p = 0.03$). In contrast, elite strength athletes had greater LVMI (81.8 ± 11.4 vs. 77.5 ± 12.1 g/m^2, $p = 0.004$), lateral mitral E'/A' ratio (2.36 ± 0.70 vs. 2.11 ± 0.71, $p < 0.01$) with greater early diastolic E' (19.30 ± 4.06 vs. 18.18 ± 4.05 cm/s, $p = 0.02$) and RVSP (29.60 ± 4.35 vs. 27.83 ± 3.71 mmHg, $p < 0.001$).

Echocardiographic Predictors of Elite Athletes

Table 4 demonstrates the results of multiple logistic regression analysis for the predictors of elite endurance and strength athletes, respectively. In model 1, greater LVMI and lateral mitral E'/A' were independent predictors of elite endurance athletes. However, the association for the lateral mitral E'/A' ratio was null after additionally controlling for BMI. In model 4, Greater LVMI, and lower heart rate and BMI were independent predictors of elite endurance athletes [odds ratio (OR): 1.03 (95% confidence intervals (CI): 1.02, 1.04), 0.96 (95% CI: 0.95, 0.98) and 0.85 (95% CI: 0.81, 0.90), respectively]. In contrast, greater LVMI, lateral mitral E'/A' and RVSP were independent predictors of elite strength athletes [OR: 1.03 (95% CI: 1.01, 1.05), 1.50 (95% CI: 1.06, 2.12) and 1.12 (95% CI: 1.05, 1.19), respectively] in model 4. Both BMI and heart rate were not independent predictors of elite strength athletes.

DISCUSSION

This study is the largest report to date to demonstrate the cardiac structure and function in Asian male athletes and compare them to physically active controls and to determine the predictors or eliteness based on endurance and muscular strength. The main findings in the present study were that elite endurance male athletes had greater LVMI and LV diastolic function which might be due to reduced heart rate. Greater LVMI, and lower heart rate and BMI were the independent predictors of falling in the elite endurance category. Elite strength male athletes also had greater LVMI and LV diastolic function; greater LVMI, lateral mitral E'/A' and RVSP were the independent predictors of being in the elite strength category.

Both elite endurance and strength athletes had greater LVMI, and endurance athletes had greater LV chamber size, which were consistent with the findings in prior studies (6, 25).

TABLE 3 | Echocardiographic characteristics of elite endurance and strength athletes and non-elite controls.

Echocardiographic characteristics	Participants attending a 3-KM run test (*N* = 1,388)			Participants attending a 2-min push-up test (*N* = 577)		
	Elite endurance athletes (≤780 s) (*N* = 233)	Controls (>780 s) (*N* = 1,155)	*P*-value	Elite strength athletes (≥54 times) (*N* = 78)	Controls (<54 times) (*N* = 499)	*P*-value
Aortic valve open (mm), PLAX	19.93 ± 1.98	20.03 ± 1.91	0.57*	20.53 ± 1.65	20.35 ± 1.86	0.61*
Aortic root dimension (mm), PALX	29.49 ± 3.23	29.68 ± 3.25	0.66*	30.13 ± 2.48	29.82 ± 2.74	0.19*
LV posterior wall (mm), PLAX*	8.44 ± 0.89	8.54 ± 0.94	0.31*	8.40 ± 0.76	8.29 ± 0.84	0.84*
LV internal dimension in diastole (mm), PLAX	50.03 ± 3.35	49.24 ± 3.42	0.003*	49.74 ± 3.19	49.07 ± 3.50	0.36*
Interventricular septum, (mm), PLAX	8.61 ± 0.95	8.74 ± 1.02	0.44*	8.53 ± 0.80	8.49 ± 0.89	0.45*
RV wall thickness (mm), PLAX*	4.72 ± 0.55	4.66 ± 0.62	0.98*	4.60 ± 0.67	4.70 ± 0.58	0.49*
RV outflow tract dimension in diastole (mm), PLAX	25.94 ± 3.84	27.19 ± 12.49	0.82*	26.47 ± 3.82	26.33 ± 3.96	0.45*
Left atrial dimension (mm), PLAX	32.55 ± 4.00	32.95 ± 3.93	0.21*	33.09 ± 3.40	32.83 ± 3.95	0.11*
LV mass (gm)	152.53 ± 28.43	151.05 ± 29.83	0.16	148.98 ± 23.54	144.45 ± 27.18	0.16
LV mass index (gm/m^2)	84.44 ± 13.56	80.52 ± 12.94	<0.001	81.76 ± 11.36	77.51 ± 12.05	0.004
LV hypertrophy	11 [4.7]	24 [2.1]	0.01	1 [1.3]	5 [1.0]	0.82
RV hypertrophy	20 [8.6]	84 [7.3]	0.48	2 [2.6]	26 [5.2]	0.31
LV ejection fraction (%), PLAX	61.79 ± 5.03	61.97 ± 5.06	0.78	62.86 ± 5.36	62.43 ± 5.32	0.51
Tricuspid valve prolapse, PSAX	34 [20.4]	206 [26.6]	0.09	13 [41.9]	94 [51.1]	0.34
Aortic regurgitation ≥ mild grade	3 [1.3]	13 [1.1]	0.83	1 [1.3]	3 [0.6]	0.50
Mitral regurgitation ≥ mild grade	190 [81.5]	890 [77.1]	0.13	69 [88.5]	429 [86.0]	0.55
Pulmonary regurgitation ≥ mild grade	162 [69.5]	763 [66.1]	0.30	61 [78.2]	354 [70.9]	0.18
Tricuspid regurgitation ≥ mild grade	196 [84.1]	928 [80.3]	0.18	73 [93.6]	462 [92.6]	0.75
RV systolic pressure (mmHg)	27.68 ± 4.35	27.19 ± 4.36	0.27	29.60 ± 4.35	27.83 ± 3.71	<0.001
Mitral inflow power Doppler E-wave (m/s)	87.00 ± 14.13	86.21 ± 14.87	0.45	90.07 ± 13.63	87.41 ± 14.59	0.13
Mitral inflow power Doppler A-wave (m/s)	46.44 ± 9.59	48.69 ± 9.81	0.001	48.81 ± 9.42	49.31 ± 9.88	0.67
E/A ratio	1.94 ± 0.46	1.83 ± 0.46	0.001	1.91 ± 0.48	1.84 ± 0.47	0.20
Mitral lateral annulus tissue Doppler E' (cm/s)	17.33 ± 3.83	17.04 ± 3.75	0.29	19.30 ± 4.06	18.18 ± 4.05	0.02
Mitral lateral annulus tissue Doppler A' (cm/s)	7.77 ± 2.16	8.30 ± 3.69	0.03	8.51 ± 1.82	9.31 ± 4.95	0.16
E'/A' ratio	2.37 ± 0.73	2.22 ± 0.76	0.007	2.36 ± 0.70	2.11 ± 0.71	0.004

Continuous variables are expressed as mean ± SD (standard deviation), and categorical variables as N [%].
LV, left ventricle; RV, right ventricl; PLAX, echocardiographic parasternal long axis view; PSAX, echocardiographic parasternal short axis view.
**Analysis of covariance (ANCOVA) with adjustment for body surface area.*

Mechanisms for the LV hypertrophy induced by exercises have been proposed by a physiological compensation of cardiac muscle cells elongation in response to chronic hemodynamic overload that is regulated in part by the renin-angiotensin system (26, 27). The greater LV chamber size related to endurance exercises has been explained mainly by volume overload, but the LV chamber size is not enlarged in response to strength exercises (28). Although the LVMI of elite Asian male athletes in the present study was generally smaller than that reported in prior studies for Black and White male athletes, possibly due to the ethnical or racial differences in the genetic aspect, this study further confirmed the concept that LVMI could independently predict the performance of endurance and strength exercises in physically active males.

With regard to the enhanced LV diastolic function, the present study for elite Asian male athletes showed consistent results that elite endurance athletes had slightly greater E/A ratio due to a decrease in peak A wave velocity, and elite strength athletes had similar E/A ratio compared to their non-elite controls (11). In addition, with regard to the tissue Doppler image results, the greater lateral mitral E'/A' ratio in elite endurance athletes were due to a reduced A' velocity, whereas the greater lateral mitral E'/A' ratio in elite strength athletes were due to an increased peak E' velocity (6–8). In the multiple logistic regression model, the enhanced LV diastolic function in elite endurance athletes was due to a reduced resting heart rate, (29) and that in elite strength athletes might be related to an improved LV compliance. The reduced heart rate related to endurance exercise has been associated with an increase of parasympathetic tone (30). On the contrary, physically active Asian males regardless of endurance or strength exercise in the present study had a similar RVSP (25–29 mmHg) compared to non-Asian endurance athletes (26–27 mmHg), which was higher than that in sedentary controls in prior studies (16–22 mmHg) (25, 31). D'Andrea et al. reported that the RVSP was associated with RV chamber size and was higher in endurance athletes than strength athletes (20 mmHg) (25). However, the findings for right heart structure and function were contrary to the present study results whether these conflicts

TABLE 4 | Multivariable logistic regression analysis for elite endurance and strength athletes.

	Model 1			Model 2			Model 3			Model 4		
Characteristics	**OR**	**95% CI**	***P*-value**	**OR**	**95% CI**	***P*-value**	**OR**	**95% CI**	***P*-value**	**OR**	**95% CI**	***P*-value**
Elite endurance athletes (*N* = 1,388)												
Age	0.998	0.959–1.039	0.93	1.025	0.983–1.068	0.24	1.028	0.986–1.071	0.19	1.021	0.979–1.065	0.32
Tobacco smoking	0.704	0.525–0.943	0.01	0.694	0.515–0.936	0.01	0.687	0.509–0.927	0.01	0.759	0.560–1.029	0.07
LV mass index	1.023	1.012–1.034	<0.001	1.031	1.020–1.043	<0.001	1.032	1.021–1.044	<0.001	1.027	1.015–1.039	<0.001
RV systolic pressure	1.027	0.994–1.061	0.11	1.018	0.985–1.053	0.28	1.018	0.984–1.053	0.30	1.019	0.985–1.054	0.28
E'/A' ratio	1.291	1.072–1.556	0.007	1.163	0.958–1.411	0.12	1.159	0.955–1.407	0.13	1.076	0.883–1.312	0.46
Body mass index	–	–	–	0.847	0.806–0.890	<0.001	0.854	0.812–0.898	<0.001	0.852	0.809–0.897	<0.001
Mean blood pressure	–	–	–	–	–	–	0.987	0.970–1.004	0.12	0.991	0.974–1.008	0.29
Heart rate	–	–	–	–	–	–	–	–	–	0.964	0.949–0.979	<0.001
Elite strength athletes (*N* = 577)												
Age	1.013	0.947–1.085	0.70	1.023	0.954–1.096	0.52	1.028	0.958–1.103	0.44	1.030	0.960–1.106	0.40
Tobacco smoking	1.171	0.714–1.918	0.53	1.191	0.726–1.954	0.49	1.189	0.724–1.954	0.49	1.170	0.710–1.928	0.53
LV mass index	1.027	1.007–1.048	0.008	1.029	1.008–1.050	0.006	1.030	1.009–1.051	0.005	1.031	1.010–1.053	0.004
RV systolic pressure	1.124	1.056–1.197	<0.001	1.122	1.053–1.195	<0.001	1.121	1.052–1.195	<0.001	1.121	1.052–1.194	<0.001
E'/A' ratio	1.540	1.108–2.141	0.01	1.480	1.058–2.072	0.02	1.470	1.050–2.056	0.02	1.500	1.063–2.116	0.02
Body mass index	–	–	–	0.954	0.882–1.033	0.25	0.966	0.890–1.048	0.96	0.964	0.888–1.046	0.38
Mean blood pressure	–	–	–	–	–	–	0.981	0.952–1.012	0.22	0.980	0.951–1.011	0.20
Heart rate	–	–	–	–	–	–	–	–	–	1.007	0.983–1.032	0.57

Data are presented as odds ratios (OR) and 95% CI (confidence intervals) using multiple logistic regression.
LV, left ventricle; RV, right ventricle.
Model 1 covariates included age, tobacco smoking and left ventricular mass index; Model 2 covariates included Model 1 covariates plus body mass index; Model 3 covariates included Model 2 covariates plus mean blood pressure; Model 4 covariates included Model 3 covariates plus heart rate.

were because of racial/ethnic differences or for a presence of confounders such as the smoking habit which was not considered in prior studies requires further investigation.

Study Strengths and Limitations

The major strength of the present study was that the male participants were enrolled in the same army camp in Taiwan where the training program was standardized. In addition, since the army base is a closed system, the living environment for the participants is very similar and their daily schedule, such as the wake up time, bed time, meal time and the frequency of sentry duty is unified. Third, the detailed information for the baseline confounders to both physical fitness and cardiac structure and function, such as tobacco smoking and alcohol consumption, were considered in this study, which could reduce a potential bias. By contrast, there were merely 36.8% of the overall males randomly selected to attend the push-up test, possibly leading to a selection bias, despite that the baseline characteristics between those with and without attending the push-up test were similar (**Supplementary Table 1**). Second, the endurance and muscular strength capacity for males were measured only by a short- to medium- distance run and a 2-min push-up test that the cardiac structure results might not be appropriately applied to other elite athletes for different kinds of exercise. Third, this study reported data from males only that might not be the same for females. Fourth, since the study was a cross-sectional design, the interval changes in cardiac structure and function could not be evaluated. At last, in many prior studies in Western Countries, athletes were defined to be at Olympic or Professional levels, and whether the present study results for the male athletes in military were consistent with more competitive male athletes in Taiwan needs further investigations.

CONCLUSION

Our study uncovered that cardiac structural and functional characteristics differ between endurance and strength elite athletes in a physically active Asian male population. While greater LVMI predicts elite status in both groups of Asian athletes, consistent with findings from Western elite athletes, greater diastolic function and RV systolic pressure characterize strength elite athletes, while lower heart rate at rest predicts endurance elite athletic status.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

This study was approved by the Institutional Review Board of the Mennonite Christian Hospital (No. 16-05-008) in Taiwan, and

written informed consent was obtained from all participants. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

P-YL and G-ML wrote the paper. K-ZT made the statistical analyses. JL and CL raised critical comments for the paper and edited the manuscript. G-ML was the principal investigator for the study. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2021.725852/full#supplementary-material

REFERENCES

1. Kodama S, Saito K, Tanaka S, Maki M, Yachi Y, Asumi M, et al. Cardiorespiratory fitness as a quantitative predictor of all-cause mortality and cardiovascular events in healthy men and women: a meta-analysis. *JAMA*. (2009) 301:2024–35. doi: 10.1001/jama.2009.681
2. Yang J, Christophi CA, Farioli A, Baur DM, Moffatt S, Zollinger TW, et al. Association between push-up exercise capacity and future cardiovascular events among active adult men. *JAMA Netw Open.* (2019) 2:e188341. doi: 10.1001/jamanetworkopen.2018.8341
3. Caselli S, Di Paolo FM, Pisicchio C, Pandian NG, Pelliccia A. Patterns of left ventricular diastolic function in Olympic athletes. *J Am Soc Echocardiogr.* (2015) 28:236–44. doi: 10.1016/j.echo.2014.09.013
4. Kim JH, Hollowed C, Liu C, Al-Badri A, Alkhoder A, Dommisse M, et al. Hypertension, and the emergence of a maladaptive cardiovascular phenotype among US football players. *JAMA Cardiol.* (2019) 4:1221–9. doi: 10.1001/jamacardio.2019.3909
5. Colan SD, Sanders SP, MacPherson D, Borow KM. Left ventricular diastolic function in elite athletes with physiologic cardiac hypertrophy. *J Am Coll Cardiol.* (1985) 6:545–9. doi: 10.1016/S0735-1097(85)80111-X
6. Pluim BM, Zwinderman AH, van der Laarse A, van der Wall EE. The athlete's heart. a meta-analysis of cardiac structure and function. *Circulation.* (2000) 101:336–44. doi: 10.1161/01.CIR.101.3.336
7. George KP, Somauroo J. Left ventricular diastolic function in athletes. *Dtsch Z Sportmed.* (2012) 63:63–8. doi: 10.5960/dzsm.2012.008
8. Baldi JC, McFarlane K, Oxenham HC, Whalley GA, Walsh HJ, Doughty RN. Left ventricular diastolic filling and systolic function of young and older trained and untrained men. *J Appl Physiol.* (2003) 95:2570–5. doi: 10.1152/japplphysiol.00441.2003
9. Rawlins J, Carre F, Kervio G, Papadakis M, Chandra N, Edwards C, et al. Ethnic differences in physiological cardiac adaptation to intense physical exercise in highly trained female athletes. *Circulation.* (2010) 121:1078–85. doi: 10.1161/CIRCULATIONAHA.109.917211
10. Papadakis M, Wilson MG, Ghani S, Kervio G, Carre F, Sharma S. Impact of ethnicity upon cardiovascular adaptation in competitive athletes: relevance to preparticipation screening. *Br J Sports Med.* (2012) 46(Suppl. 1):i22–8. doi: 10.1136/bjsports-2012-091127
11. Sheikh N, Sharma S. Impact of ethnicity on cardiac adaptation to exercise. *Nat Rev Cardiol.* (2014) 11:198–217. doi: 10.1038/nrcardio.2014.15
12. Brown B, Millar L, Somauroo J, George K, Sharma S, La Gerche A, et al. Left ventricular remodeling in elite and sub-elite road cyclists. *Scand J Med Sci Sports.* (2020) 30:1132–9. doi: 10.1111/sms.13656
13. Chao WH, Su FY, Lin F, Yu YS, Lin GM. Association of electrocardiographic left and right ventricular hypertrophy with physical fitness of military males: the CHIEF study. *Eur J Sport Sci.* (2019) 19:1214–20. doi: 10.1080/17461391.2019.1595741
14. Tsai KZ, Lai SW, Hsieh CJ, Lin CS, Lin YP, Tsai SC, et al. Association between mild anemia and physical fitness in a military male cohort: the CHIEF study. *Sci Rep.* (2019) 9:11165. doi: 10.1038/s41598-019-47625-3
15. Lin GM, Li YH, Lee CJ, Shiang JC, Lin KH, Chen KW, et al. Rationale and design of the cardiorespiratory fitness and hospitalization events in armed forces study in Eastern Taiwan. *World J Cardiol.* (2016) 8:464–71. doi: 10.4330/wjc.v8.i8.464
16. Lin GM, Liu K. An electrocardiographic system with anthropometrics via machine learning to screen left ventricular hypertrophy among young adults. *IEEE J Transl Eng Health Med.* (2020) 8:1800111. doi: 10.1109/JTEHM.2020.2990073
17. Lin GM, Lu HH. A 12-Lead ECG-based system with physiological parameters and machine learning to identify right ventricular hypertrophy in young adults. *IEEE J Transl Eng Health Med.* (2020) 8:1900510. doi: 10.1109/JTEHM.2020.2996370
18. Du Bois D, Du Bois EF. A formula to estimate the approximate surface area if height and weight be known. *Arch Intern Med.* (1916) 17:863–871. doi: 10.1001/archinte.1916.00080130010002
19. Spurway NC. Aerobic exercise, anaerobic exercise and the lactate threshold. *Br Med Bull.* (1992) 48:569–91. doi: 10.1093/oxfordjournals.bmb.a072564
20. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr.* (2015) 28:1–39.e14. doi: 10.1016/j.echo.2014.10.003
21. Fernandes T, Hashimoto NY, Magalhães FC, Fernandes FB, Casarini DE, Carmona AK, et al. Aerobic exercise training-induced left ventricular hypertrophy involves regulatory MicroRNAs, decreased angiotensin-converting enzyme-angiotensin ii, and synergistic regulation of angiotensin-converting enzyme 2-angiotensin (1-7). *Hypertension.* (2011) 58:182–9. doi: 10.1161/HYPERTENSIONAHA.110.168252
22. Su FY, Li YH, Lin YP, Lee CJ, Wang CH, Meng FC, et al. A comparison of Cornell and Sokolow-Lyon electrocardiographic criteria for left ventricular hypertrophy in a military male population in Taiwan: the Cardiorespiratory fitness and HospItalization Events in armed Forces study. *Cardiovasc Diagn Ther.* (2017) 7:244–51. doi: 10.21037/cdt.2017.01.16
23. Sokolow M, Lyon TP. The ventricular complex in left ventricular hypertrophy as obtained by unipolar precordial and limb leads. *Am Heart J.* (1949) 37:161–86. doi: 10.1016/0002-8703(49)90562-1
24. Bazett HC. An analysis of the time-relations of the electrocardiograms. *Ann Noninvasive Electrocardiol.* (1997) 2:177–94. doi: 10.1111/j.1542-474X.1997.tb00325.x
25. D'Andrea A, Riegler L, Morra S, Scarafile R, Salerno G, Cocchia R, et al. Right ventricular morphology and function in top-level athletes: a three-dimensional echocardiographic study. *J Am Soc Echocardiogr.* (2012) 25:1268–76. doi: 10.1016/j.echo.2012.07.020
26. Dostal DE. The cardiac renin-angiotensin system: novel signaling mechanisms related to cardiac growth and function. *Regul Pept.* (2000) 91:1–11. doi: 10.1016/S0167-0115(99)00123-8
27. Morganroth J, Maron BJ, Henry WL, Epstein SE. Comparative left ventricular dimensions in trained athletes. *Ann Intern Med.* (1975) 82:521–4. doi: 10.7326/0003-4819-82-4-521
28. Notomi Y, Martin-Miklovic MG, Oryszak SJ, Shiota T, Deserranno D, Popovic ZB, et al. Enhanced ventricular untwisting during exercise: a mechanistic manifestation of elastic recoil described by Doppler tissue imaging.

Circulation. (2006) 113:2524–33. doi: 10.1161/CIRCULATIONAHA.105.596502
29. Gourine AV, Ackland GL. Cardiac vagus and exercise. *Physiology*. (2019) 34:71–80. doi: 10.1152/physiol.00041.2018
30. Mirea O, Corîci OM, Istrătoaie O, Donoiu I, Iancău M, Militaru C. Left and right ventricular morphology and function in athletes with elevated pulmonary systolic arterial pressure. *Echocardiography*. (2018) 35:769–76. doi: 10.1111/echo.14016
31. Devereux RB, Casale PN, Eisenberg RR, Miller DH, Kligfield P. Electrocardiographic detection of left ventricular hypertrophy using echocardiographic determination of left ventricular mass as the reference standard. comparison of standard criteria, computer diagnosis and physician interpretation. *J Am Coll Cardiol*. (1984) 3:82–7. doi: 10.1016/S0735-1097(84)80433-7

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Obesity Phenotypes and Electrocardiographic Characteristics in Physically Active Males: CHIEF Study

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Background: Metabolically unhealthy obesity (MUO) has been associated with surface electrocardiographic (ECG) left ventricular hypertrophy (LVH), left atrial enlargement (LAE), and inferior *T* wave inversions (TWI) in the middle- and old-aged populations. However, the relationship between obesity phenotypes and these ECG abnormalities in physically active young adults is yet to be determined.

Methods: A total of 2,156 physically active military males aged 18–50 in Taiwan were analyzed. Obesity and metabolically unhealthy status were, respectively, defined as the body mass index ≥27 kg/m^2 and the presence of metabolic syndrome based on the ATPIII criteria for Asian male adults. Four groups were classified as the metabolically healthy non-obesity (MHNO, $n = 1{,}484$), metabolically unhealthy non-obesity (MUNO, $n = 86$), metabolically healthy obesity (MHO, $n = 376$), and MUO ($n = 210$). ECG-LVH was based on the Sokolow–Lyon and Cornell voltage criteria, ECG-LAE was defined as a notched *P* wave ≥0.12 s in lead II or a notch of ≥0.04 s, and inferior TWI was defined as one negative *T* wave axis in limb leads II, III, or aVF. Physical performance was evaluated by time for a 3-km run. Multiple logistic regression analysis with adjustment for age, smoking, alcohol drinking, and physical performance was utilized to investigate the associations between obesity phenotypes and the ECG abnormalities.

Results: As compared to MHNO, MUNO, MHO, and MUO were associated with lower risk of Sokolow–Lyon-based ECG-LVH [odds ratios (OR) and 95% confidence intervals: 0.80 (0.51–1.25), 0.46 (0.36–0.58), and 0.39 (0.28–0.53), respectively; *p* for trend <0.001], and with greater risk of ECG-LAE [OR: 0.87 (0.44–1.72), 2.34 (1.77–3.10), and 3.02 (2.13–4.28), respectively; *p* for trend <0.001] and inferior TWI [OR: 2.21 (0.74–6.58),

3.49 (1.97–6.19), and 4.52 (2.38–8.60), respectively; p for trend <0.001]. However, no associations between obesity phenotypes and Cornell-based ECG-LVH were found.

Conclusion: In physically active young males, obesity was associated with higher risk of ECG-LAE and inferior TWI, whereas the risk between obesity and ECG-LVH might vary by the ECG criteria, possibly due to a high prevalence of exercise induced-LVH in military and greater chest wall thickness in obesity. The cardiovascular prognosis of ECG-LVH in physically active obese adults requires further study.

Keywords: aerobic fitness, electrocardiography, metabolic syndrome, obesity, military males, left ventricular hypertrophy

INTRODUCTION

Obesity has increased dramatically over the past few decades, which results in main public health issues because it is a major factor contributing to the global burden of chronic diseases, including type 2 diabetes mellitus, coronary heart disease, sleep-breathing disorders, and certain types of cancer (1). Obesity was defined initially according to body mass index [BMI] (2). However, BMI could not precisely estimate the visceral adiposity, ectopic fat deposition, and the risk of future obesity associated atherosclerosis and cardiometabolic cormobilities (1, 3). In the 1950s, Professor Jean Vague showed that the obese with different body fat distribution may have different propensity to develop diabetes or coronary heart disease (4). Recently, the concepts of metabolically healthy obesity (MHO) and metabolically unhealthy obesity (MUO) have been established (5).

MUO is an obesity phenotype that 70–90% of obese individuals belong to this category and MHO is another phenotype that the prevalence is 10–30% in obese individuals and more common in women than in men and decreased with age (5). Most studies have defined MHO as the absence of metabolic disturbances including insulin resistance, impaired glucose metabolism, type 2 diabetes, and dyslipidemia (5, 6). On the other hand, the body fat disposition in MUO persons is located in ectopic areas including visceral tissues and the liver, which leads to abdominal obesity and increases the future risk of cardiovascular disease and type 2 diabetes (7). Previous literatures have reported that MUO individuals have higher risk of developing cardiometabolic diseases as compared to individuals with MHO (8, 9).

Obesity has been reported with an association with some electrocardiographic (ECG) abnormalities such as inferior T wave inversions (TWI) (10), left ventricular hypertrophy (LVH) (11, 12), and left atrial enlargement (LAE) (12) in the middle- and old-aged general populations. For a few ECG markers like prolonged QT interval (11), Ahmad et al. revealed an association with metabolic syndrome rather than obesity. The US third national health and nutrition examination survey (13) also demonstrated the prevalence of ECG-LVH highest in MUO and lowest in metabolically healthy non-obese individuals (MHNO) (11), which was in line with the reports for echocardiographic LVH in obesity (14, 15). However, the association between obesity and echocardiographic LVH decreased much and was reversed with adjustment for the baseline blood pressure (BP) levels (15). It was clear that metabolically healthy and unhealthy obesity phenotypes (lean and obesity) and other confounding factors, such as different lifestyles, substance use habits, and physical fitness affecting the ECG abnormalities, should be taken into account. Therefore, we conducted a study in physically active young males to examine the relationships between obesity phenotypes and the ECG abnormalities.

Abbreviations: BP, blood pressure; CHIEF, Cardiorespiratory Fitness and Hospitalization Events in Armed Forces study; CRF, cardiorespiratory fitness; ECG, electrocardiography; MHNO, metabolically healthy non-obesity; MHO, metabolically healthy obesity; MUNO, metabolically unhealthy non-obesity; MUO, metabolically unhealthy obesity; LAE, left atrial enlargement; LVH, left ventricular hypertrophy; TWI, T wave inversion.

METHODS

Study Population

The data in this study was obtained from the Cardiorespiratory Fitness and Hospitalization Events in Armed Forces (CHIEF) study in Eastern Taiwan (16). The protocol and research design of the CHIEF study have been described in detail previously (17–22). In brief, this study included 2,567 military individuals, aged 18–50 years, who underwent the annual health examinations including a self-report questionnaire survey, which included demographic factors, medical history, cigarette smoking habits (current vs. former/never), and alcohol intake status (current vs. former/never) in the past 6 months in the Hualien Armed Forces General Hospital, and performed the 3-km run test at the Military Physical Training and Testing Center in Hualien in 2014. As there were only 8 female MHO samples defined as BMI $\geq$ 27 kg/m^2 and waist circumference <80 cm in metabolic syndrome, all female cases (n = 411) were excluded for a small sample size which had insufficient power to be analyzed, and the male subjects (n = 2,156) were left for the analyses. The study protocol was approved by the Institutional Review Board of the Mennonite Christian Hospital (No. 16-05-008) in Taiwan and the written informed consents were obtained from all subjects.

Definitions of Obesity Phenotypes and Metabolic Syndrome

For Asian male adults, obesity was defined as BMI $\geq$ 27 kg/m^2 according to the Taiwan's Health Promotion Administration

guideline (23). Metabolic syndrome was diagnosed as having the following three or more features: (1) abdominal obesity: waist circumference ≥90 cm in men (ethnic-specifically for Chinese); (2) elevated fasting serum triglycerides ≥150 mg/dL or on lipid-lowering therapy; (3) low high-density lipoprotein cholesterol <40 mg/dL in men; (4) increased systolic BP ≥ 130 mmHg and/or diastolic BP ≥ 85 mmHg or on antihypertensive therapy; (5) high fasting plasma glucose ≥100 mg/dL or on antidiabetic therapy, according to an updated clinical criteria of International Diabetes Federation (24). Four groups were thus classified into MHNO [BMI < 27.0 kg/m^2 and metabolic syndrome (–), n = 1,484], MUNO [BMI < 27.0 kg/m^2 and metabolic syndrome (+), n = 86], MHO [BMI ≥ 27.0 kg/m^2 and metabolic syndrome (–), n = 376], and MNO [BMI ≥ 27.0 kg/m^2 and metabolic syndrome (+), n = 210].

Measurements

Body height, body weight, waist circumference, and BP were measured in the standard manner. Physical examinations were performed by experienced nurses and physicians. Body height was measured in meters (without shoes), and body weight was measured in kilograms (take off heavy clothes). The definition of BMI was calculated as body weight in kilograms divided by the square of body height in meters. Waist circumference was measured at the midpoint between the rib cage and the iliac crest in the standing position. Hemodynamic status of BP was automatically measured once over the right upper arm in a sitting posture, after a rest for at least 15 min by the FT201 blood pressure monitor (Parama-Tech Co., Ltd, Fukuoka, Japan), which used the oscillometric method *via* the cuff inflated to exceed systolic BP and then deflated at a rate of 3 mmHg per second. The procedure of BP measurement was operated by an experienced outpatient nurse. If the BP level was too high to be detected, the whole procedure would be repeated for three times with a 15-min interval, and the latest two measurements were averaged to be the final level. Overnight fasting blood specimens were collected from each individual to measure serum concentrations of total cholesterol, high-density lipoprotein, low-density lipoprotein, triglycerides, and fasting glucose on an auto analyzer (AU640, Olympus, Kobe, Japan).

Surface Electrocardiography

Resting 12-lead ECGs were obtained by the Schiller AG CARDIOVIT MS-2015 (Baar, Switzerland). If the quality of ECG report was not visually interpretable, the technician would repeat for a new one. The ECG analysis was achieved by an automated process and interpreted by a board-certified cardiologist. ECG-LVH was diagnosed if (S-V1 or S-V2 + R-V5 or R-V6) ≥35 mm, according to the Sokolow–Lyon voltage criteria (25) and if (R-aVL + S-V3) ≥18 mm, on the basis of the Cornell voltage criteria specially for Asian young male adults (26). ECG-LAE was diagnosed as a notched P wave ≥0.12 s in lead II or a notch of ≥0.04 s (27). Inferior TWI was defined as at least one negative T wave axis in limb leads II, III, or aVF. ECG-RVH was defined if (R-V1 + S-V5 or S-V6) >10.5 mm according to the Sokolow–Lyon voltage criteria (28) or if (1) R/S ratio of V1 >1 or R/S ratio of V5 or V6 <1, or (2) R-V1 >6 mm, based on the Myers et al. criteria (29).

Statistical Analysis

Clinical characteristics of the four obesity phenotypes (MHNO, MUNO, MHO, and MUO) were presented as mean ± standard deviation (SD) for continuous variables and compared by analysis of variance (ANOVA) among four groups. Numbers and percentage (%) reported for categorical variables were compared by chi-squared test or Fisher's exact-test among the four groups. Multiple logistic regression analysis model was utilized to compute odds ratio (OR) and 95% confidence interval (CI) for the association of the four obesity phenotypes MHNO (reference), MUNO, MHO, and MUO with ECG-LVH, ECG-LAE, and inferior TWI, respectively. Model was adjusted for age, smoking status, alcohol intake status, and the cardiorespiratory fitness level assessed by time for a 3,000-m run. In addition, multiple logistic regression analysis was utilized to examine the associations of the ECG characteristics that were significantly different across four obesity phenotypes and metabolic syndrome components with ECG-LVH in those without and with obesity. Finally, multiple logistic regression analysis was used to identify the independent factors (age, obesity, metabolic syndrome, systolic BP, diastolic BP, heart rate, smoking status, alcohol consumption status, and physical fitness) of ECG-LVH, ECG-LAE, and inferior TWI, respectively. A 2-tailed value of $p < 0.05$ was considered significant. All statistical analyses were performed using with SPSS statistical software (IBM Corp. Released 2013. IBM SPSS statistics for windows, version 22.0. Armonk, NY: IBM Corp.).

RESULTS

Baseline Group Characteristics

Table 1 shows the characteristics of each group stratified by obesity phenotypes. The prevalence of MHNO, MUNO, MHO, and MUO was 68.8, 4.0, 17.4, and 9.7%, respectively. All variables were statistically significant across obesity phenotypes except alcohol intake habits. Participants with obesity (MHO and MUO) were older and had lower levels of cardiorespiratory fitness.

Table 2 reveals the ECG characteristics of each group by obesity phenotypes. Across the four groups, MHNO had the lowest heart rate, PR interval, and QTc interval. In addition, MHNO had the greatest QRS axis and was more likely to have Sokolow–Lyon-based ECG-LVH, sinus bradycardia, right axis deviation, and prolonged QT interval. However, there were no significant differences in the prevalence of Cornell-based ECG-LVH and ECG-RVH. On the contrary, the obese groups were more likely to have ECG-LAE, first degree atrioventricular block, and inferior TWI.

Table 3 reveals the results of multiple logistic regression analyses for MUNO, MHO, and MUO compared to MHNO with ECG-LVH, ECG-LAE, and inferior TWI. As compared to MHNO, MUNO, MHO, and MUO were associated with lower risk of Sokolow–Lyon-based ECG-LVH [OR and 95% CI: 0.80 (0.51–1.25), 0.46 (0.36–0.58), and 0.39 (0.28–0.53), respectively; p for trend <0.001] and with greater risk of ECG-LAE [OR: 0.87

TABLE 1 | Clinical characteristics of four obesity phenotypes classified by body mass index and metabolic syndrome.

ECG characteristics	Non-obesity		Obesity		*p*-value
	Metabolically healthy (*N* = 1,484)	Metabolically unhealthy (*N* = 86)	Metabolically healthy (*N* = 376)	Metabolically unhealthy (*N* = 210)	
Age (years)	26.77 ± 5.63	30.56 ± 5.68	28.55 ± 5.78	31.38 ± 5.76	<0.001
Body mass index (kg/m^2)	23.02 ± 2.38	25.13 ± 1.64	29.20 ± 1.86	30.26 ± 2.61	<0.001
(Range: min–max)	(15.87–26.99)	(19.47–26.94)	(27.00–37.03)	(27.01–43.28)	
Waist circumference (cm)	79.14 ± 7.27	87.54 ± 5.48	92.97 ± 6.47	97.42 ± 6.67	<0.001
Prior history of hypertension	59 (4.0)	11 (12.8)	38 (10.1)	59 (28.1)	<0.001
Prior history of hyperlipidemia	199 (13.4)	27 (31.4)	94 (25.0)	69 (32.9)	<0.001
Systolic blood pressure (mmHg)	116.44 ± 11.58	128.81 ± 13.84	123.32 ± 13.43	131.53 ± 14.26	<0.001
Diastolic blood pressure (mmHg)	69.07 ± 9.26	77.13 ± 10.99	72.24 ± 10.66	78.85 ± 12.28	<0.001
Blood test					
Total cholesterol (mg/dL)	166.39 ± 31.22	185.43 ± 43.03	179.11 ± 30.39	191.30 ± 40.38	<0.001
HDL-C (mg/dL)	50.48 ± 9.77	38.49 ± 7.94	48.21 ± 8.14	39.92 ± 7.56	<0.001
LDL-C (mg/dL)	100.75 ± 27.73	112.19 ± 32.29	114.70 ± 27.16	120.91 ± 31.55	<0.001
Triglycerides (mg/dL)	87.85 ± 49.83	246.06 ± 167.17	104.30 ± 60.01	209.08 ± 144.10	<0.001
FPG (mg/dL)	92.48 ± 9.50	103.37 ± 15.92	92.91 ± 7.32	102.40 ± 24.31	<0.001
Blood pressure ≥130/85 mmHg	243 (15.7)	52 (60.5)	125 (33.2)	137 (65.2)	<0.001
Serum triglycerides ≥150 mg/dL	136 (8.8)	69 (80.2)	46 (12.2)	142 (67.6)	<0.001
HDL-C <40 mg/dL	139 (9.0)	61 (70.9)	38 (10.1)	119 (56.7)	<0.001
Waist circumference ≥90 cm	87 (5.6)	36 (41.9)	266 (70.7)	202 (96.2)	<0.001
FPG ≥100 mg/dL	218 (14.1)	56 (65.1)	45 (12.0)	112 (53.3)	<0.001
Unhealthy behavior					
Current cigarette smoker	634 (42.7)	49 (57.0)	165 (43.9)	100 (47.6)	0.04
Current alcohol drinker	704 (47.4)	43 (50.0)	189 (50.3)	106 (50.5)	0.67
3,000-m running (s)	849.98 ± 76.74	907.15 ± 101.10	908.61 ± 105.32	946.96 ± 106.35	<0.001
Top 25% performance	664 (44.7)	30 (34.9)	99 (26.3)	65 (31.0)	<0.001
Middle 50% performance	589 (39.7)	29 (33.7)	146 (38.8)	50 (23.8)	
Bottom 25% performance	231 (15.6)	27 (31.4)	131 (34.8)	95 (45.2)	

Continuous variables are expressed as mean ± standard deviation, and categorical variables as n (%).
ECG, electrocardiography; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LVH, left ventricular hypertrophy; FPG, fasting plasma glucose.
Obesity was defined as the body mass index ≥27.0 kg/m^2.
Metabolically health was defined as absence of metabolic syndrome, according to the International Diabetes Federation criteria for Asian male adults.

(0.44–1.72), 2.34 (1.77–3.10), and 3.02 (2.13–4.28), respectively; p for trend <0.001] and inferior TWI [OR: 2.21 (0.74–6.58), 3.49 (1.97–6.19), and 4.52 (2.38–8.60), respectively; p for trend <0.001]. However, no associations between obesity phenotypes and Cornell-based ECG-LVH were found.

Table 4 reveals the results of multiple logistic regression analyses for specific ECG characteristics and metabolic syndrome components with ECG-LVH in those with and without obesity. In the non-obese, Sokolow–Lyon-based ECG-LVH was associated with higher risk of sinus bradycardia [OR: 1.27 (1.01–1.60)], but with lower risk of right axis deviation [OR: 0.53 (0.39–0.72)]; while Cornell-based ECG-LVH was associated with greater risk of right axis deviation [OR: 2.72 (1.91–3.87)]. ECG-LAE, first degree atrioventricular block, and inferior TWI were not associated with Sokolow–Lyonor Cornell-based ECG-LVH in both the non-obese and the obese groups except that a marginal association of ECG-LAE with Cornell-based ECG-LVH was observed in the non-obese [OR: 1.45 (0.99–2.12), $p = 0.053$]. Of the metabolic components, low high-density lipoprotein was associated with lower risk of both Sokolow–Lyon and Cornell-based ECG-LVH in the non-obese [OR: 0.70 (0.51–0.96) and 0.58 (0.35–0.96), respectively]. High BP was associated with greater risk of both Sokolow–Lyon and Cornell-based ECG-LVH in the obese [OR: 1.45 (1.01–2.07) and 1.70 (1.07–2.69), respectively]. No other metabolic syndrome components were significantly associated with the risk of ECG-LVH.

Table 5 shows the results of multiple logistic regression model to determine the independent predictors of the ECG abnormalities. Older age, obesity, metabolic syndrome, and current smokers were protective factors of Sokolow–Lyon-based ECG-LVH [OR: 0.95 (0.93–0.97), 0.42 (0.33–0.52), 0.73 (0.55–0.99), and 0.80 (0.65–0.99), respectively], and in contrast, systolic BP and current alcohol consumer were risk factors of Sokolow–Lyon-based ECG-LVH [OR: 1.02 (1.01–1.03) and 1.48 (1.20–1.82), respectively]. However, diastolic BP was the only risk factor of Cornell-based ECG-LVH [OR: 1.02 (1.01–1.04)]. For ECG-LAE and inferior TWI, obesity was a risk factor [OR: 2.51 (1.92–3.28) and 2.73 (1.59–4.67), respectively], whereas slower heart

TABLE 2 | Electrocardiographic characteristics of four obesity phenotypes classified by body mass index and metabolic syndrome.

ECG characteristics	Non-obesity		Obesity		*p*-value
	Metabolically healthy (*N* = 1,484)	Metabolically unhealthy (*N* = 86)	Metabolically healthy (*N* = 376)	Metabolically unhealthy (*N* = 210)	
Heart rate (beats/min)	65.68 ± 10.40	68.08 ± 11.53	66.44 ± 10.34	72.07 ± 12.81	<0.001
P duration (ms)	105.98 ± 14.19	109.43 ± 13.48	106.45 ± 15.65	107.97 ± 15.66	0.06
PR interval (ms)	156.29 ± 19.65	157.18 ± 14.52	159.78 ± 20.82	161.51 ± 21.44	<0.001
QRS duration (ms)	97.81 ± 10.78	97.56 ± 12.10	97.66 ± 10.04	97.42 ± 11.91	0.96
QTc interval (ms)	388.49 ± 21.84	392.01 ± 22.44	393.77 ± 26.14	401.68 ± 25.17	<0.001
QRS axis (degree)	67.89 ± 29.11	50.85 ± 36.75	51.20 ± 33.26	44.36 ± 33.71	<0.001
Sokolow-Lyon based ECG-LVH (%)	890 (60.0)	42 (48.8)	145 (38.6)	66 (31.4)	<0.001
Cornell based ECG-LVH (%)	213 (14.4)	11 (12.8)	59 (15.7)	38 (18.1)	0.47
ECG-RVH (%)	226 (15.2)	6 (7.0)	61 (16.2)	27 (12.9)	0.13
Sinus bradycardia (%)	432 (29.1)	19 (22.1)	88 (23.4)	32 (15.2)	<0.001
Ectopic P rhythm (%)	58 (3.9)	4 (4.7)	14 (3.7)	11 (5.2)	0.79
ECG-LAE (%)	205 (13.8)	10 (11.6)	99 (26.3)	64 (30.5)	<0.001
First degree atrioventricular block (%)	37 (2.5)	0 (0.0)	16 (4.3)	15 (7.1)	0.001
Left axis deviation (%)	19 (1.3)	3 (3.5)	7 (1.9)	6 (2.9)	0.16
Right axis deviation (%)	186 (12.5)	8 (9.3)	24 (6.4)	13 (6.2)	0.001
Complete right bundle branch block (%)	51 (3.4)	4 (4.7)	12 (3.2)	10 (4.8)	0.70
Incomplete right bundle branch block (%)	101 (6.8)	8 (9.3)	29 (7.7)	8 (3.8)	0.22
QT interval prolongation (%)	16 (1.1)	0 (0.0)	9 (2.4)	6 (2.9)	0.04
QTc interval prolongation (%)	6 (0.4)	0 (0.0)	4 (1.1)	2 (1.0)	0.32
Inferior TWI (%)	27 (1.8)	4 (4.7)	25 (6.6)	20 (9.5)	<0.001

Continuous variables are expressed as mean ± standard deviation, and categorical variables as n (%).
Obesity was defined as body mass index ≥27.0 kg/m^2.
Metabolically health was defined as absence of metabolic syndrome, according to the International Diabetes Federation criteria for Asian male adults.
Sokolow-Lyon ECG based-LVH was diagnosed if (S-V1 or S-V2 + R-V5 or R-V6) ≥35 mm and Cornell ECG-based LVH was defined if R-aVL + S-V3 ≥18 mm, specifically for Asian young male adults.
ECG, electrocardiography; LAE, left atrial enlargement; LVH, left ventricular hypertrophy; RVH, right ventricular hypertrophy; TWI, T wave inversion.

rate was a protective factor [OR: 0.97 (0.96–0.98) and 0.98 (0.95–0.99), respectively]. Systolic BP was also a risk factor of inferior TWI [OR: 1.03 (1.00–1.05)].

DISCUSSION

In this study conducted in a well-controlled military environment, we found some interesting and important points. First, the prevalenceof Sokolow–Lyon-based ECG-LVH was highest in MHNO followed by MUNO, MHO, and then MNO; however, the prevalence of Cornell-based ECG-LVH was similar across the four groups. On the contrary, the prevalence of ECG-LAE and inferior TWI in the obese were higher than that in MUNO and MHNO. Second, MHO and MUO were associated with lower risk of Sokolow–Lyon-based ECG-LVH, while were with higher risk of ECG-LAE and inferior TWI with adjustments for age, cigarette smoking status, alcohol intake status, and physical performance level. There were no associations of obesity phenotypes with Cornell-based ECG-LVH. Third, greater BP was associated with higher risk of Sokolow–Lyon and Cornell-based ECG-LVH in obese participants; however, low high-density lipoprotein was associated with lower risk of Sokolow–Lyon and Cornell-based ECG-LVH in non-obese participants. For right axis deviation, there was an association for Cornell-based ECG-LVH, which was contradictory to an inverse association for Sokolow–Lyon-based ECG-LVH in the non-obese. Finally, in physically active male adults, younger age, obesity, metabolic syndrome, and cigarette smoking were independent protective factors of Sokolow–Lyon-based ECG-LVH, while greater systolic BP and alcohol consumption were independent risk factors of Sokolow–Lyon-based ECG-LVH. Diastolic BP was the only risk factor of Cornell-based ECG-LVH. Obesity was the independent factor of ECG-LAE and inferior TWI.

Prior studies reported that the components of metabolic syndrome such as high waist circumference were associated with ECG-LVH in general population (13, 15). The present study revealed that the prevalence of Sokolow–Lyon-based ECG-LVH and high level of the endurance capacity (the top 25% performance in the 3,000-m run test) were highest in MHNO and lowest in MUO among young physically active males. Obesity and metabolic syndrome were found inversely associated with Sokolow–Lyon-based ECG-LVH; however, the association was null for Cornell-based ECG-LVH. The mechanism might be reasoned in part by the distance between the heart and the ECG precordial leads is shorter and less insulated in

TABLE 3 | Associations of obesity phenotypes with ECG-LVH, ECG-LAE and inferior TWI.

	Sokolow-Lyon based ECG-LVH		Cornell based ECG-LVH		ECG-LAE		Inferior TWI	
Obesity phenotypes	**OR (95% CI)**	***p*-value**	**OR (95% CI)**	***p*-value**	**OR (95% CI)**	***p*-value**	**OR (95% CI)**	***p*-value**
MHNO	1.00		1.00		1.00		1.00	
MUNO	0.80 (0.51–1.25)	0.32	0.79 (0.41–1.53)	0.48	0.87 (0.44–1.72)	0.68	2.21 (0.74–6.58)	0.15
MHO	0.46 (0.36–0.58)	<0.001	1.08 (0.79–1.50)	0.62	2.34 (1.77–3.10)	<0.001	3.49 (1.97–6.19)	<0.001
MUO	0.39 (0.28–0.53)	<0.001	1.19 (0.80–1.77)	0.39	3.02 (2.13–4.28)	<0.001	4.52 (2.38–8.60)	<0.001
p-value for trend		<0.001		0.39		<0.001		<0.001

Data are presented as odds ratios (OR) and 95% CI (confidence intervals) using multiple logistic regression analysis.
Model adjusted for age, cigarette smoking status, alcohol drinking status and 3,000-m running categorical performance.
Sokolow-Lyon ECG based-LVH was diagnosed if (S-V1 or S-V2 + R-V5 or R-V6) ≥35 mm and Cornell ECG-based LVH was defined if R-aVL + S-V3 ≥18 mm, specifically for Asian young male adults.
MHNO, metabolically healthy non-obesity, defined as body mass index <27.0 kg/m^2 and absence of metabolic syndrome, according to the International Diabetes Federation criteria for Asian male adults; MHO, metabolically healthy obesity defined as body mass index ≥27.0 kg/m^2 and absence of metabolic syndrome; MUNO, metabolically unhealthy non-obesity defined as body mass index <27.0 kg/m^2 and presence of metabolic syndrome; MUO, metabolically unhealthy obesity defined as body mass index ≥27.0 kg/m^2 and presence of metabolic syndrome; ECG, electrocardiography; LAE, left atrial enlargement; LVH, left ventricular hypertrophy; TWI, T wave inversion.

TABLE 4 | Associations of specific ECG characteristics and metabolic components with ECG-LVH in the obese and non-obese.

	Sokolow-Lyon based ECG-LVH				Cornell based ECG-LVH			
	Non-obesity		Obesity		Non-obesity		Obesity	
	OR (95% CI)	***p*-value**	**OR (95% CI)**	***p*-value**	**OR (95% CI)**	***p*-value**	**OR (95% CI)**	***p*-value**
ECG characteristics								
Sinus bradycardia	1.27 (1.01–1.60)	0.04	0.89 (0.58–1.37)	0.59	1.13 (0.83–1.55)	0.43	0.85 (0.48–1.53)	0.60
Right axis deviation	0.53 (0.39–0.72)	<0.001	1.06 (0.53–2.12)	0.87	2.72 (1.91–3.87)	<0.001	1.49 (0.65–3.44)	0.34
ECG-LAE	1.02 (0.76–1.37)	0.90	1.09 (0.75–1.06)	0.64	1.45 (0.99–2.12)	0.053	1.14 (0.70–1.85)	0.61
First degree atrioventricular block	0.96 (0.49–1.88)	0.90	1.56 (0.74–3.28)	0.24	0.73 (0.25–2.08)	0.55	1.36 (0.55–3.33)	0.50
Inferior TWI	1.06 (0.51–2.21)	0.87	0.76 (0.38–1.50)	0.42	1.78 (0.76–4.19)	0.18	1.64 (0.78–3.41)	0.19
Metabolic components								
Blood pressure ≥130/85 mmHg	1.22 (0.93–1.59)	0.15	1.45 (1.01–2.07)	0.04	1.15 (0.80–1.63)	0.45	1.70 (1.07–2.69)	0.02
Serum triglycerides ≥150 mg/dL	1.18 (0.85–1.64)	0.32	0.86 (0.57–1.29)	0.46	0.79 (0.50–1.25)	0.31	1.21 (0.75–1.94)	0.44
HDL-C <40 mg/dL	0.70 (0.51–0.96)	0.02	0.86 (0.57–1.30)	0.48	0.58 (0.35–0.96)	0.03	0.80 (0.48–1.34)	0.39
Waist circumference ≥90 cm	0.71 (0.48–1.05)	0.08	0.70 (0.45–1.07)	0.10	1.28 (0.77–2.13)	0.33	1.45 (0.78–2.70)	0.24
FPG ≥100 mg/dL	0.99 (0.75– 1.30)	0.92	1.25 (0.84–1.87)	0.27	0.86 (0.58– 1.27)	0.44	0.80 (0.48–1.33)	0.38

Data are presented as odds ratios (OR) and 95% CI (confidence intervals) using multiple logistic regression.
Model adjusted for age plus cigarette smoking status, alcohol drinking status and 3,000-m running categorical performance.
Sokolow-Lyon based ECG-LVH was diagnosed if (S-V1 or S-V2 + R-V5 or R-V6) ≥35 mm and Cornell based ECG-LVH was defined if R-aVL + S-V3 ≥18 mm, specifically for Asian young male adults.
ECG, electrocardiography; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; LAE, left atrial enlargement; LVH, left ventricular hypertrophy; TWI, T wave inversion.

lean individuals, leading to the electrical signals stronger than the obese individuals. Similarly, a meta-analysis showed that the prevalence of exercise-induced LVH (athlete heart) is higher in highly trained male athletes (30). Consistent to our findings, the work performed by Scharf et al. showed that interval changes in the left ventricular structure were highly correlated with an increase of high-intensity aerobic training (31). As compared with Sokolow–Lyon-based ECG-LVH, Cornell-based ECG-LVH, which utilized a limb lead voltage in the criteria to reduce the effect of chest wall thickness on the signals received in precordial leads, has shown higher accuracy to echocardiographic LVH in young males (26).

Among the components of metabolic syndrome, hyperglycemia and elevated BP were regarded as independent risk factors for the development of LVH (32–34). Similarly in the present study, we observed an association between higher BP and ECG-LVH in the obesity subgroup. However, there was no association of higher BP with ECG-LVH in non-obese participants. These findings suggested a marked attenuation in association between hypertension and ECG-LVH as the impact of lean body mass was taken into account among physically active obese individuals, which highlights a possibility of the presence of pathological LVH in this population. Consistent with our findings, Manolio et al. demonstrated that moderate and high alcohol consumption was positively associated with left ventricular mass in men (35). It is believed that alcohol has a direct toxic effect on the myocardium through ethanol or its major metabolite, acetaldehyde (36).

TABLE 5 | Associations between cardiometabolic risk factors and ECG-LVH, ECG-LAE and Inferior TWI.

	Sokolow-Lyon based ECG-LVH		Cornell based ECG-LVH		ECG-LAE		Inferior TWI	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Age (years)	0.95 (0.93–0.97)	<0.001	1.02 (0.99–1.04)	0.15	0.99 (0.96–1.01)	0.17	1.01 (0.97–1.06)	0.65
Obesity	0.42 (0.33–0.52)	<0.001	1.09 (0.81–1.47)	0.57	2.51 (1.92–3.28)	<0.001	2.73 (1.59–4.67)	<0.001
Metabolic syndrome	0.73 (0.55–0.99)	0.04	0.87 (0.59–1.27)	0.46	1.26 (0.90–1.78)	0.18	1.27 (0.71–2.28)	0.42
Systolic blood pressure (mmHg)	1.02 (1.01–1.03)	<0.001	0.99 (0.98–1.01)	0.86	1.00 (0.99–1.02)	0.96	1.03 (1.00–1.05)	0.03
Diastolic blood pressure (mmHg)	1.00 (0.98–1.01)	0.46	1.02 (1.01–1.04)	0.006	1.01 (0.99–1.02)	0.26	1.01 (0.98–1.04)	0.68
Heart rate (beats per min)	0.99 (0.98–1.00)	0.05	1.00 (0.99–1.01)	0.91	0.97 (0.96–0.98)	<0.001	0.98 (0.95–0.99)	0.02
Current cigarette smoking	0.80 (0.65–0.99)	0.03	1.15 (0.87–1.51)	0.32	1.19 (0.91–1.54)	0.20	1.56 (0.91–2.66)	0.10
Current alcohol beverages intake	1.48 (1.20–1.82)	<0.001	1.00 (0.76–1.32)	0.99	0.92 (0.71–1.20)	0.53	0.93 (0.55–1.58)	0.77
3,000-m running categorical levels								
Top 25% performance	1.03 (0.84–1.27)	0.75	1.09 (0.83–1.43)	0.54	0.93 (0.71–1.21)	0.58	1.25 (0.68–2.29)	0.46
Middle 50% performance	1.00		1.00		1.00		1.00	
Bottom 25% performance	0.94 (0.74–1.20)	0.62	0.95 (0.69–1.33)	0.77	0.91 (0.67–1.24)	0.54	1.83 (0.99–3.36)	0.06

Data are presented as odds ratios (OR) and 95% CI (confidence intervals) using multiple logistic regression.
Obesity was defined as body mass index ≥27.0 kg/m^2.
Metabolic syndrome was defined according to the International Diabetes Federation criteria for Asian male adults.
Sokolow-Lyon based ECG -LVH was diagnosed if (S-V1 or S-V2 + R-V5 or R-V6) ≥35 mm and Cornell based ECG- LVH was defined if R-aVL + S-V3 ≥18 mm, specifically for Asian young male adults.
ECG, electrocardiography; LAE, left atrial enlargement; LVH, left ventricular hypertrophy; TWI, T wave inversion.

With regard to the ECG-LAE and inferior TWI, the present study findings for physically active young adults were consistent to the results in prior studies for middle- and old-aged general populations that the obese ones have higher risk of ECG-LAE and inferior TWI (10–12). Eisenstein et al. have uncovered that inferior TWI was possibly due to leftward and horizontal displacement of the base of the heart in central obesity (10). In addition, both obesity and metabolic syndrome have been associated with greater *P* wave duration as compared to the thin and metabolically healthy counterparts (11, 12). However, there were some controversies for other ECG characteristics with obesity among studies. Compared to MHNO, MUO had longer QRS duration and QT interval in the US third national health and nutrition examination survey (11), but not in the epidemiology of obesity study in the Netherlands (12). In the present study, MUO had longer QTc interval but with similar length in the QRS duration. The mechanisms for the conflicting findings were not fully understood and need further investigations.

There were a number of strengths of this study. First, the study sample size had sufficient numbers of military males for analyses of the four classified groups. Second, all the military males lived in the same environment and all laboratory measurements were standardized and performed in a referral medical center to minimize the potential confounders to affect the study results. On the other hand, several limitations of this study should be considered. First, this study recruited only physically active young male individuals so that the results may not be appropriately extrapolated to the age-matched general population of males. Second, we could not avoid the presence of potential bias that affect the ECG results such as a lack of information regarding the body temperature and duration of cardiovascular risk factors presence such as hypertension, despite that the effects were small in young adults. Third, the echocardiographic data were lacking to investigate the correlation with obesity phenotypes. Finally, we employed a cross-sectional design, the causality between the metabolic healthy status, obesity, and toxic substance use, and the risk of ECH-LVH could not be clarified. For example, an association of active tobacco smoking with Sokolow–Lyon-based ECG-LVH was not fully understood, which was possibly related to a higher prevalence of current smoking in participants of thin body weight.

In conclusion, our findings suggested that in physically active young males, the obese had higher risk of ECG-LAE and inferior TWI. Although higher BP level remained the potential risk factor of ECG-LVH, both metabolic syndrome and obesity were associated with the lower risk of Sokolow–Lyon-based ECG-LVH, but not associated with Cornell-based ECG-LVH, possibly due to a high prevalence of exercise induced-physiological LVH in military and low signal strengths of greater chest wall thickness in obesity. The cardiovascular prognosis of various ECG-LVH in physically active obese adults requires further study.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institutional Review Board of the Mennonite Christian Hospital (No. 16-05-008) in Taiwan. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

Y-KL wrote the paper. K-ZT made the statistical analyses. Y-PL, C-LH, and J-TL raised critical comments for the paper. G-ML was the principal investigator for the study. All authors contributed to the article and approved the submitted version.

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REFERENCES

1. Kopelman PG. Obesity as a medical problem. *Nature.* (2000) 404:635–43. doi: 10.1038/35007508
2. Garrow JS, Webster J. Quetelet's index (W/H2) as a measure of fatness. *Int J Obes.* (1985) 9:147–53.
3. Neeland IJ, Ross R, Despres JP, Matsuzawa Y, Yamashita S, Shai I, et al. Visceral and ectopic fat, atherosclerosis, and cardiometabolic disease: a position statement. *Lancet Diabetes Endocrinol.* (2019) 7:715–25. doi: 10.1016/S2213-8587(19)30084-1
4. Vague J. The degree of masculine differentiation of obesities: a factor determining predisposition to diabetes, atherosclerosis, gout, and uric calculous disease. *Am J Clin Nutr.* (1956) 4:20–34.
5. van Vliet-Ostaptchouk JV, Nuotio ML, Slagter SN, Doiron D, Fischer K, Foco L, et al. The prevalence of metabolic syndrome and metabolically healthy obesity in Europe: a collaborative analysis of ten large cohort studies. *BMC Endocr Disord.* (2014) 14:9. doi: 10.1186/1472-6823-14-9
6. Stefan N, Haring HU, Hu FB, Schulze MB. Metabolically healthy obesity: epidemiology, mechanisms, and clinical implications. *Lancet Diabetes Endocrinol.* (2013) 1:152–62. doi: 10.1016/S2213-8587(13)70062-7
7. Smith U. Abdominal obesity: a marker of ectopic fat accumulation. *J Clin Invest.* (2015) 125:1790–2. doi: 10.1172/JCI81507
8. Eckel N, Li Y, Kuxhaus O, Stefan N, Hu FB, Schulze MB. Transition from metabolic healthy to unhealthy phenotypes and association with cardiovascular disease risk across BMI categories in 90 257 women (the Nurses' Health Study):30 year follow-up from a prospective cohort study. *Lancet Diabetes Endocrinol.* (2018) 6:714–24. doi: 10.1016/S2213-8587(18)30137-2
9. Bluher M. Obesity: the myth of innocent obesity. *Nat Rev Endocrinol.* (2017) 13:691–2. doi: 10.1038/nrendo.2017.146
10. Eskerud I, Gerdts E, Larsen TH, Lonnebakken MT. Left ventricular hypertrophy contributes to myocardial ischemia in non-obstructive coronary artery disease (the MicroCAD study). *Int J Cardiol.* (2019) 286:1–6. doi: 10.1016/j.ijcard.2019.03.059
11. Ahmad MI, Mongraw-Chaffin M, Lewis KH, Chen H, Ard JD, Soliman EZ. Association of obesity phenotypes with electrocardiographic markers of poor outcomes in the general population. *Obesity (Silver Spring, Md).* (2019) 27:2076–83. doi: 10.1002/oby.22647
12. Elffers TW, de Mutsert R, Lamb HJ, Maan AC, Macfarlane PW. Willems van Dijk K, et al. Association of metabolic syndrome and electrocardiographic markers of subclinical cardiovascular disease. *Diabetol Metab Syndr.* (2017) 9:40. doi: 10.1186/s13098-017-0238-9
13. Ahmad MI, Li Y, Soliman EZ. Association of obesity phenotypes with electrocardiographic left ventricular hypertrophy in the general population. *J Electrocardiol.* (2018) 51:1125–30. doi: 10.1016/j.jelectrocard.2018.10.085
14. Lee HJ, Kim HL, Chung J, Lim WH, Seo JB, Kim SH, et al. Interaction of metabolic health and obesity on subclinical target organ damage. *Metab Syndr Relat Disord.* (2018) 16:46–53. doi: 10.1089/met.2017.0078
15. Zhang N, Chen Y, Guo X, Sun G, Dai D, Sun Y. Metabolic abnormalities, but not metabolically healthy obesity, are associated with left ventricular hypertrophy. *Heart Lung Circ.* (2017) 26:251–7. doi: 10.1016/j.hlc.2016.06.1212
16. Lin GM, Li YH, Lee CJ, Shiang JC, Lin KH, Chen KW, et al. Rationale and design of the cardiorespiratory fitness and hospitalization events in armed forces study in Eastern Taiwan. *World J Cardiol.* (2016) 8:464–71. doi: 10.4330/wjc.v8.i8.464
17. Lin YK, Lin YP, Lee JT, Lin CS, Wu TJ, Tsai KZ, et al. Sex-specific association of hyperuricemia with cardiometabolic abnormalities in a military cohort: the CHIEF study. *Medicine (Baltimore).* (2020) 99:e19535. doi: 10.1097/MD.0000000000019535
18. Tsai KZ, Lai SW, Hsieh CJ, Lin CS, Lin YP, Tsai SC, et al. Association between mild anemia and physical fitness in a military male cohort: the CHIEF study. *Sci Rep.* (2019) 9:11165. doi: 10.1038/s41598-019-47625-3
19. Lin JW, Tsai KZ, Chen KW, Su FY, Li YH, Lin YP, et al. Sex-specific association between serum uric acid and elevated alanine aminotransferase in a military cohort: the CHIEF study. *Endocr Metab Immune Disord Drug Targets.* (2019) 19:333–40. doi: 10.2174/1871530319666181129163802
20. Chung PS, Tsai KZ, Lin YP, Lin YK, Lin GM. Association between leukocyte counts and physical fitness in male military members: the CHIEF study. *Sci Rep.* (2020) 10:6082. doi: 10.1038/s41598-020-63147-9
21. Liu PY, Lin YK, Chen KW, Tsai KZ, Lin YP, Takimoto E, et al. Association of liver transaminase levels and long-term blood pressure variability in military young males: the CHIEF study. *Int J Environ Res Public Health*. (2020). 17:94. doi: 10.3390/ijerph17176094
22. Wang SH, Chung PS, Lin YP, Tsai KZ, Lin SC, Fan CH, et al. Metabolically healthy obesity and physical fitness in military males in the CHIEF study. *Sci Rep.* (2021) 11:9088. doi: 10.1038/s41598-021-88728-0
23. Sun ZJ, Lee HC, Huang KC, Lin WY, Chung CH, Yang YC, et al. A Preliminary assessment on implementability of "evidences-based guidelines on obesity prevention and management" for health promoting hospital accreditation. *Health Prom Res Pract.* (2019) 2:1–14. doi: 10.29442/HPRP.201907_2(2).0001
24. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. *Circulation.* (2005) 112:2735–52. doi: 10.1161/CIRCULATIONAHA.105.169404
25. Sokolow M, Lyon TP. The ventricular complex in left ventricular hypertrophy as obtained by unipolar precordial and limb leads. *Am Heart J.* (1949) 37:161–86. doi: 10.1016/0002-8703(49)90562-1
26. Su FY Li YH, Lin YP, Lee CJ, Wang CH, Meng FC, et al. A comparison of Cornell and Sokolow-Lyon electrocardiographic criteria for left ventricular hypertrophy in a military male population in Taiwan: the Cardiorespiratory fitness and hospitalization events in armed forces study. *Cardiovasc Diagn Ther.* (2017) 7:244–51. doi: 10.21037/cdt.2017.01.16
27. Alpert MA, Munuswamy K. Electrocardiographic diagnosis of left atrial enlargement. *Arch Intern Med.* (1989) 149:1161–5. doi: 10.1001/archinte.149.5.1161
28. Meng FC, Lin YP, Su FY, Yu YS, Lin GM. Association between electrocardiographic and echocardiographic right ventricular hypertrophy in a military cohort in Taiwan: the CHIEF study: ECG criteria for RVH. *Indian Heart J.* (2017) 69:331–3. doi: 10.1016/j.ihj.2017.04.016
29. Myers GB, Klein HA, Stofer BE. The electrocardiographic diagnosis of right ventricular hypertrophy. *Am Heart J.* (1948) 35:1–40. doi: 10.1016/0002-8703(48)90182-3
30. Pluim BM, Zwinderman AH, van der Laarse A, van der Wall EE. The athlete's heart. A meta-analysis of cardiac structure and function. *Circulation.* (2000) 101:336–44. doi: 10.1161/01.CIR.101.3.336
31. Scharf M, Schmid A, Kemmler W, von Stengel S, May MS, Wuest W, et al. Myocardial adaptation to high-intensity (interval) training in previously untrained men with a longitudinal cardiovascular magnetic resonance imaging study (Running Study and Heart Trial). *Circ Cardiovasc Imaging.* (2015) 8:66. doi: 10.1161/CIRCIMAGING.114.002566

32. Woodiwiss AJ, Norton GR. Obesity and left ventricular hypertrophy: the hypertension connection. *Curr Hypertens Rep.* (2015) 17:539. doi: 10.1007/s11906-015-0539-z
33. De Jong KA, Czeczor JK, Sithara S, McEwen K, Lopaschuk GD, Appelbe A, et al. Obesity and type 2 diabetes have additive effects on left ventricular remodelling in normotensive patients-a cross sectional study. *Cardiovasc Diabetol.* (2017) 16:21. doi: 10.1186/s12933-017-0504-z
34. Hendriks T, Said MA, Janssen LMA, van der Ende MY, van Veldhuisen DJ, Verweij N, et al. Effect of systolic blood pressure on left ventricular structure and function: a mendelian randomization study. *Hypertension (Dallas, Tex: 1979).* (2019) 74:826–32. doi: 10.1161/HYPERTENSIONAHA.119.12679
35. Manolio TA, Levy D, Garrison RJ, Castelli WP, Kannel WB. Relation of alcohol intake to left ventricular mass: the Framingham Study. *J Am Coll Cardiol.* (1991) 17:717–21. doi: 10.1016/S0735-1097(10)80189-5
36. Rubin E. Alcoholic myopathy in heart and skeletal muscle. *N Engl J Med.* (1979) 301:28–33. doi: 10.1056/NEJM197907053010107

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Associations of Walking Activity With Hypertensive Mediated Organ Damage in Community-Dwelling Elderly Chinese: The Northern Shanghai Study

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Background: Walking, as the most common campaign in older people, is recommended to improve their cardiovascular health. However, the direct association between weekly walking activity and asymptomatic hypertensive mediated organ damage (HMOD) remains unclear.

Methods: 2,830 community-dwelling elderly subjects (over 65 years) in northern Shanghai were recruited from 2014 to 2018. Weekly walking activity was assessed by International Physical Activity Questionnaires (IPAQ). Within the framework of comprehensive cardiovascular examinations, HMOD, including left ventricular mass index, peak transmitral pulsed Doppler velocity/early diastolic tissue Doppler velocity, creatinine clearance rate, urinary albumin–creatinine ratio, carotid-femoral pulse wave velocity (cf-PWV), carotid intima–media thickness (CIMT), arterial plaque, and ankle-brachial index (ABI), were all evaluated.

Results: 1,862 (65.8%) participants with weekly walking activity showed lower CIMT, lower cf-PWV, fewer abnormal ABI, and lower prevalence of hypertension and coronary heart disease ($p < 0.05$). Walking activity was negatively correlated with age and smokers (correlation coefficient: −0.066, −0.042; both $p < 0.05$). After adjusting for cardiovascular risk factors and concomitant diseases, walking activity was significantly associated with better indicator of most vascular HMOD in multivariate logistic regressions, including arterial stiffness [odds ratio (OR) = 0.75, $p = 0.01$], increased CIMT (OR = 0.70, $p = 0.03$), and peripheral artery disease (OR = 0.72, $p = 0.005$), but not cardiac or renal HMOD. Subgroup analysis further showed that walking duration ≥1 h/day was significantly associated with decreased risk of most vascular HMOD after adjustment for confounders and moderate-to-vigorous physical activity based on IPAQ (all $p < 0.05$).

Conclusions: In the community-dwelling elderly Chinese, there was a significant negative association of weekly walking activity with vascular HMOD, but not cardiac or renal HMOD. Increased daily walking duration, but not walking frequency, was significantly associated with improved vascular HMOD. Hence, increasing daily walking duration seems to encourage a healthy lifestyle in terms of vascular protection.

Clinical Trial Registration: ClinicalTrials.gov, identifier: NCT02368938.

Keywords: walking activity, cardiovascular disease risk factors, hypertensive mediated organ damage, elderly, vascular protection

INTRODUCTION

Epidemiological studies in China showed a rapidly increasing prevalence of hypertension from 18.0% in 2002 to 27.8% in 2014 (1). Although awareness and treatment of hypertension were improved, the control rate of hypertension remains extremely low, resulting in the increasing mortality and huge economic burden to the society. Effective therapies to manage hypertension and hypertensive mediated organ damage (HMOD) are needed at a population level, especially in the elderly. Notably, besides treatment with anti-hypertensive medicine, physical activity also plays an important role in the prevention and control of elevated blood pressure, such as walking, morning exercise, square dancing, Yoga, etc. (2). Therefore, physical activity could be a potential nature therapy for many cardiovascular diseases (CVDs).

Accumulating evidence demonstrated that physical activity (including low, moderate, and vigorous intensity) could prevent CVD, exhibit multi-system anti-aging effects (3), and extend the life expectancy of the world's population, partly due to the improvement in cardiovascular (CV) risk factors (4, 5). The American College of Sports Medicine (ACSM) recommends that older adults do moderate intensity cardiorespiratory physical activity training for 30 min/day on 5 days/week, vigorous intensity training for 20 min/day on 3 days/week, or a combination of moderate and vigorous intensity training to consume up to 500–1,000 MET-minutes/week of energy (6). Similarly, WHO recommends more than 150 min/week of moderate intensity or more than 75 min/week of vigorous intensity physical activity, or an equivalent combination of moderate and vigorous intensity physical activity (version 2010) (7). However, the level of physical activity among the elderly tends to decrease along with the increase of age. Hence, elderly with hypertension presents a challenge to achieve the recommended physical activity, especially moderate or vigorous intensity physical activity (8). Walking as a low level of physical activity is easily to be accepted in the elderly. Walking involves the interaction of neuromuscular, sensory, and cognitive functions without a high risk of injury, great difficulties, additional cost, or exercise equipment (9). Numerous studies have demonstrated the beneficial effects of walking on cardiovascular protection (10–13); nevertheless, there are no detailed guidelines on the suggested walking time and weekly frequency for the elderly. It is noteworthy that walking over 60 min/week at a leisurely pace did not improve cardiorespiratory fitness (14). Furthermore, Foster et al. in the Framingham Heart Study found no association between physical activity with indices of kidney function over an average follow-up of 6.6 years (15). Thus, it is controversial whether weekly walking activity influenced the HMOD. Considering asymptomatic HMOD in the elderly as critical prodromes of CV events and mortality, we investigated the association of weekly walking activity with asymptomatic HMOD (cardiac HMOD, renal HMOD, and vascular HMOD) based on self-reported walking participation within the framework of CV risk assessment in a community-dwelling elderly.

METHODS

Study Design

The Northern Shanghai Study is a prospective, ongoing, and multistage study, and aims to investigate the CV risk assessment system in the elderly Chinese, as previously described (16, 17). We recruited residents from urban communities in the north of Shanghai (aged 65 years or more), who are also available for long-term follow-up. Subjects with severe cardiac disease (NYHA IV) or end-stage renal disease (CKD $>$ 4), or malignant tumor with life expectancy $<$ 5 years, or stroke history within 3 months were excluded. Finally, 2,830 participants were enrolled from June 2014 to May 2018, including 1,259 (44.5%) male, 722 (25.5%) smokers, 1,530 (54.1%) with hypertension, 566 (20.0%) with diabetes mellitus, and 937 (33.1%) with coronary heart disease. The study was approved by the Ethics Committee of Shanghai Tenth People's Hospital, and written informed consent was obtained from each participant. Of note, the current study is a cross-sectional study from the Northern Shanghai Study to investigate the direct association between weekly walking activity and asymptomatic HMOD.

Definition of Weekly Walking Activity

Weekly walking activity was evaluated by standard questionnaires based on the International Physical Activity Questionnaires-short form (IPAQ, including how many days spent on walking at least 10 min at a time and walking duration time) (http://www.ipaq.ki.se), which has been validated and widely used in many clinical trials (18–20). In subgroup analysis, walking duration was classified into four groups (non-walking activity; 10–29 min/day; 30–59 min/day; $\geq$1 h/day), and walking frequency were categorized into $<$3 days/week and $\geq$3

days/week, with reference to the Korean National Health and Nutrition Examination Surveys (KNHANES) (18).

Furthermore, the metabolic equivalent of tasks (METs) was calculated as follows: walking activity METs = 3.3 × walking minutes × walking days (20). Then, physical activity was divided into three levels (low, moderate, vigorous intensity) as previously reported: vigorous, seven or more days of walking achieving at least 3,000 MET-minutes/week; moderate, five or more days of walking achieving at least 600 MET-minutes/week; low, not meeting the criteria of moderate or vigorous intensity (20, 21).

Social, Clinical, and Biological Parameters

We obtained social and clinical information from standard questionnaires, including gender, age, body weight, body height, smoking habits, history of hypertension/diabetes mellitus/coronary heart disease, etc. (16).

As to biological markers, venous blood samples and urine samples were obtained from subjects after an overnight fast. Biological markers were measured in the Department of Laboratory Medicine of Shanghai Tenth People's Hospital, including plasma creatinine (PCr), urinary microalbumin and creatinine, etc. We calculated creatinine clearance rate (CCR) and urinary albumin–creatinine ratio (UACR) based on the modified MDRD formula for Chinese and urinary microalbumin divided by urinary creatinine, respectively (16, 17).

Measurement of Blood Pressure, Ankle-Brachial Index, and Carotid-Femoral Pulse Wave Velocity

Specialized physicians measured the blood pressure (BP) of each subject in the morning by the electronic device three times after at least 10 min of rest in the sitting position, according to the recommendations of the European Society of Hypertension (22). The average of three BP readings was used in the subsequent statistical analysis.

Bilateral brachial and ankle blood pressures were measured and ankle-brachial index (ABI, calculated as ankle systolic BP divided by brachial systolic BP) was automatically calculated via the VP1000 system (Omron, Japan), according to the recommendations of the American Heart Association (23). Lower ABI was used for analysis in the present study.

Carotid-femoral pulse wave velocity (Cf-PWV) as a non-invasive golden standard was recommended to assess the arterial stiffness (Class I, Level of Evidence A) using SphygmoCor system (AtCor Medical, Australia) (24, 25). Briefly, after a 10-min rest, peripheral BP was recorded twice with an interval of 3 min, and measurements of the superficial distance directly from the carotid to the femoral artery were performed. Subsequently, pressure waveforms in the right carotid and right femoral arteries were recorded, and transit time for each artery was automatically calculated *via* ECG data. Finally, cf-PWV was calculated by traveling distance divided by traveling time. Notably, an operator index > 80% indicated a high-quality waveform.

Ultrasonography

All ultrasonographic measurements were performed by a single experienced sonographer. Arterial plaque and common carotid artery intima–media thickness (CIMT) was assayed by the MyLab 30 Gold CV system (ESAOTE SpA, Genoa, Italy). The presence or absence of plaques in the left and right carotid arteries was recorded. Also, CIMT was measured on the left common carotid artery (always on plaque-free arterial segments), 2 cm from the bifurcation, as previously described (16, 17). The average value of three CIMT measurements was used for further analysis.

Furthermore, M-mode and 2-dimensional echocardiography were performed using the same device, according to the guidelines of the American Society of Echocardiography (ASE) (16, 17). From the parasternal view, we measured left ventricular end-diastolic diameter (LVEDd), interventricular septal (IVSd) and posterior wall thickness at end-diastole (PWTd), and then calculated left ventricular mass index (LVMI) as previously described (18, 19). Simultaneously, peak transmitral pulsed Doppler velocity/early diastolic tissue Doppler velocity (E/Ea) was calculated for the evaluation of LV diastolic function. In addition, left atrial volume index (LAVI) was calculated using model formula as previously described (18, 19).

Definition of Asymptomatic Hypertensive Mediated Organ Damage

Asymptomatic HMOD included cardiac, renal, and vascular HMOD. With regard to cardiac HMOD, left ventricular hypertrophy was defined as LVMI $\geq$ 115 g/m^2 (male) or LVMI $\geq$ 95 g/m^2 (female) (26), and LV diastolic dysfunction was defined as E/Ea $\geq$ 15, or 15 > E/Ea > 8 with any of the following: LAVI > 40 ml/m^2 or LVMI > 149 g/m^2 (male) or LVMI $\geq$ 122 g/m^2 (female) (27). Chronic kidney diseases (CCR < 60 ml/min/1.73 m^2) and microalbuminuria (UACR > 30) represented renal HMOD (28), while vascular HMOD included the presence of arterial plaque, increased CIMT (CIMT > 900 μm), arterial stiffness (cf-PWV $\geq$ 12 m/s), and peripheral artery disease (ABI < 0.9) (16, 17, 29).

Statistical Analysis

Data are presented as means ± SD or frequencies (percentage). Continuous variables were compared by unpaired Student's *t*-test for normally distributed variables or the Mann–Whitney *U* test when variables were not normally distributed. For multiple comparisons, the ANOVA test was conducted using Duncan's multiple range test to investigate the association of walking duration with vascular HMOD. Comparison of categorical variables was evaluated by χ^2 test. Pearson's correlation analysis was applied to investigate the correlation of CV risk factors with weekly walking activity. The odds ratio (OR) and 95% CI of weekly walking activity were calculated for the risk of HMOD. Multivariate logistic regressions were performed to investigate the association of walking activity with HMOD, together with CV risk factors (including age, gender, smokers, body mass index, systolic blood pressure) and concomitant diseases (hypertension, diabetes mellitus, coronary heart disease). In subgroup analysis, we conducted multivariate logistic regressions to assess the relationship between risk of vascular HMOD and walking duration/frequency/different levels of physical activity. Statistical

analysis was performed using SAS software, version 9.3 (SAS Institute, Cary, NC, USA). $P < 0.05$ was considered statistically significant.

RESULTS

Characteristics of Study Participants

Detailed characteristics of participants are presented in **Table 1**, including CV risk factors, asymptomatic HMOD, and concomitant diseases. There were 1,862 (65.8%) participants enrolled in weekly walking activity. Participants with walking activity, compared with non-walking activity, were younger and had fewer smokers (both $p < 0.05$). Interestingly, there was no significant difference between participants with and without walking activity in cardiac and renal HMOD (all $p > 0.05$). As to vascular HMOD, participants with walking activity had significantly lower cf-PWV ($p = 0.004$), lower CIMT ($p = 0.001$), and lower percentage of participants with abnormal ABI ($p = 0.003$). In addition, in comparison with non-walking activity group, participants with walking activity had a lower percentage of concomitant diseases, such as hypertension ($p = 0.006$) and coronary heart disease ($p = 0.008$).

TABLE 1 | Characteristics of participants by walking activity.

	Overall (n = 2,830)	Walking activity (n = 1,862)	Non-walking activity (n = 968)	*P*
Cardiovascular risk factors				
Age (years)	71.53 ± 6.25	71.23 ± 6.04	72.10 ± 6.61	**<0.001**
Male gender, *n* (%)	1,259 (44.5)	836 (44.9)	423 (43.7)	0.54
Smokers, *n* (%)	722 (25.5)	451 (24.2)	271 (28.0)	**0.03**
Body weight (kg)	62.69 ± 0.80	62.61 ± 10.51	62.84 ± 11.34	0.60
Body height (cm)	159.8 ± 8.4	159.9 ± 8.3	159.7 ± 8.7	0.52
Body mass index (kg/m^2)	24.02 ± 3.64	23.97 ± 3.54	24.11 ± 3.83	0.35
Systolic blood pressure (mmHg)	135.1 ± 17.4	134.7 ± 17.4	135.8 ± 17.4	0.09
Hypertensive mediated organ damage				
Left ventricular mass index (g/m^2)	90.4 ± 28.9	90.4 ± 28.2	90.5 ± 30.2	0.92
E/Ea	9.67 ± 3.91	9.59 ± 3.83	9.82 ± 4.05	0.18
Creatinine clearance rate (ml/min/1.73 m^2)	93.2 ± 24.3	93.7 ± 24.7	92.3 ± 23.5	0.65
Urinary albumin–creatinine ratio (mg/g)	65.3 ± 153.5	64.5 ± 172.5	67.1 ± 107.6	0.65
Carotid-femoral pulse wave velocity (m/s)	9.49 ± 2.33	9.39 ± 2.23	9.67 ± 2.50	**0.004**
CIMT (μm)	638.1 ± 159.1	631.1 ± 156.8	650.8 ± 162.8	**0.001**
Arterial plaque, *n* (%)	1,780 (63.6)	1,166 (63.1)	614 (63.4)	0.48
Ankle-brachial index < 0.9, *n* (%)	358 (13.5)	212 (12.1)	146 (15.1)	**0.003**
Concomitant diseases				
Hypertension, *n* (%)	1,530 (54.1)	973 (52.3)	557 (57.5)	**0.006**
Diabetes mellitus, *n* (%)	566 (20.0)	381 (20.5)	185 (19.1)	0.41
Coronary heart disease, *n* (%)	937 (33.1)	586 (31.5)	351 (36.3)	**0.008**

Bold values indicate significant results (P < 0.05). Walking activity was defined as walking more than 10 min at a time per week. Data are means ± SD or numbers with percentages in parentheses. Student's t-test (or Mann–Whitney U test) and χ^2 test were conducted to compare the differences between walking activity and non-walking activity groups for quantitative and qualitative variables, respectively. Creatinine clearance rate was calculated with modified MDRD formula for Chinese. CIMT, carotid intima–media thickness; E/Ea, peak transmitral pulsed Doppler velocity/early diastolic tissue Doppler velocity.

Correlation of Cardiovascular Risk Factor With Walking Activity

Correlation analysis was performed to investigate the correlation of CV risk factors with weekly walking activity. In line with the results in **Table 1**, walking activity was only correlated with age and smokers (both $p < 0.05$), but not male gender, body weight, body height, body mass index, or systolic blood pressure (all $p > 0.05$) (**Supplementary Table 1**).

Association of Weekly Walking Activity With Asymptomatic HMOD

To investigate the association of weekly walking activity with asymptomatic HMOD, multivariate logistic regressions were conducted, together with CV risk factors and concomitant diseases. As demonstrated in **Figure 1**, weekly walking activity is significantly associated with a low risk of most vascular HMOD, including arterial stiffness (OR = 0.75, 95% CI: 0.60–0.94, $p =$

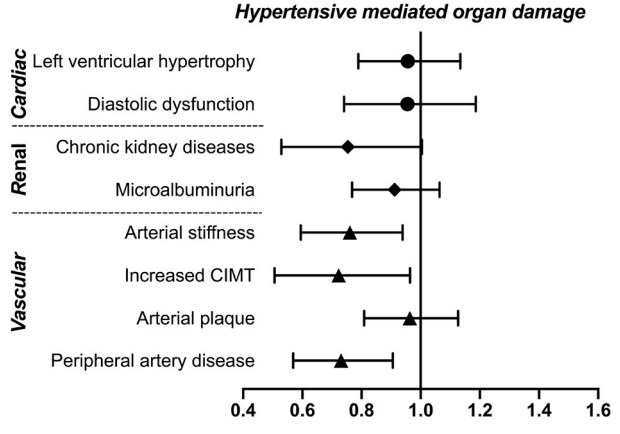

FIGURE 1 | Association of weekly walking activity with asymptomatic HMOD. Weekly walking activity was defined as walking more than 10 min at a time per week. The ORs and 95% CI of walking activity were presented after adjustment for cardiovascular risk factors (including age, gender, smokers, body mass index, systolic blood pressure) and concomitant diseases (hypertension, diabetes mellitus, coronary heart disease) using multivariate logistic regressions. CIMT, carotid intima–media thickness; HMOD, hypertensive mediated organ damage; OR, odds ratio.

0.01), increased CIMT (OR = 0.70, 95% CI: 0.51–0.96, $p = 0.03$), and peripheral artery disease (OR = 0.72, 95% CI: 0.57–0.91, $p = 0.005$), but not cardiac or renal HMOD (all $p > 0.05$).

TABLE 2 | Risk of vascular HMOD across different walking duration.

Vascular HMOD		Crude OR (95% CI)	Adjusted OR (95% CI)
Arterial stiffness ($n = 2,723$)	Non-walking activity	1	1
	≥10–29 min/day	0.75 (0.41–1.37)	**0.38 (0.17–0.85)**
	≥30–59 min/day	0.84 (0.63–1.10)	**0.38 (0.20–0.74)**
	≥1 h/day	**0.67 (0.52–0.87)**	**0.29 (0.15–0.58)**
Increased CIMT ($n = 2,810$)	Non-walking activity	1	1
	≥10–29 min/day	0.74 (0.31–1.74)	0.94 (0.33–2.66)
	≥30–59 min/day	0.82 (0.58–1.17)	0.68 (0.30–1.56)
	≥1 h/day	**0.52 (0.33–0.81)**	1.12 (0.49–2.56)
Arterial plaque ($n = 2,807$)	Non-walking activity	1	1
	≥10–29 min/day	0.93 (0.62–1.41)	0.78 (0.47–1.30)
	≥30–59 min/day	0.89 (0.73–1.09)	0.73 (0.49–1.08)
	≥1 h/day	1.00 (0.83–1.20)	0.80 (0.54–1.20)
Peripheral artery disease ($n = 2,663$)	Non-walking activity	1	1
	≥10–29 min/day	0.81 (0.45–1.46)	0.69 (0.33–1.46)
	≥30–59 min/day	0.78 (0.59–1.03)	0.65 (0.35–1.18)
	≥1 h/day	**0.65 (0.50–0.84)**	**0.53 (0.28–0.99)**

Bold values indicate significant results (P < 0.05). Multivariate logistic regressions were performed to investigate the risk of vascular HMOD across different walking duration without and with adjustment for walking days per week, together with cardiovascular risk factors (including age, gender, smokers, body mass index, systolic blood pressure) and concomitant diseases (hypertension, diabetes mellitus, coronary heart disease). CIMT, carotid intima–media thickness; HMOD, hypertensive mediated organ damage; OR, odds ratio.

Association of Walking Duration and Frequency With Vascular HMOD

Next, we performed subgroup analysis to investigate the association of walking duration and frequency with vascular HMOD. First, all participants were divided into four groups according to walking duration as previously described (18), including non-walking activity, 10–29 min/day, 30–59 min/day, and ≥1 h/day groups. Along with the increase of walking duration, cf-PWV, CIMT, and ABI were significantly and gradually improved, as well as the decreased prevalence of arterial stiffness, increased CIMT, and peripheral artery disease (all $p < 0.05$) based on Duncan's multiple range tests (**Supplementary Table 2**). Moreover, multivariate logistic regressions were performed to validate the risk of vascular HMOD across different walking duration without and with adjustment for walking days per week, together with risk factors and concomitant diseases. Walking duration ≥1 h/day was closely associated with lower crude ORs and adjusted ORs for most vascular HMOD than non-walking activity ($p < 0.05$) (**Table 2**; **Figure 2**).

Then, walking frequency was categorized into walking <3 days/week and ≥3 days/week, and we found significant differences between the two groups in the prevalence of arterial stiffness, increased CIMT, and peripheral artery disease (all $p < 0.05$), except arterial plaque ($p = 0.93$) (**Supplementary Table 3**). Further, multivariate logistic regressions were conducted to confirm the risk of vascular HMOD across different walking frequency without and with adjustment for walking duration. The crude ORs of walking ≥ 3 days/week relative to <3 days/week were 0.79 (0.63–0.98), 0.65 (0.48–0.89), and 0.73 (0.58–0.91) for vascular HMOD (arterial stiffness, increased CIMT, peripheral artery disease), respectively (**Table 3**). Of note, after adjustment for walking duration, there was no association between walking frequency and vascular HMOD (all $p > 0.05$) (**Table 3**; **Figure 2**).

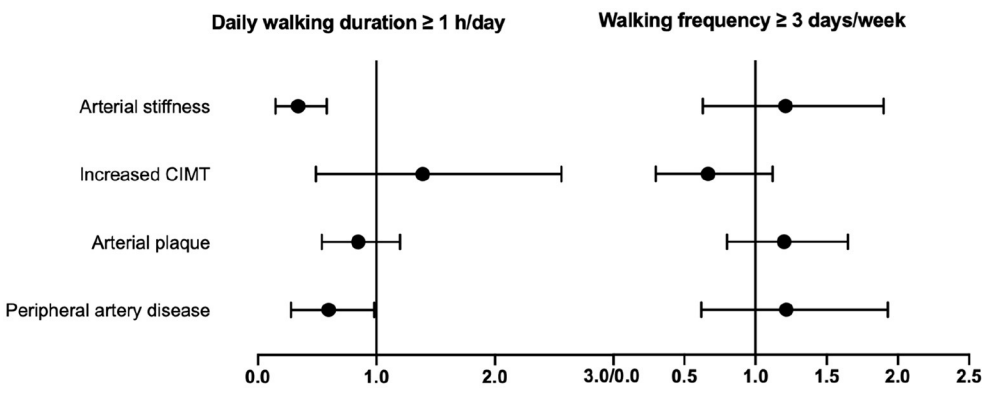

FIGURE 2 | Subgroup analysis of the association of daily walking duration or walking frequency with vascular HMOD. Multivariate logistic regressions were performed to investigate the association of walking duration ≥1 h/day or walking frequency ≥ 3 days/week with vascular HMOD. Adjusted ORs and 95% CI are presented after adjustment for walking frequency or walking duration, together with cardiovascular risk factors (including age, gender, smokers, body mass index, systolic blood pressure) and concomitant diseases (hypertension, diabetes mellitus, coronary heart disease), respectively. CIMT, carotid intima–media thickness; HMOD, hypertensive mediated organ damage; OR, odds ratio.

Association of Walking Activity With Vascular HMOD Using Different Cut-Off Walking Duration

Afterwards, we used different cut-off walking duration per time (≥30 min/day or ≥1 h/day) to further confirm the association of walking frequency with vascular HMOD. As shown in **Supplementary Table 4**, under different cut-off walking duration, the prevalence of vascular HMOD, except arterial plaque, are consistently decreased between walking <3 and ≥3 days/week ($p < 0.05$). Subsequently, we checked the association of walking activity using different cut-off walking duration with vascular HMOD through multivariate logistic regressions. Consistent with aforementioned results using walking duration ≥10 min/day, weekly walking activity was also significantly associated with vascular HMOD using walking duration ≥30 min/day and ≥1 h/day (≥30 min/day: arterial stiffness, OR = 0.61, 95% CI: 0.77–0.96, $p = 0.02$; peripheral artery disease, OR = 0.73, 95% CI: 0.58–0.91, $p = 0.006$; ≥1 h/day: arterial stiffness, OR = 0.74, 95% CI: 0.58–0.94, $p = 0.01$; increased CIMT, OR = 0.72, 95% CI: 0.53–0.99, $p = 0.04$; peripheral artery disease, OR = 0.74, 95% CI: 0.58–0.94, $p = 0.02$).

Association Between Different Levels of Physical Activity and Vascular HMOD

Furthermore, we calculated the METs and categorized into three levels of physical activity based on IPAQ (20), including low ($n = 1{,}379$), moderate ($n = 1{,}411$), and vigorous ($n = 40$). To investigate the relationship between different levels of physical activity and vascular HMOD, we conducted multivariate logistic regressions after adjustment for confounders, and the results indicated that only the resulting OR for peripheral artery disease was significantly negatively associated with a moderate-to-vigorous level of physical activity (OR: 0.74, 95% CI: 0.60–0.93, $p = 0.009$) relative to a low level of physical activity (**Table 4**). Finally, to enhance the association between walking duration/frequency and vascular HMOD, multivariate logistic regressions were conducted after adjusting for moderate-to-vigorous physical activity and similar results were observed (**Table 5**). These findings validated the association of increased daily walking duration with improved vascular HMOD.

TABLE 3 | Risk of vascular HMOD across different walking frequency.

Vascular HMOD		Crude OR (95% CI)	Adjusted OR (95% CI)
Arterial stiffness ($n = 2{,}723$)	<3 days/week	1	1
	≥3 days/week	**0.79 (0.63–0.98)**	1.10 (0.63–1.90)
Increased CIMT ($n = 2{,}810$)	<3 days/week	1	1
	≥3 days/week	**0.65 (0.48–0.89)**	0.58 (0.30–1.12)
Arterial plaque ($n = 2{,}807$)	<3 days/week	1	1
	≥3 days/week	0.97 (0.83–1.14)	1.15 (0.80–1.65)
Peripheral artery disease ($n = 2{,}663$)	<3 days/week	1	1
	≥3 days/week	**0.73 (0.58–0.91)**	1.10 (0.62–1.93)

Bold values indicate significant results (P < 0.05). Multivariate logistic regressions were performed to investigate the risk of vascular HMOD across different walking days per week without and with adjustment for walking duration, together with cardiovascular risk factors (including age, gender, smokers, body mass index, systolic blood pressure), and concomitant diseases (hypertension, diabetes mellitus, coronary heart disease). CIMT, carotid intima–media thickness; HMOD, hypertensive mediated organ damage; OR, odds ratio.

DISCUSSION

The present study had two major findings. First, weekly walking activity was significantly associated with a lower risk of vascular HMOD, but not cardiac or renal HMOD. Second, subgroup analysis indicated that there was a significant association between increasing daily walking duration (≥1 h/day) and improved vascular HMOD in community-dwelling elderly population.

Accumulating evidence revealed that physical activity has an anti-aging effects in multi-system and increase the life expectancy (3). Both ACSM and WHO recommend adults engaging in moderate or vigorous intensity physical activity, or an equivalent combination (6, 7). Unlike moderate and vigorous intensity physical activity in elderly could potentially increase the risk of mortality, walking as a low intensity physical activity with a lower risk of injury than running or sport participation is easily accessible without any requirements of special equipment or training (30). Numerous studies have reported that walking exerts beneficial effects on reduction of CV risk, blood pressure, exercise capacity, cardiac capacity, maximal oxygen consumption, and quality of life in hypertensive patients with concomitant diseases (31–35), which is recommended to a wide range of people as primary and secondary prevention. Nevertheless, in our present study, walking activity was only

TABLE 4 | Risk of vascular HMOD across different levels of physical activity.

Vascular HMOD		OR (95% CI)
Arterial stiffness ($n = 2{,}723$)	Low	1
	Moderate to vigorous	0.90 (0.72–1.12)
Increased CIMT ($n = 2{,}810$)	Low	1
	Moderate to vigorous	0.73 (0.54–1.01)
Arterial plaque ($n = 2{,}807$)	Low	1
	Moderate to vigorous	1.06 (0.91–1.23)
Peripheral artery disease ($n = 2{,}663$)	Low	1
	Moderate to vigorous	**0.74 (0.60–0.93)**

Bold values indicate significant results (P < 0.05). Multivariate logistic regressions were performed to investigate the risk of vascular HMOD across different levels of physical activity, together with cardiovascular risk factors (including age, gender, smokers, body mass index, systolic blood pressure) and concomitant diseases (hypertension, diabetes mellitus, coronary heart disease). CIMT, carotid intima–media thickness; HMOD, hypertensive mediated organ damage; OR, odds ratio.

TABLE 5 | Risk of vascular HMOD across different walking duration and frequency after adjustment for moderate-to-vigorous physical activity.

Vascular HMOD	Walking duration	OR (95% CI)	Frequency	OR (95% CI)
Arterial stiffness (n = 2,723)	Non-walking activity	1	<3 days/week	1
	≥10–29 min/day	0.35 (0.11–1.08)		
	≥30–59 min/day	**0.37 (0.18–0.75)**	≥3 days/week	0.80 (0.41–1.53)
	≥1 h/day	**0.29 (0.14–0.58)**		
Increased CIMT (n = 2,810)	Non-walking activity	1	<3 days/week	1
	≥10–29 min/day	0.80 (0.19–3.37)		
	≥30–59 min/day	1.06 (0.44–2.57)	≥3 days/week	0.54 (0.23–1.24)
	≥1 h/day	0.64 (0.26–1.58)		
Arterial plaque (n = 2,807)	Non-walking activity	1	<3 days/week	1
	≥10–29 min/day	1.07 (0.53–2.15)		
	≥30–59 min/day	0.82 (0.53–1.26)	≥3 days/week	0.98 (0.65–1.49)
	≥1 h/day	0.88 (0.58–1.36)		
Peripheral artery disease (n = 2,663)	Non-walking activity	1	<3 days/week	1
	≥10–29 min/day	0.41 (0.14–1.22)		
	≥30–59 min/day	0.54 (0.28–1.04)	≥3 days/week	1.14 (0.60–2.17)
	≥1 h/day	**0.48 (0.24–0.89)**		

Bold values indicate significant results ($P < 0.05$). Multivariate logistic regressions were performed to investigate the risk of vascular HMOD across different walking duration and frequency after adjustment for moderate-to-vigorous physical activity, together with cardiovascular risk factors (including age, gender, smokers, body mass index, systolic blood pressure) and concomitant diseases (hypertension, diabetes mellitus, coronary heart disease). CIMT, carotid intima–media thickness; HMOD, hypertensive mediated organ damage; OR, odds ratio.

significantly correlated with age and smokers, and no significant correlation existed between walking activity and body height, body weight, body mass index, or systolic blood pressure. The inconsistent findings might be partly due to a different level of physical activity and inclusive criteria. Thus, more randomized clinical trials are warranted to validate the correlation of walking activity and CV risk factors in the future.

In literature, physical activity is associated with adverse clinical outcomes of CVD (36, 37). However, it was still unclear whether weekly walking activity was associated with asymptomatic HMOD in an elderly population. First, few studies were conducted to investigate the relationship of walking activity with asymptomatic cardiac HMOD. Notably, a meta-analysis of prospective studies in 2021 showed that walking were not significantly associated with heart failure, although total physical activity, leisure-time activity, and vigorous activity were associated with a statistically significant decrease in the risk of heart failure (10). Similarly, there was no evidence of any association of self-reported walking activity on cardiac HMOD in our study, including left ventricular hypertrophy and LV diastolic dysfunction. Regarding the relationship between physical activity and renal HMOD, conflicting findings indeed existed. Some studies suggested that a high level of physical activity was associated with higher CCR and lower risk of CCR decline (38–40), while others showed no relationship between physical activity with CCR or UACR (15, 41–44). In this community-based elderly population, no association was observed between weekly walking activity and renal HMOD. With regard to vascular HMOD, several population-based studies indicated that physical activity was favorably associated with arterial stiffness (45) and atherosclerosis (46). In line with these results, our data indicated a significant association of walking activity on reduction of most vascular HMOD (including arterial stiffness, increased CIMT, and peripheral artery disease). Taken together, these findings suggested that vascular function and structure seemed to be influenced more than cardiac/renal abnormalities during walking activity in our community-based elderly population. Additional studies are needed to determine whether weekly walking activity prevent the onset or progression of vascular HMOD.

Accordingly, encouraging elderly subjects to walk could enable them to exercise at a low level against vascular HMOD. However, the required daily walking duration and walking frequency based on IPAQ remain unclear. Results of subgroup analysis showed a significant association of daily walking duration (especially ≥ 1 h/day) with most vascular HMOD after adjustment for walking frequency and all confounders. Intriguingly, there was no significant association of walking frequency with vascular HMOD after adjustment for walking duration and confounders. These outcomes suggested that daily walking duration ≥ 1 h/day was recommended to protect the elderly against vascular HMOD, but not walking frequency ≥ 3 days/week. To the best of our knowledge, this is the first study to investigate the relationship of self-reported weekly walking activity and asymptomatic HMOD according to daily walking duration and frequency of weekly walking activity in the elderly population. We indicated that, from the viewpoint of organ-protection-driven physical activity management, weekly walking activity (daily walking duration ≥ 1 h/day) was recommended for the Chinese elderly, especially those suffering from the vascular abnormalities.

Limitations

Our results should be interpreted within the limitations. First, this study was a cross-sectional study using data from the Northern Shanghai Study. Therefore, it is difficult to derive causal relationship between weekly walking activity and HMOD. With ongoing follow-up studies, more accurate data will be provided in the future. Second, weekly walking activity was evaluated based on self-reported questionnaires (leisure time). The data were

subject to error and potentially systematic bias. More studies will be required through targeting heart rate or moderate/vigorous physical activity. Third, we could not adjust for the influence of medications, especially anti-hypertensive medication.

CONCLUSIONS

In the community-dwelling elderly Chinese, weekly walking activity was significantly associated with a low risk of vascular HMOD (including arterial stiffness, increased CIMT, peripheral artery disease), but not cardiac or renal HMOD. Subgroup analysis demonstrated a significant association between increased daily walking duration and improved vascular HMOD. Hence, increasing daily walking duration ($\geq$1 h/day) would be encouraged in terms of vascular protection.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of Shanghai Tenth People's Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

YZ and YX conceived and designed the study. JP put forward many constructive comments for the final version. YL, SY, CC, and JT acquired the data and conducted the statistical analysis. JL, JB, and JP helped data interpretation. YL drafted the manuscript. All authors have read and approved the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2021.734766/full#supplementary-material

REFERENCES

1. Li Y, Yang L, Wang L, Zhang M, Huang Z, Deng Q, et al. Burden of hypertension in China: a nationally representative survey of 174,621 adults. *Int J Cardiol.* (2017) 227:516–23. doi: 10.1016/j.ijcard.2016.10.110
2. Zhou P, Grady SC, Chen G. How the built environment affects change in older people's physical activity: a mixed- methods approach using longitudinal health survey data in urban China. *Soc Sci Med.* (2017) 192:74–84. doi: 10.1016/j.socscimed.2017.09.032
3. Garatachea N, Pareja-Galeano H, Sanchis-Gomar F, Santos-Lozano A, Fiuza-Luces C, Morán M, et al. Exercise attenuates the major hallmarks of aging. *Rejuvenation Res.* (2015) 18:57–89. doi: 10.1089/rej.2014.1623
4. Wen CP, Wai JP, Tsai MK, Yang YC, Cheng TY, Lee MC, et al. Minimum amount of physical activity for reduced mortality and extended life expectancy: a prospective cohort study. *Lancet.* (2011) 378:1244–53. doi: 10.1016/S0140-6736(11)60749-6
5. Lee IM, Shiroma EJ, Lobelo F, Puska P, Blair SN, Katzmarzyk PT, et al. Effect of physical inactivity on major non-communicable diseases worldwide: an analysis of burden of disease and life expectancy. *Lancet.* (2012) 380:219–29. doi: 10.1016/S0140-6736(12)61031-9
6. Nelson ME, Rejeski WJ, Blair SN, Duncan PW, Judge JO, King AC, et al. Physical activity and public health in older adults: recommendation from the American College of Sports Medicine and the American Heart Association. *Circulation.* (2007) 116:1094–105. doi: 10.1161/CIRCULATIONAHA.107.185650
7. Team WHO. *Global Recommendations on Physical Activity for Health.* (2010). Available online at: https://www.who.int/publications/i/item/9789241599979
8. Miyazaki R, Kotani K, Tsuzaki K, Sakane N, Yonei Y, Ishii K. Effects of a year-long pedometer-based walking program on cardiovascular disease risk factors in active older people. *Asia Pac J Public Health.* (2015) 27:155–63. doi: 10.1177/1010539513506603
9. An KY. Comparison between walking and moderate-to-vigorous physical activity: associations with metabolic syndrome components in Korean older adults. *Epidemiol Health.* (2020) 42:e2020066. doi: 10.4178/epih.e2020066
10. Aune D, Schlesinger S, Leitzmann MF, Tonstad S, Norat T, Riboli E, et al. Physical activity and the risk of heart failure: a systematic review and dose-response meta-analysis of prospective studies. *Eur J Epidemiol.* (2021) 36:367–81. doi: 10.1007/s10654-020-00693-6
11. Alpsoy S. Exercise and hypertension. *Adv Exp Med Biol.* (2020) 1228:153–67. doi: 10.1007/978-981-15-1792-1_10
12. Weng SC, Chen YC, Hsu CY, Lin CS, Tarng DC, Lin SY. Impacts of heart failure and physical performance on long-term mortality in old patients with chronic kidney disease. *Front Cardiovasc Med.* (2021) 8:680098. doi: 10.3389/fcvm.2021.680098
13. Moghetti P, Balducci S, Guidetti L, Mazzuca P, Rossi E, Schena F, et al. Walking for subjects with type 2 diabetes: a systematic review and joint AMD/SID/SISMES evidence-based practical guideline. *Nutr Metab Cardiovasc Dis.* (2020) 30:1882–98. doi: 10.1016/j.numecd.2020.08.021
14. Anton SD, Duncan GE, Limacher MC, Martin AD, Perri MG. How much walking is needed to improve cardiorespiratory fitness? An examination of the 2008 Physical Activity Guidelines for Americans. *Res Q Exerc Sport.* (2011) 82:365–70. doi: 10.1080/02701367.2011.10599766
15. Foster MC, Hwang SJ, Massaro JM, Jacques PF, Fox CS, Chu AY. Lifestyle factors and indices of kidney function in the Framingham Heart Study. *Am J Nephrol.* (2015) 41:267–74. doi: 10.1159/000430868
16. Ji H, Xiong J, Yu S, Chi C, Fan X, Bai B, et al. Northern Shanghai Study: cardiovascular risk and its associated factors in the Chinese elderly-a study protocol of a prospective study design. *BMJ Open.* (2017) 7:e013880. doi: 10.1136/bmjopen-2016-013880

17. Lu Y, Zhu M, Bai B, Chi C, Yu S, Teliewubai J, et al. Comparison of Carotid-Femoral and Brachial-Ankle pulse-wave velocity in association with target organ damage in the community-dwelling elderly Chinese: the Northern Shanghai Study. *J Am Heart Assoc.* (2017) 6:e004168. doi: 10.1161/JAHA.116.004168
18. Park SM, Kim GU, Kim HJ, Kim H, Chang BS, Lee CK, et al. Walking more than 90minutes/week was associated with a lower risk of self-reported low back pain in persons over 50years of age: a cross-sectional study using the Korean National Health and Nutrition Examination Surveys. *Spine J.* (2019) 19:846–52. doi: 10.1016/j.spinee.2018.11.007
19. Chun MY. Validity and reliability of korean version of international physical activity questionnaire short form in the elderly. *Korean J Fam Med.* (2012) 33:144–51. doi: 10.4082/kjfm.2012.33.3.144
20. Chang PY, Lyu SY, Lin YF, Huang CC. High level of physical activity reduces the risk of renal progression in hypertensive patients. *Int J Environ Res Public Health.* (2020) 17:1669. doi: 10.3390/ijerph17051669
21. Craig CL, Marshall AL, Sjostrom M, Bauman AE, Booth ML, Ainsworth BE, et al. International physical activity questionnaire: 12-country reliability and validity. *Med Sci Sports Exerc.* (2003) 35:1381–95. doi: 10.1249/01.MSS.0000078924.61453.FB
22. O'Brien E, Asmar R, Beilin L, Imai Y, Mancia G, Mengden T, et al. Practice guidelines of the European Society of Hypertension for clinic, ambulatory and self blood pressure measurement. *J Hypertens.* (2005) 23:697–701. doi: 10.1097/01.hjh.0000163132.84890.c4
23. Aboyans V, Criqui MH, Abraham P, Allison MA, Creager MA, Diehm C, et al. Measurement and interpretation of the ankle-brachial index: a scientific statement from the American Heart Association. *Circulation.* (2012) 126:2890–909. doi: 10.1161/CIR.0b013e318276fbcb
24. Ji H, Xiong J, Yu S, Chi C, Bai B, Teliewubai J, et al. Measuring the carotid to femoral pulse wave velocity (Cf-PWV) to evaluate arterial stiffness. *J Vis Exp.* (2018) 135:57083. doi: 10.3791/57083
25. Laurent S, Cockcroft J, Van Bortel L, Boutouyrie P, Giannattasio C, Hayoz D, et al. Expert consensus document on arterial stiffness: methodological issues and clinical applications. *Eur Heart J.* (2006) 27:2588–605. doi: 10.1093/eurheartj/ehl254
26. Zhang Y, Kollias G, Argyris AA, Papaioannou TG, Tountas C, Konstantonis GD, et al. Association of left ventricular diastolic dysfunction with 24-h aortic ambulatory blood pressure: the SAFAR study. *J Hum Hypertens.* (2015) 29:442–8. doi: 10.1038/jhh.2014.101
27. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF 3rd, Dokainish H, Edvardsen T, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging.* (2016) 17:1321–60. doi: 10.1093/ehjci/jew082
28. Vaidya SR, Aeddula NR. *Chronic Renal Failure*. Treasure Island, FL: StatPearls (2021).
29. Piko N, Bevc S, Hojs R, Naji FH, Ekart R. The association between pulse wave analysis, carotid-femoral pulse wave velocity and peripheral arterial disease in patients with ischemic heart disease. *BMC Cardiovasc Disord.* (2021) 21:33. doi: 10.1186/s12872-021-01859-0
30. Hootman JM, Macera CA, Ainsworth BE, Martin M, Addy CL, Blair SN. Association among physical activity level, cardiorespiratory fitness, and risk of musculoskeletal injury. *Am J Epidemiol.* (2001) 154:251–8. doi: 10.1093/aje/154.3.251
31. Tschentscher M, Niederseer D, Niebauer J. Health benefits of Nordic walking: a systematic review. *Am J Prev Med.* (2013) 44:76–84. doi: 10.1016/j.amepre.2012.09.043
32. Arija V, Villalobos F, Pedret R, Vinuesa A, Jovani D, Pascual G, et al. Physical activity, cardiovascular health, quality of life and blood pressure control in hypertensive subjects: randomized clinical trial. *Health Qual Life Outcomes.* (2018) 16:184. doi: 10.1186/s12955-018-1008-6
33. Paula TP, Viana LV, Neto AT, Leitao CB, Gross JL, Azevedo MJ. Effects of the DASH diet and walking on blood pressure in patients with type 2 diabetes and uncontrolled hypertension: a randomized controlled trial. *J Clin Hypertens.* (2015) 17:895–901. doi: 10.1111/jch.12597
34. Fan M, Lv J, Yu C, Guo Y, Bian Z, Yang S, et al. Association between active commuting and incident cardiovascular diseases in Chinese: a prospective cohort study. *J Am Heart Assoc.* (2019) 8:e012556. doi: 10.1161/JAHA.119.012556
35. Murtagh EM, Nichols L, Mohammed MA, Holder R, Nevill AM, Murphy MH. The effect of walking on risk factors for cardiovascular disease: an updated systematic review and meta-analysis of randomised control trials. *Prev Med.* (2015) 72:34–43. doi: 10.1016/j.ypmed.2014.12.041
36. Pelliccia A, Sharma S, Gati S, Bäck M, Börjesson M, Caselli S, et al. 2020 ESC guidelines on sports cardiology and exercise in patients with cardiovascular disease. *Eur Heart J.* (2021) 42:17–96. doi: 10.1093/eurheartj/ehaa605
37. Nichols S, McGregor G, Breckon J, Ingle L. Current insights into exercise-based cardiac rehabilitation in patients with coronary heart disease and chronic heart failure. *Int J Sports Med.* (2021) 42:19–26. doi: 10.1055/a-1198-5573
38. Hallan S, de Mutsert R, Carlsen S, Dekker FW, Aasarod K, Holmen J. Obesity, smoking, and physical inactivity as risk factors for CKD: are men more vulnerable? *Am J Kidney Dis.* (2006) 47:396–405. doi: 10.1053/j.ajkd.2005.11.027
39. Finkelstein J, Joshi A, Hise MK. Association of physical activity and renal function in subjects with and without metabolic syndrome: a review of the Third National Health and Nutrition Examination Survey (NHANES III). *Am J Kidney Dis.* (2006) 48:372–82. doi: 10.1053/j.ajkd.2006.05.013
40. Robinson-Cohen C, Katz R, Mozaffarian D, Dalrymple LS, de Boer I, Sarnak M, et al. Physical activity and rapid decline in kidney function among older adults. *Arch Intern Med.* (2009) 169:2116–23. doi: 10.1001/archinternmed.2009.438
41. Bharakhada N, Yates T, Davies MJ, Wilmot EG, Edwardson C, Henson J, et al. Association of sitting time and physical activity with CKD: a cross-sectional study in family practices. *Am J Kidney Dis.* (2012) 60:583–90. doi: 10.1053/j.ajkd.2012.04.024
42. Hawkins MS, Sevick MA, Richardson CR, Fried LF, Arena VC, Kriska AM. Association between physical activity and kidney function: National Health and Nutrition Examination Survey. *Med Sci Sports Exerc.* (2011) 43:1457–64. doi: 10.1249/MSS.0b013e31820c0130
43. White SL, Dunstan DW, Polkinghorne KR, Atkins RC, Cass A, Chadban SJ. Physical inactivity and chronic kidney disease in Australian adults: the AusDiab study. *Nutr Metab Cardiovasc Dis.* (2011) 21:104–12. doi: 10.1016/j.numecd.2009.08.010
44. Parvathaneni K, Surapaneni A, Ballew SH, Palta P, Rebholz CM, Selvin E, et al. Association between midlife physical activity and incident kidney disease: the atherosclerosis risk in communities (ARIC) study. *Am J Kidney Dis.* (2021) 77:74–81. doi: 10.1053/j.ajkd.2020.07.020
45. Konigstein K, Infanger D, Klenk C, Carrard J, Hinrichs T, Schmidt-Trucksass A. Physical activity is favorably associated with arterial stiffness in patients with obesity and elevated metabolic risk. *Int J Clin Pract.* (2020) 74:e13563. doi: 10.1111/ijcp.13563
46. Peri-Okonny PA, Patel S, Spertus JA, Jackson EA, Malik AO, Provance J, et al. Physical activity after treatment for symptomatic peripheral artery disease. *Am J Cardiol.* (2021) 138:107–13. doi: 10.1016/j.amjcard.2020.10.011

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Population and Age-Based Cardiorespiratory Fitness Level Investigation and Automatic Prediction

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Maximal oxygen consumption (VO_2max) reflects aerobic capacity and is crucial for assessing cardiorespiratory fitness and physical activity level. The purpose of this study was to classify and predict the population-based cardiorespiratory fitness based on anthropometric parameters, workload, and steady-state heart rate (HR) of the submaximal exercise test. Five hundred and seventeen participants were recruited into this study. This study initially classified aerobic capacity followed by VO_2max predicted using an ordinary least squares regression model with measured VO_2max from a submaximal cycle test as ground truth. Furthermore, we predicted VO_2max in the age ranges 21–40 and above 40. For the support vector classification model, the test accuracy was 75%. The ordinary least squares regression model showed the coefficient of determination (R^2) between measured and predicted VO_2max was 0.83, mean absolute error (MAE) and root mean square error (RMSE) were 3.12 and 4.24 ml/kg/min, respectively. R^2 in the age 21–40 and above 40 groups were 0.85 and 0.75, respectively. In conclusion, this study provides a practical protocol for estimating cardiorespiratory fitness of an individual in large populations. An applicable submaximal test for population-based cohorts could evaluate physical activity levels and provide exercise recommendations.

Keywords: physical activity, aerobic capacity, cardiorespiratory fitness, maximal oxygen consumption (VO_2max), machine learning, support vector machine (SVM)

INTRODUCTION

The WHO identified physical inactivity as the fourth leading risk factor for non-communicable diseases accounting for high-mortality rates every year (1). Physical inactivity may cause heart disease, stroke, colon cancer, breast cancer, depression, and anxiety (2). Furthermore, low cardiorespiratory fitness has been associated with all causes of mortality and is an independent predictor of cardiovascular diseases (3).

The WHO recommends adults aged 18–64 years should attend regular moderate-intensity (≥150–300 min) or vigorous-intensity (≥75–150 min) aerobic physical activity per week (4).

According to the Lancet Physical Activity Series Working Group (5), around 30% of adults worldwide are physically inactive, and inactivity rises with age. Males and females also occupy different proportions, and physical inactivity appears more in women than men (5). Apart from a range of chronic diseases and early deaths associated with the pandemic of physical inactivity, it also causes a substantial economic burden (6, 7). According to a study by Ding et al. (8), physical inactivity cost more than 50 billion dollars in the healthcare system in 2013 globally. Evaluating cardiorespiratory fitness levels is crucial in preventing physical inactivity, and it can be achieved by measuring or predicting the maximal oxygen consumption (VO_2max).

Aerobic capacity is a quantifiable indicator of physical fitness level (9). VO_2max reflects the aerobic capacity and maximal cardiorespiratory function, and it is critical for assessing cardiorespiratory fitness and physical activity level. Matsuo et al. (10) found that physical activity levels of the workers (age: 30–60 years) are significantly correlated with VO_2max. People (age: 48.5 $\pm$ 14.4 years) meeting the physical activity criteria of 150 min/week of the daily moderate-intensity exercise demonstrated approximately 10% higher VO_2max than their counterparts (11). Better cardiorespiratory fitness is associated with a lower risk of all-cause mortality (12, 13). A 34-year follow-up study found life-long physical activity may reduce the risk of breast cancer among female teachers aged $\geq$ 25 years (14). Low levels of physical activity and low cardiorespiratory fitness are the indices of the development of metabolic syndrome in both male and female adolescence (15).

It is crucial to estimate VO_2max utilizing a simple, valid, and reliable method for epidemiologic studies of physical activity (16). VO_2max can be measured by direct gas analysis and submaximal cycle ergometry. Direct measurement of VO_2max from gas analysis using a progressive exercise test demands a maximal effort from the subject restricted to a well-equipped laboratory environment and technical expertise (17). Hence, maximal exercise tests on a treadmill or cycle ergometer are unappealing to some individuals, and some elderly or physically inactive individuals may endure a high risk to undertake the test. Astrand-Rhyming is one of the most administered submaximal cycle ergometry tests. It calculates VO_2max by evaluating the steady-state heart rate (HR) during a 6-min submaximal test. The test protocol and results also exhibited good validity and reliability in healthy populations (17, 18). Hoehn et al. (18) showed that the difference between the estimated VO_2max from the Astrand-Rhyming cycle ergometer test and VO_2max from the maximal cycle ergometer test was <1 ml/kg/min. Test-retest reliability analysis over 1 week also showed no mean difference (17). Huerta et al. (9) evaluated physical fitness among Israeli soldiers using the Astrand-Rhyming 6-min cycle ergometer test and found a sex-specific difference of the estimated VO_2max.

Machine learning is the study of computer algorithms that improve automatically through experience and by the use of data (19). Machine learning has been widely utilized in health informatics and physical fitness investigation in the recent years (20, 21). Machine and deep learning techniques have accelerated human experiments and tests conducted from the laboratory to the real world in the past decades (22–25). Inertial wearable sensors combined with machine learning algorithms could predict and evaluate biomechanics performances and energy expenditure (26–28). Human activity, such as walking, running, sitting, and cycling, could be accurately detected and classified using supervised learning methods (29–31). Therefore, sedentary behavior and physical activity level can be estimated by wearable technology (27). AI-Mallah et al. (32) demonstrated that cardiorespiratory fitness data could predict all-cause mortality by classifying the data into predetermined categories using the K-Nearest Neighbor (KNN) algorithm. Sakr et al. (33) found that the cardiorespiratory fitness data could be used to predict the prevalence rate of hypertension.

Predicting VO_2max by machine learning approaches is emerging recently. Anthropometric parameters, time of exercise, workload, and HR self-reported rating of perceived exertion (RPE) are commonly used variables or predictors (34–36). Beltrame et al. (35) revealed that machine learning algorithms successfully predicted VO_2max of forty-five health participants during the early stages of the test at maximal cardiopulmonary exercise testing. Machine learning methods can also predict VO_2max based on a 20 m shuttle run test with root mean square error (RMSE) < 5.5 ml/kg/min with a sample size of 308 (37). Artificial neural networks (ANNs) could predict VO_2max based on a single-stage submaximal exercise test of 126 healthy adults (34). Support Vector Machine (SVM) estimated VO_2max of 100 healthy participants also achieved high accuracy (36, 38).

However, the previous studies were conducted from relatively small sample sizes and predicted VO_2max based on general healthy participants. Furthermore, no study validates the prediction accuracy of cardiorespiratory fitness between age-based populations. Therefore, this study aimed to classify and predict the population-based (university teachers) cardiorespiratory fitness based on anthropometric parameters, workload, and steady-state HR of the submaximal exercise test. It was hypothesized that: (1) VO_2max is correlated with physical fitness levels and could be predicted and classified by physical fitness tests; (2) increased age contributed to the decreased cardiorespiratory fitness in age-based groups and it can be predicted.

MATERIALS AND METHODS

Participants

This study evaluated cardiorespiratory fitness among a large population and aged-based sample. Five hundred and seventeen (255 males and 262 females, age: 40.75 $\pm$ 9.16 years; height: 165.40 $\pm$ 7.70 cm; weight: 63.49 $\pm$ 11.33 kg; BMI: 23.09 $\pm$ 3.04 kg/m^2) university teachers from a university in the southeast of China were recruited into our study. Anthropometric parameters contain height, weight, and BMI. Maximal HR was calculated based on the age-predicted maximal HR: max HR = 220–age. All participants were healthy and free of any medical condition that may potentially affect VO_2max and exercise activities. All subjects were informed of the purpose, requirements, and details of this study, and written consent was obtained from each participant before the test. The study was approved by the ethics committee in Ningbo University (RAGH20190825).

Experimental Setting and Test Protocol

All cardiopulmonary aerobic tests were conducted from April 2020 to July 2020. Monark ergometer (928E, Varberg, Sweden) was utilized for the Astrand-Rhyming 6 min cycle ergometer test. The approach estimates aerobic capacity based on HR and power during the sub-max intensity test on the cycle ergometer. Each participant was given 5 min to warm up and familiarize the test environment. Participants were introduced to adjust the heights of the cycle ergometer seat and handlebar before the test. Borg's rating of perceived exertion (RPE) scale was adopted to monitor fatigue. The speed of the cycle ergometer was set at 50 r/min before the test. The whole test lasted 6 min, and during the first 3 mins, the workload was adjustable to obtain the stable HR between 125 and 175 beats/min (approximately 75% max HR). HR was monitored during the tests by a Polar Electro (H10, Kempele, Finland). Test workload was recorded and accepted HR was evaluated for each participant. VO_2max was estimated using the Astrand-Rhyming nomogram based on cardiac response to 6 min of constant submaximal cycle work (9). Each participant's cardiorespiratory fitness was further divided into poor, average, good, and excellent classes based on measured VO_2max in Monark 1.0.15.0 (Vansbro, Sweden).

Machine Learning Approaches

This study initially classified the aerobic capacity followed by VO_2max predicted using an ordinary least squares regression model with measured VO_2max from submaximal cycle test as ground-truth. Furthermore, we predicted VO_2max in the age 21–40 years and above 40 years groups. All predictors were z score normalized with a mean value of 0 and a standard deviation of 1 (39). XGBoost, KNN, logistic regression, decision tree, random forest, Naïve Bayes, and SVM algorithm were considered for this classification task. KNN assigned ten neighbors and used the standard Euclidean metric. The logistic regression algorithm employed the penalty algorithm of L1 and the LibLinear algorithm as the solver. We chose the kernel and C in the SVM as linear and 10, respectively. Gaussian naïve Bayes was picked in this study. The entropy criterion was selected for the decision tree and random forest algorithms, with maximum tree depth and the number of trees as 10 and 100, respectively. The number of trees, maximum tree depth, and learning rate were set as 10, 100, and 0.1, respectively, in the XGBoost model. SVM with linear kernel was selected as it performed the best prediction accuracy of the 10-fold cross-validation model. Based on the performance of the cycle ergometer test, cardiorespiratory fitness was classified into the following four categories: poor, average, good, and excellent.

Data were split into 60, 20, and 20% for training, validation, and testing, respectively. Twenty percent of the raw dataset was initially selected for testing. The remained 80% of the data was used for training and validation. Then, we further divided training and validation into the ratio of 75 and 25%. The SVM algorithm constructs hyperplanes between categories by maximizing the margin using support vectors. The soft margin parameter of C balances the trade-off between margin width and misclassification rate (40). To achieve a good trade-off between training and test accuracies and avoid underfitting and overfitting problems, we performed hyperparameter tuning based on four-fold grid search cross-validation (GridSearchCV) on the training dataset to determine the best C parameter of support vector classification (SVC) model from range 0.01, 0.1, 1, 10–100 [37]. Finally, C = 10 was selected as the best parameter and adopted for the test dataset.

The ordinary least squares regression was employed to predict VO_2max of each participant. For classification and regression, gender, age, height, weight, body mass index (BMI), maximal HR, test workload, and accepted HR were adopted as predictors. The SVM classification model was evaluated by accuracy, precision, recall, F1-score, and Matthews correlation coefficient. The linear regression model was estimated by Pearson product-moment correlation coefficients (R^2), the mean absolute error (MAE), and RMSE. The coefficient of each predictor was extracted to rank the feature importance of the regression model.

Statistical Analysis

Participants were divided into four groups, age 21–30, 31–40, 41–50, and above 50. The accepted HR, test workload, and aerobic capacity between groups were compared utilizing ANOVA analysis in R (version 4.0.5, R Foundation for Statistical Computing, Vienna, Austria). Tukey's honest significance differences (HSD) *post hoc* analysis was used to conduct statistical analysis of VO_2max between groups with the significance level $p < 0.01$.

RESULTS

The Anthropometric and Submaximal Test Information

The anthropometric and cycle ergometer test information is presented in **Table 1**. The accepted HR during tests was decreased with the increase of age (from 137.6 ± 11.6 bpm in the age 21–30 group decreased to 133.8 ± 11.5 bmp in the age > 50 group), but no statistical significance ($F = 2.6$, $p > 0.05$). The test workload was gradually decreased with increased age in 21–30, 31–40, and 41–50 age groups (646.6 ± 198.8, 609.8 ± 190.3, and 568.4 ± 172.8 kpm/min, respectively). Also, there was no significant difference presented ($F = 1.7$, $p > 0.05$).

VO_2max in the Different Age Groups

The ANOVA analysis of VO_2max shows the statistical difference with $F = 16.6$ and $p < 0.01$. Tukey's HSD *post-hoc* analysis with 99% CI was demonstrated in **Figure 1**. Compared with the age 21–30 group, VO_2max in the age 41–50 and >50 groups were significantly decreased (both $p < 0.01$, mean difference: −7.9 and −9.9, 99% CI: −14.4 to −1.5 and −16.4 to −3.4). VO_2max was also significantly different in the age 41–50 ($p < 0.01$, mean difference −4.7, 99% CI: −8.1 to −1.3) and above 50 groups ($p < 0.01$, mean difference −6.7, 99% CI: −10.2 to −3.1) when comparing to the age 31–40 group.

The Performance of the Classifier

The four-fold cross-validation accuracy was 76%, and the accuracy in the test dataset was 75%. The precision, recall, F1-score, and Matthews correlation coefficient are presented in

TABLE 1 | The anthropometric and cardiopulmonary aerobic test information in different age groups (data was shown in mean ± SD).

	Age (years)	Height (cm)	Weight (kg)	BMI (kg/cm^2)	Test workload (kpm/min)	Accepted HR (bpm)	VO_2max (ml/kg/min)
21–30 (n = 29)	27.5 ± 1.5	168.6 ± 7.4	63.9 ± 11.1	22.4 ± 2.7	646.6 ± 198.8	137.6 ± 11.6	46.7 ± 11.5
31–40 (n = 192)	35.0 ± 2.7	166.4 ± 8.1	63.1 ± 12.3	22.6 ± 3.2	609.8 ± 190.3	136.2 ± 10.9	43.5 ± 11.3
41–50 (n = 159)	44.6 ± 2.9	164.6 ± 7.0	62.9 ± 10.7	23.1 ± 3.0	568.4 ± 172.8	135.8 ± 11.0	38.8 ± 9.3
>50 (n = 137)	54.9 ± 3.2	164.3 ± 7.7	64.6 ± 10.7	23.8 ± 2.8	583.6 ± 155.9	133.8 ± 11.5	36.8 ± 9.2

HR, heart rate; VO_2max, maximal oxygen consumption.

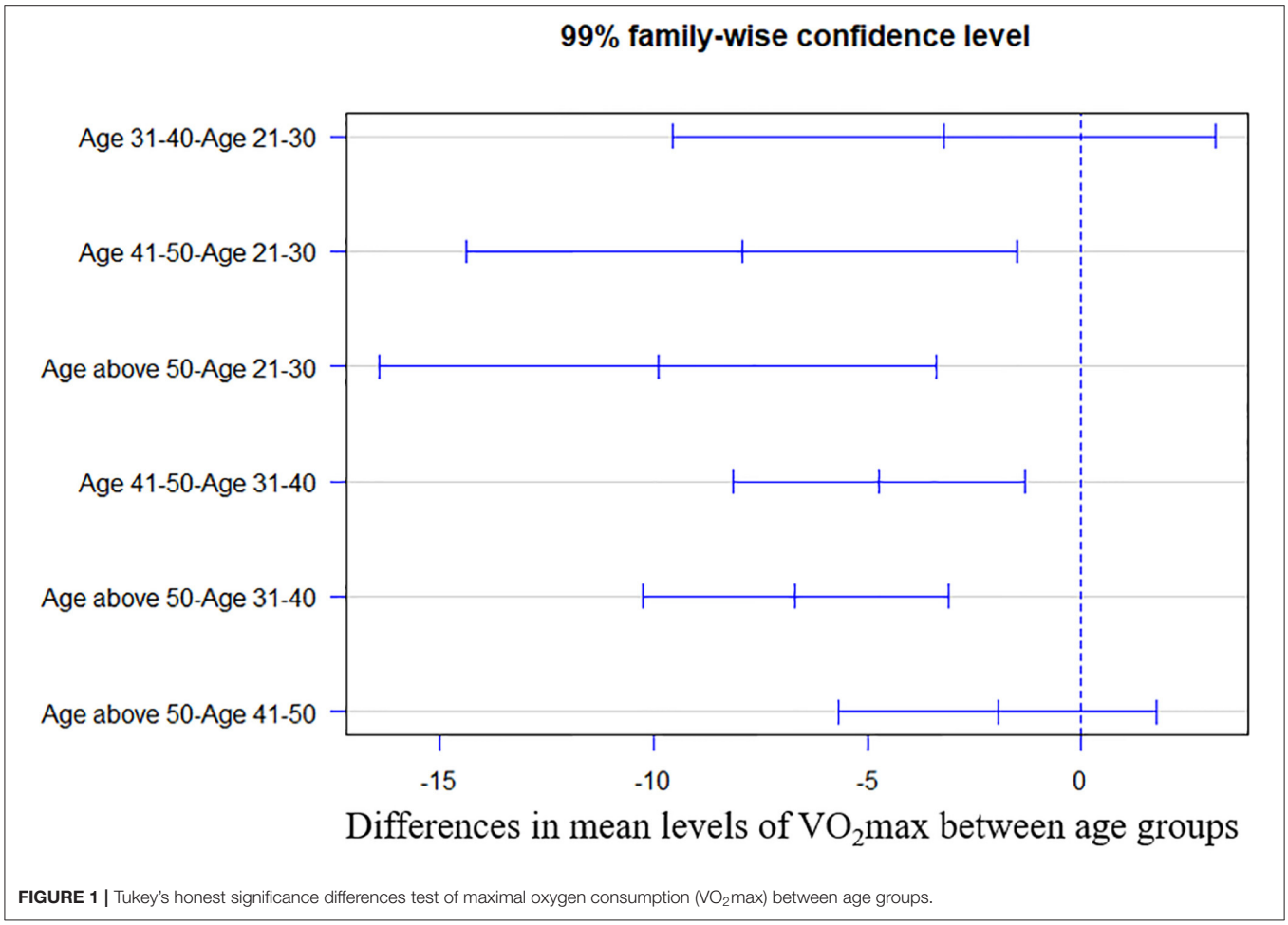

FIGURE 1 | Tukey's honest significance differences test of maximal oxygen consumption (VO_2max) between age groups.

Table 2. The accuracies of VO_2max of the classifying participants into poor, average, good, and excellent categories were shown in the confusion matrix (**Figure 2**). The X-axis showed the actual level of VO_2max, while the Y-axis depicted the predicted VO_2max utilizing an SVM classifier, and values were normalized to present the percentage of each class. The average level of VO_2max demonstrated the highest accuracy followed by the excellent level with 85 and 78%. The accuracies in the good and poor performances were relatively lower with 65 and 65%.

The Linear Regression Model

Gender, BMI, and height were the three most crucial input variables that contribute to performance of the model, followed by accepted HR, weight, age, maximal HR, and test workload. The ordinary least squares regression model showed the coefficient of determination (R^2) between actual and predicted VO_2max in the validation dataset was 0.81 and 0.83 in the test dataset (**Figure 3A**). MAE and RMSE were 3.37 and 4.45 ml/kg/min in the validation dataset, and 3.12 and 4.24 ml/kg/min in the test dataset. **Figure 3B** demonstrated the residuals plot of predicted VO_2max compared with the true VO_2max. The Bland-Altman plot exhibited the mean difference and 95% limits of agreement between the observed and predicted VO_2max (**Figure 4**). The mean difference was very close to 0, which is −0.31, and most of the points are scattered in the ±1.96 SD (above −8.59 ml/kg/min and below 7.97 mm/kg/min).

The coefficient of determination between the true and predicted VO_2max in the validation and test datasets (**Figure 5A**)

TABLE 2 | The classification report of linear SVC classifier.

	Physical performance	Number of observations	Cross-Validation accuracy	Accuracy	Precision	Recall	F1-Score	Matthews correlation coefficient
Validation dataset	Poor	59	0.76		0.74	0.73	0.74	
	Average	121			0.72	0.74	0.73	0.66
	Good	117			0.70	0.67	0.68	
	Excellent	116			0.83	0.87	0.85	
Test dataset	Poor	20		0.75	0.81	0.65	0.72	0.66
	Average	34			0.69	0.85	0.76	
	Good	23			0.68	0.65	0.67	
	Excellent	27			0.88	0.78	0.82	

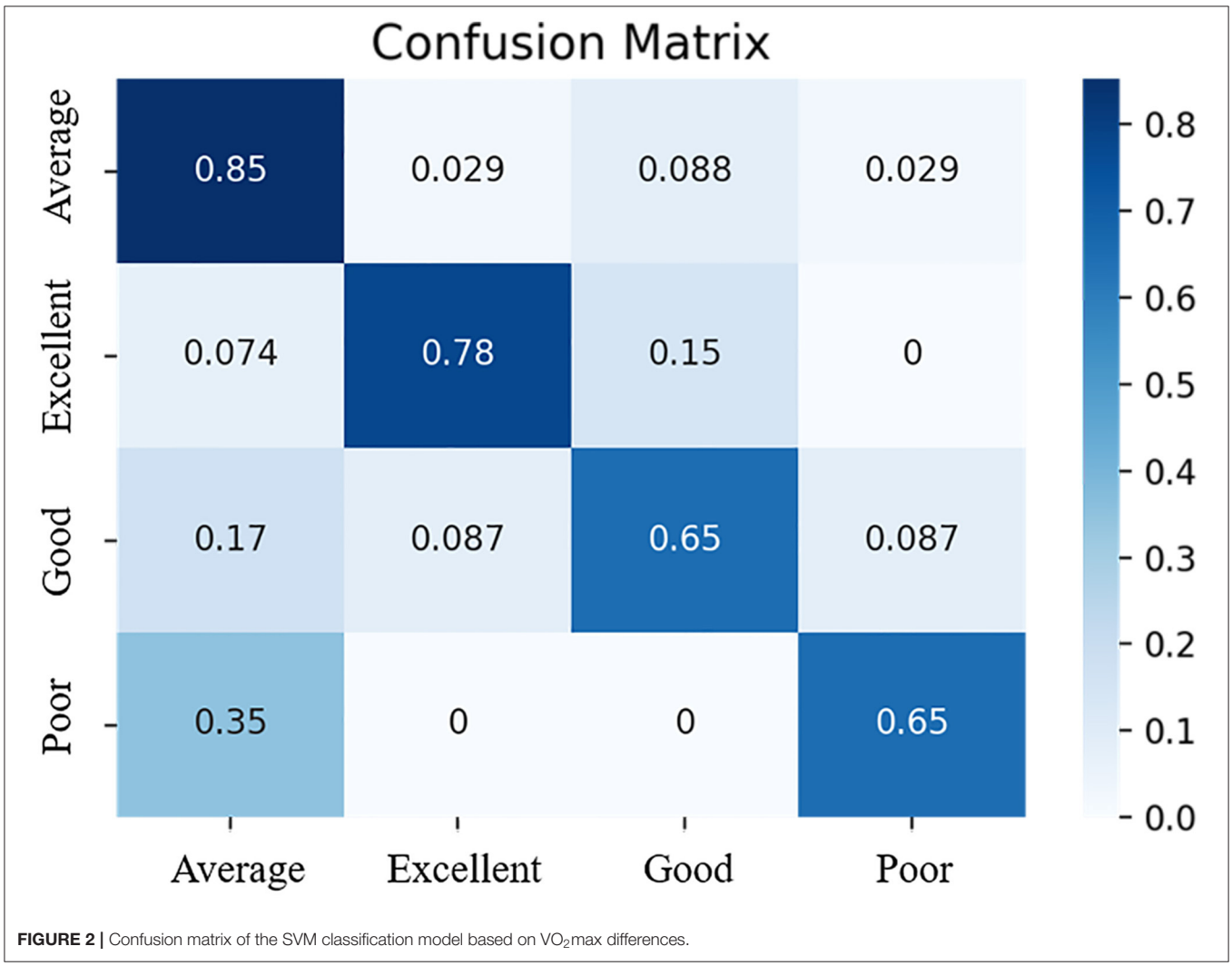

FIGURE 2 | Confusion matrix of the SVM classification model based on VO_2max differences.

of the age 21–40 group was $R^2 = 0.8$ and 0.85, respectively. MAE and RMSE in the test dataset were 2.72 and 4.02 ml/kg/min, respectively. **Figure 5B** presented $R^2 = 0.75$ of the ordinary least squares regression model in the age ≥ 40 group of the test dataset, with MAE = 3.2 ml/kg/min and RMSE = 4.26 ml/kg/min in the test dataset.

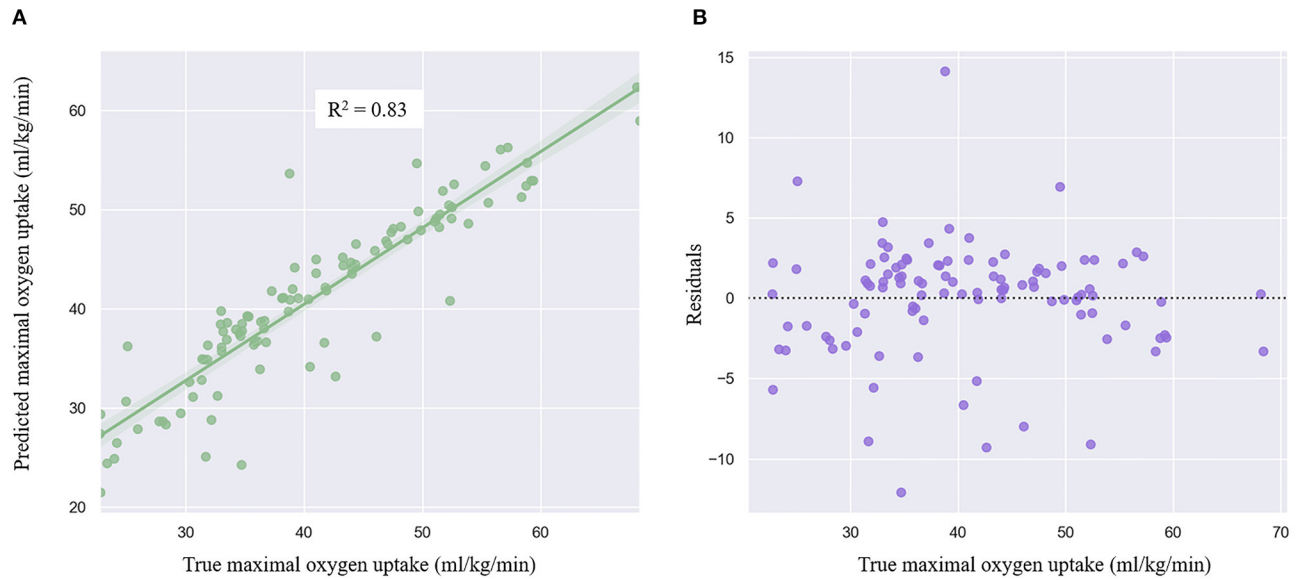

FIGURE 3 | Regression plot **(A)** and residuals plot **(B)** of the linear regression model.

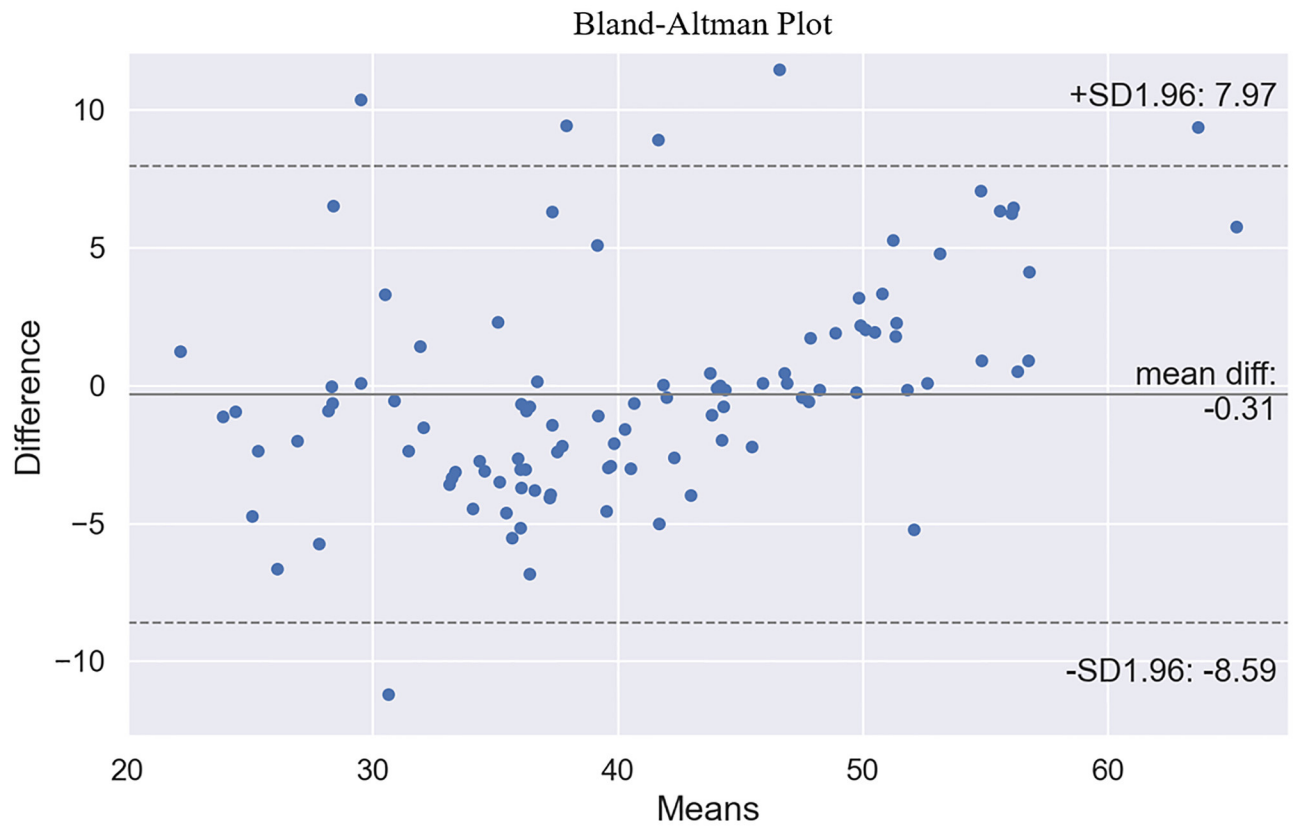

FIGURE 4 | Bland-Altman plot of true and predicted maximal oxygen uptake.

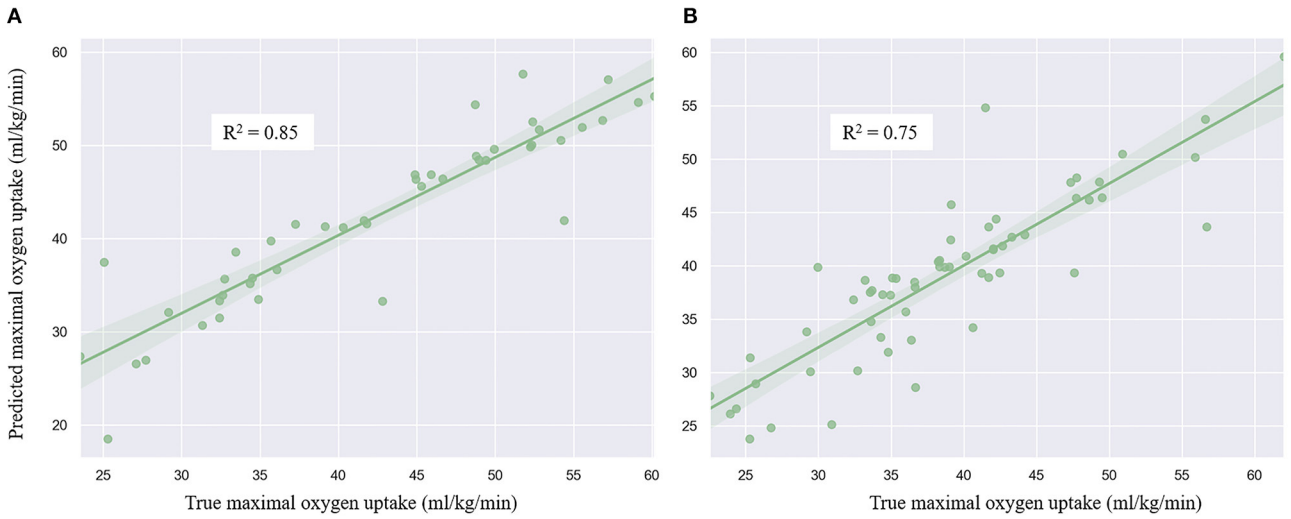

FIGURE 5 | Regression plot of the linear regression model of age 21–40 group **(A)** and age above 40 group **(B)**.

DISCUSSION

VO_2max is an essential part of health and physical fitness. This study predicted the VO_2max based on anthropometric parameters and the cycle ergometer test utilizing machine learning. Furthermore, we estimated that the ordinary least squares regression model in younger and older groups. It was found the SVC algorithm could successfully classify the cardiorespiratory fitness level into four classes (i.e., poor, average, good, and excellent). The linear regression model can predict VO_2max with gender, age, height, weight, BMI, maximal HR, test workload, and accepted HR as predictors. The ordinary least squares regression performance is better in the younger group (21–40 years old, $R^2 = 0.85$) than the group with age above 40 years ($R^2 = 0.75$).

Previous studies assessed and predicted VO_2max using different predictors and test protocols (34–38), but no study classifies the aerobic capacity into subcategories in the previous work. SVM exhibited outstanding performance in the classification tasks (36, 38, 40, 41). This study adopted it as the classifier to separate the aerobic capacity. According to the findings of this study, the VO_2max level is predictive. It can be classified based on the anthropometric parameters and workload and steady-state HR of the submaximal exercise test.

This study identified the anthropometric measurements that can be directly employed to evaluate cardiorespiratory fitness. The accuracy would be further improved by incorporating exercise parameters of an individual (i.e., HR during exercise and workload). Therefore, it provides a practical protocol for estimating cardiorespiratory fitness of an individual in large populations. By monitoring VO_2max in the different age groups, people will better understand their health condition and improve cardiovascular endurance. On the other hand, people can be guided specifically to promote health.

Our aging population presents a significant health challenge globally (42–44). The medical and healthcare system is under increased pressure with an increased economic burden (8). Estimating and predicting physical activity may play a crucial role nowadays in lessening the burden on the healthcare system. Monitoring and evaluating physical activity or cardiorespiratory fitness levels among populations, especially for the elderly, would help guide policies to increase activity levels of the populations and reduce the burden of non-communicable diseases in the public health system (5).

Przednowek et al. (37) predicted VO_2max based on a 20 m shuttle run test using ordinary least squares regression, ridge regression, Lasso regression, and ANNs. The results showed that the models for females generated less error than males, but only young participants (mean age: 20.6) were included in the study. Akay et al. (34) estimated VO_2max of 126 participants utilizing ANNs ($R^2 = 0.94$) with anthropometric parameters, steady-state HR of jogging, and jogging speed as predictors. The age range of the subjects, however, was from 17 to 40 years. VO_2max of Children and adolescents can be predicted in a submaximal run test using multiple linear regression and ANNs models (45). Huerta et al. (9) employed the cycle ergometry evaluating VO_2max among a large population-based sample of Israeli men and women with age ranging from 18 to 25 years. The submaximal cycle ergometry test has been developed as a valuable tool to estimate cardiorespiratory fitness and VO_2max due to its lower cost, lower test risk of complications, and being applicable for the elderly (34). However, previous studies only estimated or predicted physical fitness of young adults. The ordinary least squares regression model in this study showed that VO_2max is also predictable for the older population and predicted decreased cardiorespiratory fitness level with increased age, which is consistent with the previous study that physical inactivity raises with age (5).

It also showed that the predicted performance of the cycle ergometer test method is affected by age. Due to physiological changes, the elderly might potentially take less physical exercise or physical activity, and aerobic capacity is decreased with age

(5). The cycle ergometer test exhibited relatively poor ability to predict VO_2max. Using this approach to predict the VO_2max in the younger population may be better than in the older age group. It is recommended to explore the replaceable method to estimate and predict the VO_2max among the elderly population in the future. This study also found the cardiovascular endurance is significantly decreased for people aged more than 40 years. Physical inactivity in this period may contribute to decreased VO_2max. Physical activity recommendations or exercise protocol should consider providing specific guidelines for this age group in the future.

Some limitations should be noted, despite the promising findings in this study. Although we predicted the cardiorespiratory fitness between the younger and older populations, the sample size of cohorts in the age 21–30 and age above 60 groups is relatively small. Thereby, future studies should add more elderly participants to investigate their physical activity and cardiorespiratory fitness level. As physiological mechanisms differ between males and females, sex difference should also be taken into consideration. On the other hand, due to directly measuring individuals age above 40 years has the higher medical risk, VO_2max was measured from a submaximal test rather than maximal exertion test in this study. Furthermore, the ordinary least squares regression model was employed in this study. Other non-linear regression models may improve the performance of the model and decrease errors. Future studies should also attempt to predict VO_2max from larger sample sizes or consider including synthetic data.

CONCLUSION

In conclusion, this study investigated population and age-based cardiorespiratory fitness levels and classified and predicted VO_2max using classification and linear regression approaches. The findings showed that VO_2max level is predictive and can be classified based on the anthropometric parameters and workload and steady-state HR of a submaximal exercise test. Physical activity or exercise recommendations could be given to the university teachers by conducting an applicable submaximal test. Although the regression model exhibited reasonable accuracy in predicting the aerobic capacity among population above age 40 years, it is worth exploring a more comprehensive model or test protocol to estimate the cardiorespiratory fitness of an elderly more accurately.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Research Academy of Grand Health, Ningbo University (protocol code RAGH20190825). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

LX, QM, ZG, and YG worked for the conception and experiment design. LX, KD, and TY were involved in the data processing and manuscript writing. AW, JF, and YG helped in manuscript revision and final approval of the manuscript. All authors contributed to the article and agreed to the submitted version of the manuscript.

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REFERENCES

1. Bigna JJ, Noubiap JJ. The rising burden of non-communicable diseases in sub-Saharan Africa. *Lancet Glob Health.* (2019) 7:e1295–6. doi: 10.1016/S2214-109X(19)30370-5
2. Garrett NA, Brasure M, Schmitz KH, Schultz MM, Huber MR. Physical inactivity: direct cost to a health plan. *Am J Prev Med.* (2004) 27:304–9. doi: 10.1016/S0749-3797(04)00191-6
3. Wei M, Kampert JB, Barlow CE, Nichaman MZ, Gibbons LW, Paffenbarger RS Jr, et al. Relationship between low cardiorespiratory fitness and mortality in normal-weight, overweight, and obese men. *JAMA.* (1999) 282:1547–53. doi: 10.1001/jama.282.16.1547
4. World Health Organization. *Physical Activity Fact Sheet.* Geneva: World Health Organization (2021).
5. Hallal PC, Andersen LB, Bull FC, Guthold R, Haskell W, Ekelund U, et al. Global physical activity levels: surveillance progress, pitfalls, and prospects. *Lancet.* (2012) 380:247–57. doi: 10.1016/S0140-6736(12)60646-1
6. Janssen I. Health care costs of physical inactivity in Canadian adults. *Appl Physiol Nutr Metab.* (2012) 37:803–6. doi: 10.1139/h2012-061
7. Chenoweth D, Leutzinger J. The economic cost of physical inactivity and excess weight in American adults. *J Phys Act Heal.* (2006) 3:148–63. doi: 10.1123/jpah.3.2.148
8. Ding D, Lawson KD, Kolbe-Alexander TL, Finkelstein EA, Katzmarzyk PT, van Mechelen W, et al. The economic burden of physical inactivity: a global analysis of major non-communicable diseases. *Lancet.* (2016) 388:1311–24. doi: 10.1016/S0140-6736(16)30383-X
9. Huerta M, Grotto I, Shemla S, Ashkenazi I, Shpilberg O, Kark JD. Cycle ergometry estimation of physical fitness among Israeli soldiers. *Mil Med.* (2004) 169:217–20. doi: 10.7205/MILMED.169.3.217

10. Matsuo T, So R, Takahashi M. Workers' physical activity data contribute to estimating maximal oxygen consumption: a questionnaire study to concurrently assess workers' sedentary behavior and cardiorespiratory fitness. *BMC Public Health.* (2020) 20:22. doi: 10.1186/s12889-019-8067-4
11. Dyrstad SM, Anderssen SA, Edvardsen E, Hansen BH. Cardiorespiratory fitness in groups with different physical activity levels. *Scand J Med Sci Sports.* (2016) 26:291–8. doi: 10.1111/sms.12425
12. Mandsager K, Harb S, Cremer P, Phelan D, Nissen SE, Jaber W. Association of cardiorespiratory fitness with long-term mortality among adults undergoing exercise treadmill testing. *JAMA Netw Open.* (2018) 1:e183605. doi: 10.1001/jamanetworkopen.2018.3605
13. Kodama S, Saito K, Tanaka S, Maki M, Yachi Y, Asumi M, et al. Cardiorespiratory fitness as a quantitative predictor of all-cause mortality and cardiovascular events in healthy men and women: a meta-analysis. *JAMA.* (2009) 301:2024–35. doi: 10.1001/jama.2009.681
14. Rintala P, Pukkala E, Läärä E, Vihko V. Physical activity and breast cancer risk among female physical education and language teachers: a 34-year follow-up. *Int J cancer.* (2003) 107:268–70. doi: 10.1002/ijc.11390
15. Oliveira RG de, Guedes DP. Physical activity, sedentary behavior, cardiorespiratory fitness and metabolic syndrome in adolescents: systematic review and meta-analysis of observational evidence. *PLoS ONE.* (2016) 11:e0168503. doi: 10.1371/journal.pone.0168503
16. Hartung GH, Blancq JR, Lally AD, Krock PL. Estimation of aerobic capacity from submaximal cycle ergometry in women. *Med Sci Sports Exerc.* (1995) 27:452–7. doi: 10.1249/00005768-199503000-00024
17. Ekblom-Bak E, Björkman F, Hellenius ML, Ekblom B. A new submaximal cycle ergometer test for prediction of VO2max. *Scand J Med Sci Sport.* (2014) 24:319–26. doi: 10.1111/sms.12014
18. Hoehn AM, Mullenbach MJ, Fountaine CJ. Actual versus predicted cardiovascular demands in submaximal cycle ergometer testing. *Int J Exerc Sci.* (2015) 8:4–10.
19. Mitchell TM. *Machine Learning*. New York, NY: McGraw Hill (1997).
20. Ravi D, Wong C, Deligianni F, Berthelot M, Andreu-Perez J, Lo B, et al. Deep learning for health informatics. *IEEE J Biomed Heal Informatics.* (2017) 21:4–21. doi: 10.1109/JBHI.2016.2636665
21. Wiens J, Shenoy ES. Machine learning for healthcare: on the verge of a major shift in healthcare epidemiology. *Clin Infect Dis.* (2018) 66:149–53. doi: 10.1093/cid/cix731
22. Tan T, Strout ZA, Shull PB. Accurate impact loading rate estimation during running via a subject-independent convolutional neural network model and optimal IMU placement. *IEEE J Biomed Heal Informatics.* (2020) 1:1–9. doi: 10.1109/JBHI.2020.3014963
23. Hernandez V, Dadkhah D, Babakeshizadeh V, Kulić D. Lower body kinematics estimation from wearable sensors for walking and running: a deep learning approach. *Gait Posture.* (2021) 83:185–93. doi: 10.1016/j.gaitpost.2020.10.026
24. Gholami M, Napier C, Menon C. Estimating lower extremity running gait kinematics with a single accelerometer: a deep learning approach. *Sensors.* (2020) 20:2939. doi: 10.3390/s20102939
25. Rapp E, Shin S, Thomsen W, Ferber R, Halilaj E. Estimation of kinematics from inertial measurement units using a combined deep learning and optimization framework. *J Biomech.* (2021) 116:110229. doi: 10.1016/j.jbiomech.2021.110229
26. Camomilla V, Bergamini E, Fantozzi S, Vannozzi G. Trends supporting the in-field use of wearable inertial sensors for sport performance evaluation: a systematic review. *Sensors.* (2018) 18:873. doi: 10.3390/s18030873
27. Farrahi V, Niemelä M, Kangas M, Korpelainen R, Jämsä T. Calibration and validation of accelerometer-based activity monitors: a systematic review of machine-learning approaches. *Gait Posture.* (2019) 68:285–99. doi: 10.1016/j.gaitpost.2018.12.003
28. O'Reilly M, Caulfield B, Ward T, Johnston W, Doherty C. Wearable inertial sensor systems for lower limb exercise detection and evaluation: a systematic review. *Sport Med.* (2018) 48:1221–46. doi: 10.1007/s40279-018-0878-4
29. Ronao CA, Cho SB. Human activity recognition with smartphone sensors using deep learning neural networks. *Expert Syst Appl.* (2016) 59:235–44. doi: 10.1016/j.eswa.2016.04.032
30. Ordóñez FJ, Roggen D. Deep convolutional and LSTM recurrent neural networks for multimodal wearable activity recognition. *Sensors.* (2016) 16:115. doi: 10.3390/s16010115
31. Ihianle IK, Nwajana AO, Ebenuwa SH, Otuka RI, Owa K, Orisatoki MO. A deep learning approach for human activities recognition from multimodal sensing devices. *IEEE Access.* (2020) 8:179028–38. doi: 10.1109/ACCESS.2020.3027979
32. Al-Mallah MH, Elshawi R, Ahmed AM, Qureshi WT, Brawner CA, Blaha MJ, et al. Using machine learning to define the association between cardiorespiratory fitness and all-cause mortality. *Am J Cardiol.* (2017) 120:2078–84. doi: 10.1016/j.amjcard.2017.08.029
33. Sakr S, Elshawi R, Ahmed A, Qureshi WT, Brawner C, Keteyian S, et al. Using machine learning on cardiorespiratory fitness data for predicting hypertension: the henry ford exercise testing (FIT) project. *PLoS ONE.* (2018) 13:e0195344. doi: 10.1371/journal.pone.0195344
34. Akay MF, Zayid EIM, Aktürk E, George JD. Artificial neural network-based model for predicting VO2max from a submaximal exercise test. *Expert Syst Appl.* (2011) 38:2007–10. doi: 10.1016/j.eswa.2010.07.135
35. Beltrame T, Pereira L, Gois M, Frade M, Linares S, Petronilho A, et al. Predicting VO2max by machine learning models before volitional fatigue during incremental exercise. *Eur Respir J.* (2019) 54:PA4132. doi: 10.1183/13993003.congress-2019.PA4132
36. Abut F, Akay MF, George J. Developing new VO2max prediction models from maximal, submaximal and questionnaire variables using support vector machines combined with feature selection. *Comput Biol Med.* (2016) 79:182–92. doi: 10.1016/j.compbiomed.2016.10.018
37. Przednowek K, Barabasz Z, Zadarko-Domaradzka M, Przednowek KH, Niziol-Babiarz E, Huzarski M, et al. Predictive modeling of VO2max based on 20 m shuttle run test for young healthy people. *Appl Sci.* (2018) 8:1–14. doi: 10.3390/app8112213
38. Akay MF, Inan C, Bradshaw DI, George JD. Support vector regression and multilayer feed forward neural networks for non-exercise prediction of VO2max. *Expert Syst Appl.* (2009) 36:10112–9. doi: 10.1016/j.eswa.2009.01.009
39. Kettaneh N, Berglund A, Wold S. PCA and PLS with very large data sets. *Comput Stat Data Anal.* (2005) 48:69–85. doi: 10.1016/j.csda.2003.11.027
40. Fukuchi RK, Eskofier BM, Duarte M, Ferber R. Support vector machines for detecting age-related changes in running kinematics. *J Biomech.* (2011) 44:540–2. doi: 10.1016/j.jbiomech.2010.09.031
41. Clermont CA, Osis ST, Phinyomark A, Ferber R. Kinematic gait patterns in competitive and recreational runners. *J Appl Biomech.* (2017) 33:268–76. doi: 10.1123/jab.2016-0218
42. Dong B, Ding Q. Aging in China: a challenge or an opportunity? *J Am Med Dir Assoc.* (2009) 10:456–8. doi: 10.1016/j.jamda.2009.06.007
43. Khan HTA. Population ageing in a globalized world: risks and dilemmas? *J Eval Clin Pract.* (2019) 25:754–60. doi: 10.1111/jep.13071
44. Tringali V, Aldridge C. Physical activity climate and health beliefs are associated with workplace physical activity program participation of older employees of a public university. *Phys Act Heal.* (2021) 5:206–14. doi: 10.5334/paah.70
45. Silva G, Oliveira NL, Aires L, Mota J, Oliveira J, Ribeiro JC. Calculation and validation of models for estimating VO2max from the 20-m shuttle run test in children and adolescents. *Arch Exerc Heal Dis.* (2012) 3:145–52. doi: 10.5628/aehd.v3i1-2.20

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Athlete's Heart Assessed by Sit-Up Strength Exercises in Military Men and Women: The CHIEF Heart Study

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Background: Greater changes in cardiac structure and function in response to physical training have been observed more often in male athletes than in female athletes compared with their sedentary controls. However, studies for the sex-specific cardiac remodeling related to strength exercises in Asian athletes are rare.

Methods: This study included 580 men and 79 women, with an average age of 25 years, for a 6-month military training program in Taiwan. Both men and women attended a 2-min sit-up test to assess muscular strength after the training. The test performance falling one standard deviation above the mean (16%) was to define the superior eliteness of athletes. Cardiac structure and function were investigated by electrocardiography and echocardiography for men and women. Multiple logistic regression was used to determine the predictors of elite athlete status.

Results: In men, greater QTc interval, left ventricular mass adjusted to body surface area (LVMI), lateral mitral E'/A' ratio and right ventricular systolic pressure, and lower diastolic blood pressure were independent predictors of elite strength athletes in the sit-up test [odds ratio (OR) and 95% confidence intervals: 1.01 (1.00, 1.02), 1.02 (1.00, 1.04), 1.45 (1.06, 1.98), 1.13 (1.06, 1.23), and 0.96 (0.93, 0.99), respectively. In contrast, in women, the greater right ventricular outflow tract dimension was the only independent predictor of elite strength athletes in the sit-up test [OR: 1.26 (1.04, 1.53)].

Conclusions: In the 2-min sit-up test, cardiac characteristics differ between elite male and female athletes. While greater QTc interval, LVMI, and diastolic function of left ventricle predict the eliteness of male strength athletes, greater right ventricular chamber size characterizes elite female strength athletes.

Keywords: athlete's heart, cardiac remodeling, muscular strength exercise, left ventricular diastolic function, sex differences

INTRODUCTION

Changes in cardiac structure and diastolic function in response to exercises are regarded as a benign process. Greater left ventricular mass and diastolic function measured by echocardiography are more commonly observed in elite athletes for either endurance or strength exercises than in sedentary controls (1, 2). However, some cardiac adaptations may vary based on the main exercise athletes perform. With regard to the left ventricular (LV) diastolic function, assessed by the E/A ratio utilizing mitral inflow doppler, it is slightly increased or normal in athletes compared to sedentary controls (3–5). While the LV diastolic function is evaluated by tissue doppler imaging of septal or lateral wall motion for the E'/A' ratio, it is greater in athletes due to an enhanced peak early E' or a reduced late atrial A' velocity than controls (4–6). To date, these findings on athletes' hearts were mainly obtained in studies from Western populations.

Previous reports have unveiled racial and sex differences in physiological cardiac adaptions to exercise and LV pressure overload (7–9). For a given level of physical training, athletes of African/Afro-Caribbean descent reveal more marked changes to cardiac structure than Caucasian athletes (8, 9), possibly due in part to genetic variations. In addition, greater changes in cardiac structure and function in response to regular physical training have been observed in male athletes than in female athletes compared to their sedentary controls (10). However, rare studies have investigated cardiovascular health between male and female Asian athletes. Moreover, most of the prior studies compared the physiological cardiac remodeling of elite athletes to sedentary controls but rarely to those under a similar training program. Therefore, this study aimed to compare the cardiac structure and function between elite male and female athletes for a 2-min sit-up exercise relative to their physical controls in the military in Taiwan.

METHODS

Study Population

The Cardiorespiratory Fitness and Hospitalization Events in Armed Forces study (CHIEF Heart Study) included 580 men and 79 women, aged 18-34 years, from the ROC Army Huadong Defense Command Base in Taiwan and took place in January 2019 (11). All participants underwent the same training program for a 3-km run at 6:00 a.m. and 16:00 p.m., respectively, and were asked to complete the run in a limited time of 20 min. In addition, all participants had to perform at least 20 successive push-ups and subsequently 20 successive sit-ups following each run within 30 min. In July 2019, all of them attended a midterm exam for an evaluation of their muscular strength fitness, assessed by the 2-min sit-up exercise test. After the midterm physical exam, all received an annual health examination, including a self-report regarding their habits of tobacco smoking and alcohol beverage consumption (active vs. former and never) in the Hualien Armed Forces General Hospital of Eastern Taiwan. All participants carried out 12-lead electrocardiography (ECG) and transthoracic echocardiography for assessing their cardiac structure and function. The study design of the CHIEF study has been described in detail previously (12–15).

Anthropometric and Hemodynamic Measurements

The body height and body weight of each participant were measured in a standing position. Body surface area was calculated as $0.20247 \times \text{body height (m)}^{0.725} \times \text{body weight (kg)}^{0.425}$ based on the Dubois formula (16). Body mass index was calculated as body weight (kg) divided by square of body height (m^2). The Resting Blood pressure and pulse rate of each participant were measured once over the right upper arm in a sitting position by an automated blood pressure monitor (FT-201, Parama-Tech Co Ltd, Fukuoka, Japan).

Muscular Strength Measurements

The muscular strength of each participant was investigated by the performance of the 2-min sit-up exercise (17). Participants were prepared in a supine position and fixed their feet by the anchor on the pad floor with both hands attached to the ears. It was scored using a computerized infrared system merely when their upper trunk bent forward and elbows simultaneously touched the artificial sensors on both thighs. If either one of the hands left the ears temporarily, the score would not be counted by the supervisors.

Electrocardiographic and Echocardiographic Measurements

The 12-lead ECG features are interpreted *via* the software of the Schiller AG CARDIOVIT MS-2015 (Baar, Switzerland). The quality of ECG was required to be visually interpretable and with a smooth baseline; otherwise, the ECG would be repeated for acceptable quality. The echocardiography used a 1-5 MHz transducer (iE33; Philips Medical Systems, Andover, MA, USA) and was performed by an experienced technician and verified by a certificated cardiologist at the Hualien-Armed Forces General Hospital (18).

Cardiac structure such as LV wall thickness and size were measured according to the recommendations of the American Society of Echocardiography (19, 20). The corrected formula of LV mass proposed by Devereux et al. (21) was defined at end diastole as "$0.8 \times \{1.04 \times [(\text{LV internal diameter (LVIDd)} + \text{posterior wall thickness} + \text{interventricular septal thickness}]^3 - \text{LVIDd}^3\} + 0.6$." LV hypertrophy for men was defined as the LV mass index as adjusted by body surface area (LVMI) $\geq$ 116 g/m^2 based on the Dubois formula (11). Right ventricular (RV) hypertrophy for men was defined as the anterior RV wall thickness in parasternal long-axis window $>$ 5.2 mm at end diastole (13). Mitral inflow Doppler for the velocity of the diastolic wave (E wave and A wave) and the E/A ratio. Tissue Doppler imaging for the lateral mitral annulus movement velocity (E' and A') and the E'/A' ratio were used to assess LV diastolic function. RV systolic pressure was evaluated by the continuous wave Doppler for trans-tricuspid velocity in the four-chamber window.

Statistical Analysis

Elite male and female athletes were defined as the 2-min sit-up test score falling one standard deviation above the mean (16%). The controls were their physically active counterparts, who did not achieve the level for elite athletes. Demographic, anthropometric, hemodynamic, ECG, and echocardiographic profiles of elite male and female athletes and sex-specific non-elite controls were presented as mean ± standard deviation for continuous variables and numbers (percentages) for categorical variables.

Continuous variables were compared by two-sample *t*-test and categorical variables were compared by chi-square or Fisher's exact test for men and women, respectively. Multiple logistic regressions were utilized to determine the odds ratio (OR) of the ECG and echocardiographic predictors of the elite athletes to non-elite controls in men and women. In addition, multiple linear regressions were also utilized to determine the independent predictors for sit-up numbers within 2 min in men and women. A two-tailed value of $P < 0.05$ was considered significant.

All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA). This study was reviewed and approved by the Institutional Review Board of the Mennonite Christian Hospital (No. 16-05-008) in Taiwan and written informed consent was obtained from all participants.

RESULTS

Clinical Features and Laboratory Findings

In total, 93 (16.0%) of the 580 military men and 14 (17.7%) of the 79 military women who were classified as elite athletes performed >51 and 50 sit-ups within 2 min, as outlined in **Table 1**. In a study led by Ojeda et al. (22), the levels of very good or excellent young male and female athletes for sit-ups were consistent with the present study results. As compared with non-elite controls, elite strength athletes had similar levels of age, anthropometric parameters, and blood biochemistries except for lower diastolic blood pressure and greater serum levels of high-density lipoprotein and creatinine for elite male athletes, and greater serum triglycerides for elite female athletes.

Electrocardiographic Features

As indicated by **Table 2**, in men, elite strength athletes had a significantly greater corrected QT (QTc) interval defined by the Bazett's formula (393.10 ± 27.15 vs. 387.43 ± 21.36 ms, $p = 0.02$) and a higher prevalence of QTc interval prolongation > 480 ms (3.2 vs. 0.2%, $p = 0.001$) (23), compared to non-elite controls. In women, there were no significant differences in any ECG characteristics between elite strength athletes and non-elite controls.

Echocardiographic Findings

In **Table 3**, in men, elite strength athletes had greater LVMI (80.9 ± 11.7 vs. 77.5 ± 12.0 g/m^2, $p = 0.001$), RV systolic pressure

TABLE 1 | Clinical characteristics of elite male and female strength athletes and non-elite controls in the 2-min sit-up exercise.

	Male athletes (*N* = 580)			Female athletes (*N* = 79)		
	Elite (≥51 numbers) (*N* = 93)	**Non-elite controls (<51 numbers) (N = 487)**	***P*-value**	**Elite (≥50 numbers) (*N* = 14)**	**Non-elite controls (<50 numbers) (*N* = 65)**	***P*-value**
Age (years)	25.13 ± 3.69	25.21 ± 3.73	0.85	23.79 ± 2.94	24.05 ± 2.90	0.76
2-min sit-ups (numbers)	59.34 ± 6.85	43.26 ± 5.59	<0.001	53.57 ± 4.92	36.29 ± 6.06	<0.001
(Range: min-max, median)	(51-80, 60)	(20-50, 44)		(50-62, 50)	(20-45, 36)	
Height (cm)	171.57 ± 5.53	172.16 ± 5.62	0.35	160.52 ± 7.78	160.17 ± 4.82	0.82
Weight (kg)	71.09 ± 10.02	72.5 ± 11.59	0.24	60.67 ± 11.09	59.39 ± 7.87	0.61
Body surface area (m^2)	1.83 ± 0.14	1.85 ± 0.16	0.24	1.64 ± 0.18	1.62 ± 0.11	0.65
Waist circumference (cm)	80.59 ± 8.01	82.21 ± 8.93	0.24	74.92 ± 10.27	75.65 ± 7.19	0.75
Systolic blood pressure (mmHg)	116.14 ± 11.35	117.29 ± 11.91	0.38	110.57 ± 13.11	104.88 ± 10.11	0.07
Diastolic blood pressure (mmHg)	65.98 ± 8.70	68.35 ± 8.69	0.01	64.64 ± 10.73	63.11 ± 6.32	0.47
Blood test						
Serum creatinine (mg/dl)	0.97 ± 0.11	0.94 ± 0.10	0.04	0.68 ± 0.08	0.69 ± 0.07	0.92
Total cholesterol (mg/dl)	170.67 ± 34.37	168.07 ± 33.10	0.49	173.29 ± 23.99	167.28 ± 25.30	0.41
HDL-C (mmol/L)	51.41 ± 11.21	48.98 ± 9.22	0.02	57.43 ± 8.74	63.23 ± 11.70	0.08
LDL-C (mmol/L)	104.56 ± 30.45	104.08 ± 30.32	0.88	95.79 ± 21.23	91.57 ± 20.62	0.49
Serum triglyceride (mg/dl)	94.40 ± 68.46	97.50 ± 67.44	0.68	91.00 ± 60.68	59.58 ± 20.91	<0.001
Fasting plasma glucose (mg/dl)	93.66 ± 9.64	93.05 ± 8.87	0.55	95.07 ± 9.77	91.35 ± 7.42	0.11
Hemoglobin (g/dl)	15.22 ± 0.96	15.29 ± 0.90	0.55	12.65 ± 1.38	12.97 ± 0.96	0.31
Current tobacco smoking	46 [49.5]	208 [42.7]	0.22	2 [14.3]	10 [15.4]	0.91

Continuous variables are expressed as mean ± standard deviation, and categorical variables as n [%].
HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

TABLE 2 | Electrocardiographic characteristics of elite male and female strength athletes and non-elite controls in the 2-min sit-up exercise.

	Male athletes (*N* = 580)			Female athletes (*N* = 79)		
	Elite (≥51 numbers) (*N* = 93)	Non-elite controls (<51 numbers) (N = 487)	*P*-value	Elite (≥50 numbers) (*N* = 14)	Non-elite controls (<50 numbers) (*N* = 65)	*P*-value
Heart rate (beats/min)	65.82 ± 11.67	65.97 ± 10.62	0.89	67.50 ± 11.07	68.74 ± 9.46	0.66
P duration (ms)	107.88 ± 13.15	105.56 ± 14.39	0.14	99.74 ± 11.50	99.12 ± 13.72	0.87
PR interval (ms)	157.38 ± 26.14	154.45 ± 17.94	0.18	147.75 ± 21.17	151.86 ± 20.10	0.49
QRS duration (ms)	98.19 ± 10.18	97.30 ± 10.00	0.43	84.29 ± 5.42	85.88 ± 7.80	0.47
QTc interval (ms)	393.10 ± 27.15	387.43 ± 21.36	0.02	408.14 ± 17.33	411.89 ± 30.62	0.66
QRS axis (degree)	64.76 ± 23.86	65.29 ± 28.42	0.86	72.43 ± 13.60	64.11 ± 34.79	0.38
ECG based LVH (%)	59 [63.4]	287[58.9]	0.41	1 [7.1]	2 [3.1]	0.47
ECG based RVH (%)	15 [16.1]	80 [16.4]	0.94	0 [0.0]	0 [0.0]	–
Sinus bradycardia (%)	30 [32.3]	136 [27.9]	0.39	2 [14.3]	12 [18.5]	0.71
Ectopic P rhythm (%)	1 [1.1]	21 [4.3]	0.13	0 [0.0]	3 [4.6]	0.41
Left atrial enlargement (%)	11 [11.8]	83 [17.0]	0.21	1 [7.1]	12 [18.5]	0.30
First degree atrioventricular block (%)	3 [3.2]	8 [1.6]	0.30	0 [0.0]	2 [3.1]	0.50
Left axis deviation (%)	2 [2.2]	3 [0.6]	0.14	0 [0.0]	3 [4.6]	0.41
Right axis deviation (%)	5 [5.4]	50 [10.3]	0.14	2 [14.3]	9 [13.8]	0.96
Complete right bundle branch block (%)	2 [2.2]	14 [2.9]	0.69	0 [0.0]	0 [0.0]	–
Incomplete right bundle branch block (%)	10 [10.8]	28 [5.7]	0.07	0 [0.0]	0 [0.0]	–
QT interval prolongation (%)	2 [2.2]	7 [1.4]	0.61	0 [0.0]	1 [1.5]	0.64
QTc prolongation (%)	3 [3.2]	1 [0.2]	0.001	0 [0.0]	2 [3.1]	0.50
T wave inversion (%)	2 [2.2]	15 [3.1]	0.62	0 [0.0]	4 [6.2]	0.34

Categorical variables are expressed as N [%].

(29.5 ± 4.15 vs. 27.8 ± 12.0 mmHg, $p = 0.001$), and lateral mitral E'/A' (2.32 ± 0.70 vs. 2.11 ± 0.71, $p = 0.01$) compared to non-elite controls. In contrast, in women, elite strength athletes were found to have greater aortic root dimension (30.2 ± 3.70 vs. 26.9 ± 2.52 mm, $p < 0.01$), and RV outflow tract dimension compared to non-elite controls (28.5 ± 4.04 vs. 25.7 ± 3.46 mm, $p = 0.01$).

Echocardiographic Predictors of Elite Strength Athletes

In **Table 4**, the multiple logistic regression results showed that, in men, greater QTc interval, LVMI, RV systolic pressure and lateral mitral E'/A', and lower diastolic blood pressure were independent predictors of elite strength athletes [odds ratio (OR): 1.01 [95% confidence intervals (CI): 1.00, 1.02], 1.02 (95% CI: 1.00, 1.04), 1.13 (95% CI: 1.06, 1.20), 1.45 (95%CI: 1.06, 1.98) and 0.96 (95% CI: 0.93, 0.99), respectively]. In contrast, RV outflow tract dimension was the only independent predictor of elite strength athletes in women [OR: 1.26 (95% CI: 1.04, 1.53)].

As shown in **Table 5**, the results of multiple linear regressions were consistent for LVMI, RV systolic pressure, and lateral mitral E'/A' in men [β: 0.068, 0.28, and 1.61, respectively; all *p*-values ≤ 0.01] and RV outflow tract dimension in women [β: 0.28; $p = 0.01$], except that the correlations of diastolic blood pressure and QTc interval with sit-up numbers were not significant.

DISCUSSION

This study is the largest to date for the Asian population to show the sex-specific cardiac structure and function of elite athletes compared to physically active controls and to determine the ECG and echocardiographic predictors of eliteness in the 2-min sit-ups. The main findings in the present study were that in men, greater QTc interval, LVMI, LV diastolic function, and RV systolic pressure, and lower diastolic blood pressure were found as independent predictors of falling in the elite strength category. By contrast, in women, the greater RV outflow tract dimension was the only independent predictor of being in the elite strength category.

Strength exercise training has been found to increase left ventricular mass, but not alter LV chamber size in both male and female athletes in prior studies (6, 9). Exercise related LV hypertrophy could be induced by an elongation of cardiac muscle cells resistant to chronic pressure overload, which is regulated partially by the renin-angiotensin system (24, 25). Prior studies have found greater changes in cardiac structure and function following strength exercises in male athletes than in female athletes compared to their sedentary controls (9, 10). The present study further confirmed the concept that greater LVMI and lateral mitral E'/A' ratio independently predict the performance of the sit-up exercise in physically active men but not women. The mechanisms for more marked cardiac structure changes in male athletes

TABLE 3 | Echocardiographic characteristics of elite male and female strength athletes and non-elite controls in the 2-min sit-up exercise.

	Male athletes (*N* = 580)			Female athletes (*N* = 79)		
	Elite (≥51 numbers) (*N* = 93)	Non-elite controls (<51 numbers) (N = 487)	*P*-value	Elite (≥50 numbers) (*N* = 14)	Non-elite controls (<50 numbers) (*N* = 65)	*P*-value
Aortic valve open (mm), PLAX	20.53 ± 1.72	20.35 ± 1.85	0.38	19.93 ± 2.05	18.66 ± 1.81	0.02
Aortic root dimension (mm), PALX	30.09 ± 2.45	29.83 ± 2.74	0.39	30.21 ± 3.70	26.92 ± 2.52	<0.001
LV posterior wall (mm), PLAX	8.41 ± 0.82	8.29 ± 0.83	0.20	7.07 ± 0.82	7.11 ± 0.75	0.83
LV internal dimension in diastole (mm), PLAX	49.60 ± 3.37	49.07 ± 3.48	0.17	44.64 ± 3.02	44.52 ± 2.88	0.88
LV internal dimension in systole (mm), PLAX	31.38 ± 3.08	30.37 ± 3.22	0.006	30.86 ± 3.67	28.12 ± 2.84	0.003
Interventricular septum, (mm), PLAX	8.55 ± 0.80	8.48 ± 0.89	0.52	7.29 ± 0.99	7.28 ± 0.78	0.97
RV wall thickness (mm), PLAX	4.65 ± 0.63	4.69 ± 0.59	0.54	4.49 ± 0.73	4.33 ± 0.45	0.30
RV outflow tract dimension in diastole (mm), PLAX	26.47 ± 3.72	26.30 ± 3.99	0.70	28.50 ± 4.04	25.72 ± 3.46	0.01
Left atrial dimension (mm), PLAX	32.97 ± 3.34	32.83 ± 4.00	0.74	33.21 ± 3.74	30.98 ± 4.94	0.11
LV mass (gm)	148.64 ± 24.01	144.35 ± 27.16	0.15	100.87 ± 21.93	100.40 ± 18.84	0.93
LV mass index (gm/m^2)	80.93 ± 11.73	77.52 ± 12.00	0.01	61.11 ± 9.19	61.65 ± 9.28	0.84
LV hypertrophy	1 [1.1]	5 [1.0]	0.96	0 [0.0]	2 [3.1]	0.50
RV hypertrophy	2 [2.2]	26 [5.3]	0.18	2 [14.3]	2 [3.1]	0.08
LV ejection fraction (%), PLAX	62.52 ± 5.36	62.50 ± 5.32	0.97	63.43 ± 5.68	61.20 ± 4.91	0.13
Tricuspid valve prolapse, PSAX	19 [51.4]	89 [49.7]	0.85	1 [20.0]	12 [63.2]	0.08
Aortic regurgitation ≥ mild grade	1 [1.1]	3 [0.6]	0.62	2 [14.3]	2 [3.1]	0.08
Mitral regurgitation ≥ mild grade	82 [88.2]	419 [86.0]	0.58	13 [92.9]	56 [86.2]	0.49
Pulmonary regurgitation ≥ mild grade	71 [76.3]	346 [71.0]	0.29	11 [78.6]	49 [75.4]	0.80
Tricuspid regurgitation ≥ mild grade	87 [93.5]	451 [92.6]	0.74	14 [100.0]	60 [92.3]	0.28
RV systolic pressure (mmHg)	29.53 ± 4.15	27.80 ± 3.73	<0.001	28.21 ± 3.19	27.49 ± 3.75	0.50
Mitral inflow power Doppler E-wave (m/s)	89.64 ± 14.62	87.32 ± 14.45	0.15	94.35 ± 10.49	96.75 ± 13.75	0.54
Mitral inflow power Doppler A-wave (m/s)	49.25 ± 9.10	49.25 ± 9.95	0.99	47.67 ± 8.32	50.85 ± 10.43	0.29
E/A ratio	1.88 ± 0.49	1.84 ± 0.47	0.41	2.03 ± 0.44	1.98 ± 0.50	0.68
Mitral lateral annulus tissue Doppler E' (cm/s)	18.89 ± 4.21	18.20 ± 4.04	0.13	19.75 ± 3.40	18.88 ± 3.90	0.44
Mitral lateral annulus tissue Doppler A' (cm/s)	8.50 ± 1.90	9.33 ± 4.99	0.11	9.52 ± 2.75	8.92 ± 2.19	0.37
E'/A' ratio	2.32 ± 0.70	2.11 ± 0.71	0.01	2.23 ± 0.80	2.23 ± 0.68	0.97

Continuous variables are expressed as mean ± SD (standard deviation), and categorical variables as N [%].
LV, left ventricle; RV, right ventricle;PLAX, echocardiographic parasternal long axis view; PSAX, echocardiographic parasternal short axis view.

TABLE 4 | Multivariable logistic regression analysis for elite male and female strength athletes.

	Elite male athletes (*N* = 580)			Elite female athletes (*N* = 79)		
Characteristics	**OR**	**95% CI**	***P*-value**	**OR**	**95% CI**	***P*-value**
Systolic blood pressure	1.007	0.984-1.031	0.55	1.058	0.984-1.137	0.12
Diastolic blood pressure	0.962	0.931-0.994	0.02	0.988	0.894-1.091	0.80
QTc interval	1.012	1.002-1.022	0.01	1.003	0.977-1.031	0.80
LV mass index	1.020	1.000-1.040	0.04	0.980	0.911-1.055	0.59
RV outflow tract dimension	1.016	0.958-1.078	0.59	1.262	1.042-1.529	0.01
RV systolic pressure	1.126	1.060-1.196	<0.001	1.016	0.836-1.233	0.87
E'/A' ratio	1.450	1.063-1.978	0.01	1.176	0.475-2.911	0.72

Data are presented as odds ratios (OR) and 95% CI (confidence intervals) using multiple logistic regression.
LV, left ventricle; RV, right ventricle.

could be reasoned in part by an increased QTc interval, indicating a longer cardiac systolic phase and possibly leading to greater LVMI. By contrast, for physically active women, both elite and non-elite athletes had lower blood pressure at rest, causing lower LV pressure overload and thus less physiological cardiac remodeling.

For the cardiovascular structural changes in women, the present study revealed that elite female strength athletes had

TABLE 5 | Multivariable linear regression analysis for sit-up numbers in men and women.

	Sit-up numbers in men (*N* = 580)			Sit-up numbers in women (*N* = 79)		
Characteristics	β	**95% CI**	***P*-value**	β	**95% CI**	***P*-value**
Systolic blood pressure	−0.012	−0.079-0.055	0.72	0.144	−0.086-0.375	0.21
Diastolic blood pressure	−0.060	−0.150-0.030	0.19	−0.130	−0.470-0.211	0.44
QTc interval	0.013	−0.016-0.043	0.37	−0.033	−0.108-0.041	0.37
LV mass index	0.068	0.011-0.124	0.01	−0.023	−0.243-0.196	0.83
RV outflow tract dimension	0.031	−0.139-0.201	0.72	0.676	0.118-1.233	0.01
RV systolic pressure	0.284	0.112-0.456	0.001	0.127	−0.418-0.672	0.64
E'/A' ratio	1.608	0.665-2.552	0.001	−0.191	−3.065-2.684	0.89

Data are presented as odds ratios (OR) and 95% CI (confidence intervals) using multiple logistic regression.
LV, left ventricle; RV, right ventricle.

greater aortic root and RV outflow tract dimensions, implying greater stroke volume compared with non-elite controls. In addition, elite female strength athletes tended to have a higher systolic blood pressure than non-elite controls, whereas elite male strength athletes had lower diastolic blood pressure. The findings clarified that the hemodynamic changes related to the sit-up test performance might differ by sex and thus influence the cardiac structure remodeling. Moreover, prior studies showed that in athletes, RV chamber size was positively associated with RV systolic pressure (26), which was not observed in both our male and female strength athletes. Whether these conflicts were due to racial/ethnic differences or the presence of unrecognized confounders in prior studies needs further investigation.

Strengths and Limitations

A strength of the present study is that participants were enrolled from the military under the same training program. In addition, the army base was a closed system, which implies that consistency in living circumstances. Third, the performance of the sit-up exercise was standardized, which could reduce observer bias.

Limitations arise from the fact that strength capacity was assessed only by the 2-min sit-up test, meaning the cardiac structure and function results might not be applied appropriately to the athletes of other exercise modalities. Second, there were only 79 military women in the present study, meaning results might lack sufficient power to detect some important predictors of elite athletes for sit-ups. Finally, we did not have the 12-lead ECG and echocardiographic data prior to training, and the ECG and echocardiographic changes could not be compared between elite athletes and non-elite controls.

CONCLUSION

Our study revealed that in the 2-min sit-up test, the cardiac characteristics differ between elite male and female athletes compared with their physically active non-elite controls. While greater QTc interval, RV systolic pressure, LV diastolic function, and LVMI predict elite strength athletes in men, greater RV chamber size characterizes elite strength athletes in women.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

This study was reviewed and approved by the Institutional Review Board of the Mennonite Christian Hospital (No. 16-05-008) in Taiwan. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

Y-KL wrote the paper. K-ZT made the statistical analyses. C-LH and J-TL raised critical comments for the paper. G-ML was the principal investigator for the study. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2021.737607/full#supplementary-material

REFERENCES

1. Lavie CJ, Ozemek C, Carbone S, Katzmarzyk PT, Blair SN. Sedentary behavior, exercise, and cardiovascular health. *Circ Res.* (2019) 124:799-815. doi: 10.1161/CIRCRESAHA.118.312669

2. Yang J, Christophi CA, Farioli A, Baur DM, Moffatt S, Zollinger TW, et al. Association between push-up exercise capacity and future cardiovascular events among active adult men. *JAMA Netw Open.* (2019) 2:e188341. doi: 10.1001/jamanetworkopen.2018.8341

3. Mandsager K, Harb S, Cremer P, Phelan D, Nissen SE, Jaber W. Association of cardiorespiratory fitness with long-term mortality among adults undergoing exercise treadmill testing. *JAMA Netw Open.* (2018) 1:e183605. doi: 10.1001/jamanetworkopen.2018.3605
4. Caselli S, Di Paolo FM, Pisicchio C, Pandian NG, Pelliccia A. Patterns of left ventricular diastolic function in Olympic athletes. *J Am Soc Echocardiogr.* (2015) 28:236-44. doi: 10.1016/j.echo.2014.09.013
5. Kim JH, Hollowed C, Liu C, Al-Badri A, Alkhoder A, Dommisse M, et al. Hypertension, and the emergence of a maladaptive cardiovascular phenotype among US football players. *JAMA Cardiol.* (2019) 4:1221-9. doi: 10.1001/jamacardio.2019.3909
6. Sharma S, Maron BJ, Whyte G, Firoozi S, Elliott PM, McKenna WJ. Physiologic limits of left ventricular hypertrophy in elite junior athletes: relevance to differential diagnosis of athlete's heart and hypertrophic cardiomyopathy. *J Am Coll Cardiol.* (2002) 40:1431-6. doi: 10.1016/S0735-1097(02)02270-2
7. Engel DJ, Schwartz A, Homma S. Athletic cardiac remodeling in US professional basketball players. *JAMA Cardiol.* (2016) 1:80-7. doi: 10.1001/jamacardio.2015.0252
8. Colan SD, Sanders SP, MacPherson D, Borow KM. Left ventricular diastolic function in elite athletes with physiologic cardiac hypertrophy. *J Am Coll Cardiol.* (1985) 6:545-9. doi: 10.1016/S0735-1097(85)80111-X
9. Pluim BM, Zwinderman AH, van der Laarse A, van der Wall EE. The athlete's heart. A meta-analysis of cardiac structure and function. *Circulation.* (2000) 101:336-44. doi: 10.1161/01.CIR.101.3.336
10. Barnes JN, Fu Q. Sex-specific ventricular and vascular adaptations to exercise. *Adv Exp Med Biol.* (2018) 1065:329-46. doi: 10.1007/978-3-319-77932-4_21
11. Lin GM, Liu K. An electrocardiographic system with anthropometrics *via* machine learning to screen left ventricular hypertrophy among young adults. *IEEE J Transl Eng Health Med.* (2020) 8:1800111. doi: 10.1109/JTEHM.2020.2990073
12. Lin GM, Li YH, Lee CJ, Shiang JC, Lin KH, Chen KW, et al. Rationale and design of the cardiorespiratory fitness and hospitalization events in armed forces study in Eastern Taiwan. *World J Cardiol.* (2016) 8:464-71. doi: 10.4330/wjc.v8.i8.464
13. Lin GM, Lu HH. A 12-lead ECG-based system with physiological parameters and machine learning to identify right ventricular hypertrophy in young adults. *IEEE J Transl Eng Health Med.* (2020) 8:1900510. doi: 10.1109/JTEHM.2020.2996370
14. Chao WH, Su FY, Lin F, Yu YS, Lin GM. Association of electrocardiographic left and right ventricular hypertrophy with physical fitness of military males: the CHIEF study. *Eur J Sport Sci.* (2019) 19:1214-20. doi: 10.1080/17461391.2019.1595741
15. Tsai KZ, Lai SW, Hsieh CJ, Lin CS, Lin YP, Tsai SC, et al. Association between mild anemia and physical fitness in a military male cohort: the CHIEF study. *Sci Rep.* (2019) 9:11165. doi: 10.1038/s41598-019-47625-3
16. Du Bois D, Du Bois EF. A formula to estimate the approximate surface area if height and weight be known. *Arch Intern Med.* (1916) 17:863-71. doi: 10.1001/archinte.1916.00080130010002
17. Tsai KZ, Lin JW, Lin F, Su FY, Li YH, Lin YP, et al. Association of betel nut chewing with exercise performance in a military male cohort: the CHIEF study. *J R Army Med Corps.* (2018) 164:399-404. doi: 10.1136/jramc-2017-000899
18. Lin YK, Tsai KZ, Han CL, Lin YP, Lee JT, Lin GM. Obesity phenotypes and electrocardiographic characteristics in physically active males: CHIEF study. *Front Cardiovasc Med.* (2021) 8:738575. doi: 10.3389/fcvm.2021.738575
19. Liu PY, Tsai KZ, Lima JAC, Lavie CJ, Lin GM. Athlete's heart in Asian military males: the CHIEF Heart study. *Front Cardiovasc Med.* (2021) 8:725852. doi: 10.3389/fcvm.2021.725852
20. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr.* (2015) 28:1-39.e14. doi: 10.1016/j.echo.2014.10.003
21. Devereux RB, Casale PN, Eisenberg RR, Miller DH, Kligfield P. Electrocardiographic detection of left ventricular hypertrophy using echocardiographic determination of left ventricular mass as the reference standard. Comparison of standard criteria, computer diagnosis and physician interpretation. *J Am Coll Cardiol.* (1984) 3:82-7. doi: 10.1016/S0735-1097(84)80433-7
22. Ojeda AH, Galdames MS, Barahona-Fuentes G. Validity and reliability of the muscular fitness test to evaluate body strength-resistance. *Apunts Sports Med.* (2020) 55:128-36. doi: 10.1016/j.apunsm.2020.08.002
23. Bazett HC. An analysis of the time-relations of the electrocardiograms. *Heart.* (1920) 7:353-70.
24. Dostal DE. The cardiac renin-angiotensin system: novel signaling mechanisms related to cardiac growth and function. *Regul Pept.* (2000) 91:1-11. doi: 10.1016/S0167-0115(99)00123-8
25. Fernandes T, Hashimoto NY, Magalhães FC, Fernandes FB, Casarini DE, Carmona AK, et al. Aerobic exercise training-induced left ventricular hypertrophy involves regulatory MicroRNAs, decreased angiotensin-converting enzyme-angiotensin ii, and synergistic regulation of angiotensin-converting enzyme 2-angiotensin (1-7). *Hypertension.* (2011) 58:182-9. doi: 10.1161/HYPERTENSIONAHA.110.168252
26. D'Andrea A, Riegler L, Morra S, Scarafile R, Salerno G, Cocchia R, et al. Right ventricular morphology and function in top-level athletes: a three-dimensional echocardiographic study. *J Am Soc Echocardiogr.* (2012) 25:1268-76. doi: 10.1016/j.echo.2012.07.020

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Impact of Physical Activity on All-Cause Mortality According to Specific Cardiovascular Disease

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Background: Patients with cardiovascular disease (CVD) tend to have higher mortality rates and reduced physical activity (PA). We aimed to evaluate the effect of PA on mortality in older adults with specific CVD.

Methods: We enrolled 68,223 participants (n = 23,871 with CVD, n = 44,352 without CVD) aged ≥65 years with available physical activity data between 2005 and 2012 from the Korean National Health Insurance Service of Korea-Senior database. CVD was defined as a history of ischemic stroke, transient ischemic attack, heart failure, myocardial infarction, and peripheral artery disease.

Results: Patients with CVD were older than those without CVD. Compared with the sedentary group, the physically active groups with and without CVD had a lower incidence and risk of all-cause death during a median follow up period of 42 (interquartile range 30–51) months. A 500 metabolic equivalent task-min/week increase in PA resulted in an 11% and 16% reduction in the risk of mortality in the non-CVD and CVD groups, respectively. With regard to specific CVDs, the risk of mortality progressively reduced with increasing PA in patients with heart failure or myocardial infarction. However, the reduction reached a plateau in patients with stroke or peripheral artery disease, but was significantly greater in patients with stroke (20% vs. without stoke, 11%, P_{int} = 0.006) or heart failure (13% vs. without heart failure, 11%; P_{int} = 0.045)

Conclusions: PA was associated with a reduced risk of all-cause mortality in older adults with and without CVD. The benefits of PA in patients with CVD, especially patients with stroke or heart failure, were greater than those without.

Keywords: physical activity, all-cause mortality, cardiovascular disease, senior adults, stroke, heart failure

INTRODUCTION

The inverse relationship between physical activity and mortality has been proven in previous studies (1, 2). Current guidelines recommend that adults should perform at least 150–300 min/week of moderate-intensity physical activity, 75–150 min/week of vigorous physical activity, or 500–1,000 metabolic equivalent task (MET)-min/week of moderate-to-vigorous physical activity

(3, 4). Satisfying recommended guidelines for physical activity is associated with a reduced risk of all-cause mortality, cardiovascular mortality, morbidity, and frailty compared with being inactive (5, 6).

The existing evidence on the dose relationship between exercise and outcomes has mostly been obtained from studies on healthy people (7–9). Individuals with cardiovascular disease (CVD) have higher mortality and morbidity, but also tend to have a sedentary lifestyle and less physical activity than those without CVD (10). While physical activity is generally recommended for secondary CVD prevention according to current guidelines, there are limited data regarding the relationship between physical activity and mortality, specifically among patients with pre-existing CVD (11–13). Recently, Jeong et al. reported that the benefit in the secondary prevention group was greater than that in the primary prevention group: every 500 MET-min/week increase in physical activity resulted in a 14 and 7% reduction in the risk of mortality in the secondary and primary prevention groups, respectively (interaction $P < 0.001$). However, the benefits of physical activity have not been precisely elucidated, especially in elderly patients with CVD (14).

In this study, we analyzed a population-based cohort to investigate the effect of physical activity on mortality in elderly populations with or without CVD. The aims of this study were as follows: (i) to identify the relationship between physical activity and mortality among elderly patients with and without CVD and (ii) to compare the associations between physical activity and mortality according to specific CVD.

METHODS

Study Population

Data were collected from the National Health Insurance Service of Korea (NHIS)-Senior database, which includes data for 5,58,147 individuals recruited by 10% simple random sampling from a total of 5.5 million populations aged ≥60 years in the National Health Information Database (15, 16). Individuals covered by the insurance system undergo a general health screening every 2 years. The NHIS-Senior database includes data on the following parameters: sociodemographic and socioeconomic information, health check-up examinations, insurance status, and records of participants' medical histories. This study was approved by the Institutional Review Board of the Yonsei University Health System (4-2021-0894). The study complied with the requirements of the Declaration of Helsinki, and the need for informed consent was waived.

From the Korean NHIS-Senior database, 68,223 participants aged ≥65 years with available physical activity data between 2005 and 2012 were enrolled in this study and followed up until December 2014. Each individual's claims records were reviewed for a history of CVD from 2002 until the date of the health check-up. Participants with prior myocardial infarction, peripheral artery disease, other vascular diseases, ischemic/hemorrhagic stroke, transient ischemic attack, and heart failure were considered to have CVD. Patients with one or more of the CVD were based on the first diagnosed CVD. A flow chart of the study population enrollment ant analysis is presented in **Supplementary Figure 1**.

Information on comorbid conditions was identified from the International Classification of Disease-10 codes, and prescription medications before the index date (**Supplementary Table 1**). In order to ensure diagnostic accuracy, participants were considered to have comorbidities when the condition was a discharge diagnosis or was confirmed at least twice in an outpatient setting, as in our previous studies (15–24).

Physical Activity Level Assessment

The leisure-time physical activity level was assessed using self-reported intensity and frequency of exercise via structured questionnaires using a 7-day recall method (25). The survey included three questions that assessed the usual frequency (days per week) of (i) vigorous physical activity for at least 20 min, (ii) moderate physical activity for at least 30 min, and (iii) light physical activity for at least 30 min. Vigorous physical activity was defined as intense exercise that caused severe shortness of breath, such as running and cycling at high speed. Moderate physical activity was defined as exercise that caused mild shortness of breath, such as brisk walking and cycling at usual speed. Light physical activity was defined as walking at a slow or leisurely pace. Completion of physical activity level assessment was performed during health check-up between 2005 and 2012 and followed up until December 2014.

Ratings of 3.3, 4.0, and 8.0 METs were assigned for light, moderate, and vigorous physical activity, respectively (20). The physical activity-related energy expenditure (MET-min/week) was calculated by summing the products of frequency, intensity, and duration of light, moderate, and vigorous physical activity. The participants were stratified on the basis of their weekly total physical activity levels as follows: (1) sedentary group: no leisure-time physical activity beyond basic movements; (2) insufficiently active group: energy expenditure between 1 and 499 MET-min/week; (3) active group: energy expenditure between 500 and 999 MET-min/week; (4) highly active: energy expenditure between 1,000 and 1,499 MET-min/week; and (5) very highly active group: energy expenditure ≥1,500 MET-min/week according guidelines and previous studies (3, 4, 20).

Outcomes

The endpoint was all-cause mortality. Using unique personal identification numbers, information on death (date and cause of death) was confirmed from the National Population Registry of the Korea National Statistical Office, in which deaths are centrally registered on the basis of death certificates (15–24). The NHIS and National Statistical Office are national agencies serving the entire Korean population, so this approach provides a complete event check. We also analyzed cause-specific mortality based on the causes of death confirmed by the Korea National Statistical Office.

Statistical Analysis

Descriptive statistics were used to characterize baseline characteristics and comorbidities. Categorical variables are reported as frequencies (percentages). Continuous variables

are expressed as medians with interquartile ranges. Categorical variables were compared using Fisher's exact test or Pearson's chi-square test, and continuous variables were compared using Student's *t*-test.

Incidence rates of mortality were calculated by dividing the number of events by person-time at risk and presented as the rate per 1,000 person-years. We analyzed the hazard ratios and 95% confidence intervals or mortality according to the physical activity level. Competing risk regression was performed using the Fine-Gray sub distribution hazard model, with mortality as a competing risk for mortality events. Multivariable regression models were constructed by adjusting for age, sex, body mass index, smoking, alcohol consumption, hypertension, diabetes mellitus, dyslipidemia, chronic kidney

TABLE 1 | Baseline characteristics according to cardiovascular disease.

Variables	Total (*N* = 68,223)	Cardiovascular disease (*N* = 23,871)	No cardiovascular disease (*N* = 44,352)	*P* value
Demographic				
Age, years	73.6 ± 5.7	74.7 ± 6.0	73.0 ± 5.4	<0.001
Male	26,483 (38.8)	8,299 (34.8)	18,184 (41.0)	<0.001
Body mass index	23.8 ± 3.4	24.1 ± 3.5	23.6 ± 3.3	<0.001
Waist	83.1 ± 8.9	84.0 ± 9.2	82.6 ± 8.8	<0.001
Systolic blood pressure	131.3 ± 17.1	131.2 ± 17.2	131.3 ± 17.0	0.430
Diastolic blood pressure	78.3 ± 10.5	77.9 ± 10.6	78.4 ± 10.4	<0.001
Smoking	16,718 (24.5)	5,136 (21.5)	11,582 (26.1)	<0.001
Alcohol	13,431 (19.7)	3,430 (14.4)	10,001 (22.5)	<0.001
Income status				<0.001
Low	20,927 (30.7)	7,214 (30.2)	13,713 (30.9)	-
Mid	15,018 (22.0)	5,110 (21.4)	9,908 (22.3)	
High	32,278 (47.3)	11,547 (48.4)	20,731 (46.7)	
Risk scores				
Hospitality frailty risk score	2.0 ± 4.2	3.6 ± 5.8	1.1 ± 2.5	<0.001
Charlson comorbidity index	3.2 ± 2.7	5.0 ± 2.8	2.2 ± 2.2	<0.001
Pre-existing non-cardiovascular disease				
Hypertension	41,726 (61.2)	20,279 (85.0)	21,447 (48.4)	<0.001
Diabetes mellitus	14,767 (21.6)	7,430 (31.1)	7,337 (16.5)	<0.001
Dyslipidemia	35,048 (51.4)	17,202 (72.1)	17,846 (40.2)	<0.001
Chronic kidney disease	1,937 (2.8)	1,236 (5.2)	701 (1.6)	<0.001
COPD	8,505 (12.5)	4,302 (18.0)	4,203 (9.5)	<0.001
Malignancy	11,141 (16.3)	4,881 (20.4)	6,260 (14.1)	<0.001
Osteoporosis	28,476 (41.7)	12,150 (50.9)	16,326 (36.8)	<0.001
Pre-existing cardiovascular disease				
Heart failure	8,982 (13.2)	8,982 (37.6)	-	-
Ischemic stroke or TIA	13,172 (19.3)	13,172 (55.2)		
Previous MI	3,126 (4.6)	3,126 (13.1)		
Peripheral artery disease	6,623 (9.7)	6,623 (27.7)		
Laboratory findings				
Fasting blood glucose	106.1 ± 31.6	108.5 ± 34.5	104.8 ± 29.8	<0.001
Total cholesterol	196.1 ± 40.5	190.7 ± 41.8	199.0 ± 39.5	<0.001
Triglyceride	140.0 ± 80.9	142.4 ± 80.9	138.8 ± 80.9	<0.001
LDL-cholesterol	116.0 ± 37.9	111.4 ± 38.6	118.5 ± 37.3	<0.001
HDL-cholesterol	53.1 ± 25.4	51.6 ± 23.5	53.9 ± 26.4	<0.001
AST	26.5 ± 19.1	26.1 ± 18.6	26.8 ± 19.4	<0.001
ALT	21.9 ± 18.0	21.6 ± 17.3	22.1 ± 18.4	<0.001
Gamma-GT	33.6 ± 52.8	32.9 ± 46.6	34.0 ± 55.8	<0.001
Serum creatinine	1.0 ± 1.0	1.1 ± 1.2	1.0 ± 0.8	0.004
eGFR	71.2 ± 17.8	67.9 ± 19.1	73.0 ± 16.8	<0.001

**Values are presented as mean ± standard deviation, median (Q1, Q3, quartiles [25th and 75th percentiles]), or %.*

COPD, chronic obstructive pulmonary disease; TIA, transient ischemic attack; MI, myocardial infarction; LDL, low-density lipoprotein; HDL, high-density lipoprotein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; Gamma-GT, gamma-glutamyl transpeptidase; eGFR, estimated glomerular filtration rate.

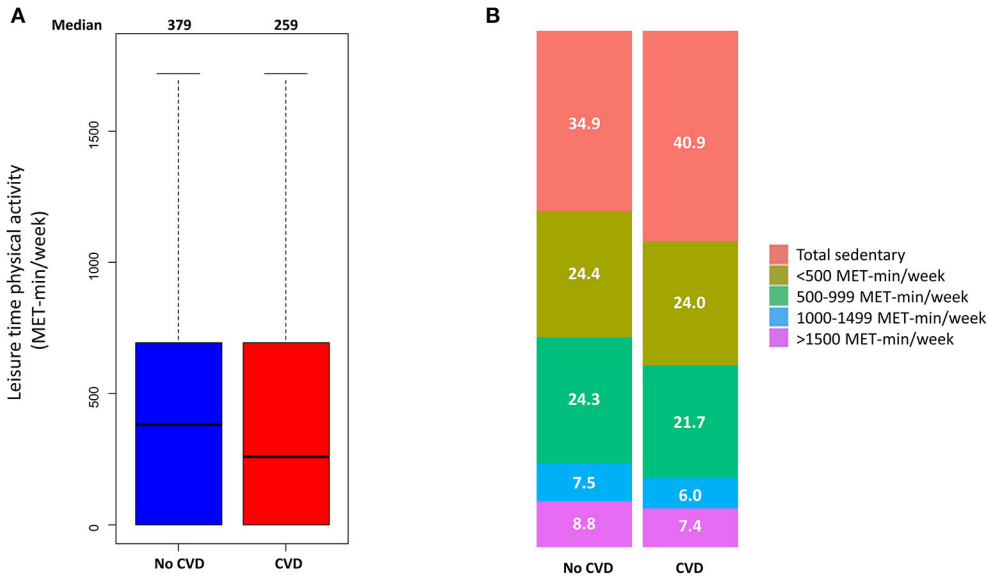

FIGURE 1 | Physical activity of participants with or without cardiovascular disease (CVD). **(A)** Box and whiskers plot for physical activity, **(B)** box plot for the proportions of physical activity classified into five categories.

disease, chronic obstructive pulmonary disease, osteoporosis, malignancy, hospital frailty risk score, and Charlson comorbidity index score. We used cubic spline curves to examine the effects of continuous values of physical activity (0 MET-min/week as reference) on all-cause mortality. We conducted subgroup analyses for the primary outcome stratified by age, sex, body mass index, and other baseline comorbidities.

All tests were two-tailed, and statistical significance was set at $p < 0.05$. Statistical analyses were conducted using R programming version 4.0.3 (The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

The baseline characteristics of the 68,223 study subjects are shown in **Table 1**. The median age of the participants was 73.6 years, and 38.8% were men. In the study population, 35.0% of participants had CVD ($n = 23,871$) and the remaining 65.0% ($n = 44,352$) had no history of CVD. In the CVD group, participants were older (74.7 vs. 73.0 years) and the proportion of men was lower (34.8 vs. 41.0%) than that in the non-CVD group ($P < 0.001$).

The range of physical activity level of the study population was 0-2653 MET-min/week. The median physical activity levels were 259 and 379 MET-min/week in the CVD and non-CVD groups, respectively (**Figure 1**). Participants with CVD were less physically active than those without CVD ($P < 0.001$). The proportion of sedentary participants was higher in the CVD group than in the non-CVD group (40.9 and 34.9%, respectively, $P < 0.001$) (**Figure 1**). **Supplementary Figure 2** shows the proportions of participants with specific CVDs. There were differences in the median physical activity according to the history of stroke or heart failure, with no significant differences in physical activity in patients with peripheral artery disease or myocardial infarction.

Baseline characteristics of the whole study population, CVD group, and non-CVD group according to leisure-time physical activity are shown in **Supplementary Tables 2–4**, respectively.

Impact of Physical Activity on All-Cause Mortality According to CVD

The median follow-up duration was 42 months (interquartile range, 30–51). **Figure 2A** shows the incidence rate of mortality per 1,000 person-years stratified according to the presence of CVD and the level of physical activity. In participants without CVD, the unadjusted risk of all-cause mortality showed a J-shaped association with the amount of physical activity. After adjustment for age, sex, body mass index, and other baseline comorbidities, mortality risk was the highest in participants with a sedentary lifestyle and the lowest in participants with a physical activity level of 1000–1499 MET-min/week. A very high level of physical activity (≥1,500 MET-min/week) was associated with a significantly higher risk of mortality than the trough.

In participants with CVD, the unadjusted risk of mortality was reduced with a higher level of physical activity. After adjusting for age, sex, body mass index, and other baseline comorbidities, mortality risk was the highest in participants with a sedentary lifestyle and the lowest in participants with a physical activity level of >1,500 MET-min/week (**Table 2**). While individuals without CVD benefited the most with physical activity levels between 1,000 and 1,499 MET-min/week, the benefits in those with CVD progressively increased at levels ≥1,500 MET-min/week. The adjusted mortality risk of individuals with CVD who performed a high level of physical activity (≥1,500 MET-min/week) was shown to be lower than that of their counterparts without CVD.

The cubic spline curve is shown in **Figure 2B**. Every 500 MET-min/week increase in physical activity resulted in an 11% and 16% reduction in the risk of mortality in the non-CVD and CVD groups, respectively (interaction $P = 0.247$). As physical activity increased, the difference in the adjusted hazard ratios between the two groups increased.

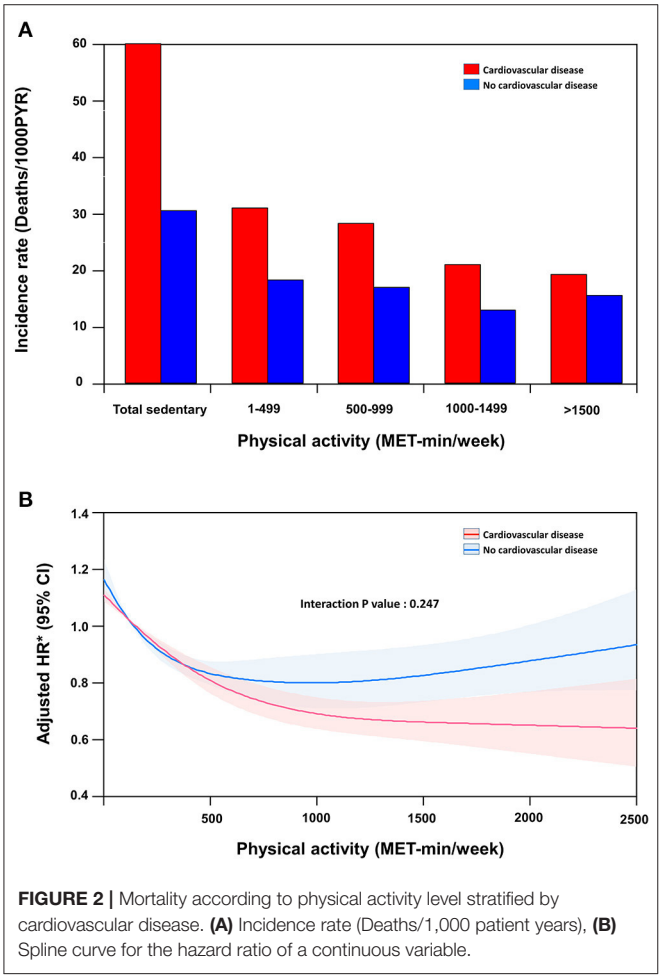

FIGURE 2 | Mortality according to physical activity level stratified by cardiovascular disease. **(A)** Incidence rate (Deaths/1,000 patient years), **(B)** Spline curve for the hazard ratio of a continuous variable.

The risks of cardiovascular and non-cardiovascular deaths according to the level of physical activity were similar to those of all-cause mortality (**Supplementary Tables 5, 6**). In the subgroup analysis, the associations between physical activity level and mortality were consistent, regardless of age, sex, body mass index, and other comorbidities (**Supplementary Table 7**).

Impact of Physical Activity on All-Cause Mortality According to Specific CVD

The incidence rates and adjusted hazard ratios according to the physical activity level for each CVD are presented in **Table 3**. The incidence and risk of all-cause death were reduced in the physically active group, irrespective of the specific CVD.

Figure 3 shows the association between the risk of mortality and continuous measures of physical activity using restricted cubic spline curves according to each CVD. The risk of mortality progressively reduced with increase in physical activity in patients with heart failure (**Figure 3B**) or myocardial infarction (**Figure 3C**), but reached a plateau in patients with stroke (**Figure 3A**) or peripheral artery disease (**Figure 3D**). The differences in reduction in the risk of mortality according to the presence of specific CVD were significant in patients with heart failure and stroke, and showed the same trend in myocardial infarction. A 500 MET-min/week increase in physical activity was associated with a 20% and 11% (interaction $P = 0.006$), and 13 and 11% (interaction $P = 0.045$) reduction in the risk of mortality in participants with and without stroke and with and without heart failure, respectively.

DISCUSSION

The present study investigated the association between physical activity and mortality according to the presence of specific CVDs

TABLE 2 | Leisure-time physical activity and the risk of all-cause mortality stratified according to the presence of cardiovascular disease.

	Patients	Deaths	Deaths/1,000 PYR	Unadjusted HR (95% CI)	*P* value	Adjusted HR (95% CI)	*P* value
With cardiovascular disease							
Sedentary	9,760	1,739	60.0	Reference		Reference	
1–499 MET-min/week	5,721	560	30.9	0.51 (0.47–0.56)	<0.001	0.69 (0.63–0.76)	<0.001
500–999 MET-min/week	5,178	463	28.2	0.47 (0.42–0.52)	<0.001	0.71 (0.64–0.79)	<0.001
1,000–1,499 MET-min/week	1,444	99	21.0	0.35 (0.28–0.43)	<0.001	0.59 (0.48–0.72)	<0.001
≥1,500 MET-min/week	1,768	112	19.2	0.32 (0.26–0.38)	<0.001	0.52 (0.43–0.63)	<0.001
Without cardiovascular disease							
Sedentary	15,494	1,567	30.5	Reference		Reference	
1–499 MET-min/week	10,838	668	18.2	0.60 (0.54–0.65)	<0.001	0.75 (0.69–0.83)	<0.001
500–999 MET-min/week	10,782	610	16.9	0.55 (0.50–0.61)	<0.001	0.73 (0.66–0.80)	<0.001
1,000–1,499 MET-min/week	3,321	146	12.9	0.42 (0.35–0.50)	<0.001	0.62 (0.52–0.74)	<0.001
≥1,500 MET-min/week	3,917	204	15.4	0.50 (0.44–0.58)	<0.001	0.72 (0.62–0.83)	<0.001

**Adjusted for age, sex, body mass index, hypertension, diabetes mellitus, dyslipidemia, chronic kidney disease, chronic obstructive pulmonary disease, malignancy, smoking, alcohol, osteoporosis, hospital frailty risk score, Charlson comorbidity index score.*

PYR, person-years; MET, metabolic equivalent task; HR, hazard ratio; CI, confidence interval.

TABLE 3 | Leisure-time physical activity and the risk of all-cause mortality stratified according to the presence of each cardiovascular disease.

	Patients	Deaths	Deaths/ 1,000 PYR	Adjusted HR (95% CI)	*P* value	Patients	Deaths	Deaths, /1,000 PYR	Adjusted HR (95% CI)	*P* value
Stroke or TIA	**With previous stroke or TIA**					**Without previous stroke or TIA**				
Sedentary	5,850	1,196	70.61	Reference		19,404	2,110	33.28	Reference	
1–499 MET-min/week	3,178	312	30.90	0.62 (0.54–0.70)	<0.001	13,381	916	20.49	0.77 (0.71–0.83)	<0.001
500–999 MET-min/week	2,905	256	27.85	0.61 (0.53–0.70)	<0.001	13,055	817	18.85	0.77 (0.70–0.83)	<0.001
1,000–1,499 MET-min/week	751	50	20.29	0.49 (0.37–0.66)	<0.001	4,014	195	14.32	0.65 (0.56–0.75)	<0.001
≥1,500 MET-min/week	935	64	20.74	0.49 (0.38-0.63)	<0.001	4750	252	15.75	0.69 (0.60-0.78)	<0.001
Heart failure	**With previous heart failure**					**Without previous heart failure**				
Sedentary	3,936	776	67.34	Reference		21,318	2,530	36.76	Reference	
1–499 MET-min/week	2,154	283	42.40	0.82 (0.71–0.94)	0.006	14,405	945	19.64	0.70 (0.64–0.75)	<0.001
500–999 MET-min/week	1,825	218	37.92	0.84 (0.71–0.98)	0.024	14,135	855	18.27	0.69 (0.64–0.75)	<0.001
1,000–1,499 MET-min/week	487	38	24.05	0.56 (0.40–0.79)	<0.001	4,278	207	14.27	0.61 (0.53–0.70)	<0.001
≥1,500 MET-min/week	580	44	23.42	0.54 (0.40–0.74)	<0.001	5,105	272	15.80	0.65 (0.57–0.74)	<0.001
Myocardial infarction	**With previous myocardial infarction**					**Without previous myocardial infarction**				
Sedentary	1,273	281	78.12	Reference		23,981	3,025	39.42	Reference	
1–499 MET-min/week	727	96	44.07	0.74 (0.58–0.94)	0.016	15,832	1,132	21.51	0.72 (0.67–0.77)	<0.001
500–999 MET-min/week	662	84	40.68	0.73 (0.57–0.94)	0.015	15,298	989	19.60	0.71 (0.66–0.77)	<0.001
1,000–1,499 MET-min/week	187	21	35.09	0.75 (0.48–1.18)	0.215	4,578	224	14.46	0.59 (0.51–0.68)	<0.001
≥1,500 MET-min/week	277	19	21.39	0.43 (0.27–0.68)	<0.001	5,408	297	16.32	0.65 (0.57–0.73)	<0.001
Peripheral artery disease	**With previous peripheral artery disease**					**Without previous peripheral artery disease**				
Sedentary	2,452	321	44.02	Reference		22,802	2,985	40.86	Reference	
1–499 MET-min/week	1,635	134	26.20	0.72 (0.59–0.89)	0.002	14,924	1,094	22.02	0.72 (0.67–0.78)	<0.001
500–999 MET-min/week	1,520	97	20.09	0.61 (0.49–0.78)	<0.001	14,440	976	20.46	0.73 (0.67–0.78)	<0.001
1,000–1,499 MET-min/week	467	35	23.28	0.78 (0.54–1.12)	0.173	4,298	210	14.40	0.58 (0.50–0.67)	<0.001
≥1,500 MET-min/week	549	35	19.68	0.61 (0.43–0.87)	0.006	5,136	281	16.23	0.63 (0.56–0.72)	<0.001

**Adjusted for age, sex, body mass index, hypertension, diabetes mellitus, dyslipidemia, chronic kidney disease, chronic obstructive pulmonary disease, malignancy, smoking, alcohol, osteoporosis, hospital frailty risk score, Charlson comorbidity index score.*

PYR, person-years; MET, metabolic equivalent task; HR, hazard ratio; CI, confidence interval.

in a nationwide elderly population. Our principal finding was that physical activity was associated with a reduced risk of all-cause mortality in older adults with or without CVD, and the benefits of physical activity were greater in patients with CVD than in those without CVD. Second, physical activity was associated with a reduced risk of all-cause mortality in older adults irrespective of the specific CVD. Third, the risk of mortality progressively reduced with increasing physical activity in patients with heart failure or myocardial infarction, but reached a plateau in patients with stroke or peripheral artery disease. Finally, the benefits of physical activity were greater, in patients with stroke or heart failure.

CVD and Physical Activity

Contemporary guidelines emphasize that physical activity can make people feel better, function better, sleep better, and reduce the risk of many chronic diseases. The suggested target range of physical activity is 500–1,000 MET-min/week of aerobic physical activity, which is equivalent to 150–300 min of moderate-intensity or 75–150 min of vigorous physical activity per week. This recommendation is based on observations that the greatest survival benefit is provided by achieving a physical activity level of 500–1,000 MET-min/week (2). The findings of the present study are consistent with these conclusions.

Previous studies that showed the survival benefits of physical activity primarily focused on healthy individuals and did not consider the presence of CVD (or specific CVD) (7–9). The present study provides a novel perspective on the preventive role of physical activity in patients with CVD in an elderly population. In the present study, individuals with CVD tended to have lower level of physical activity. Not only were they typically older with multiple comorbidities, but their cardiac condition also limited their physical capacity. Nevertheless, clinicians should emphasize the importance of a physically active lifestyle for those patients, as they may experience greater benefits than their counterparts without CVD at the same levels of physical activity.

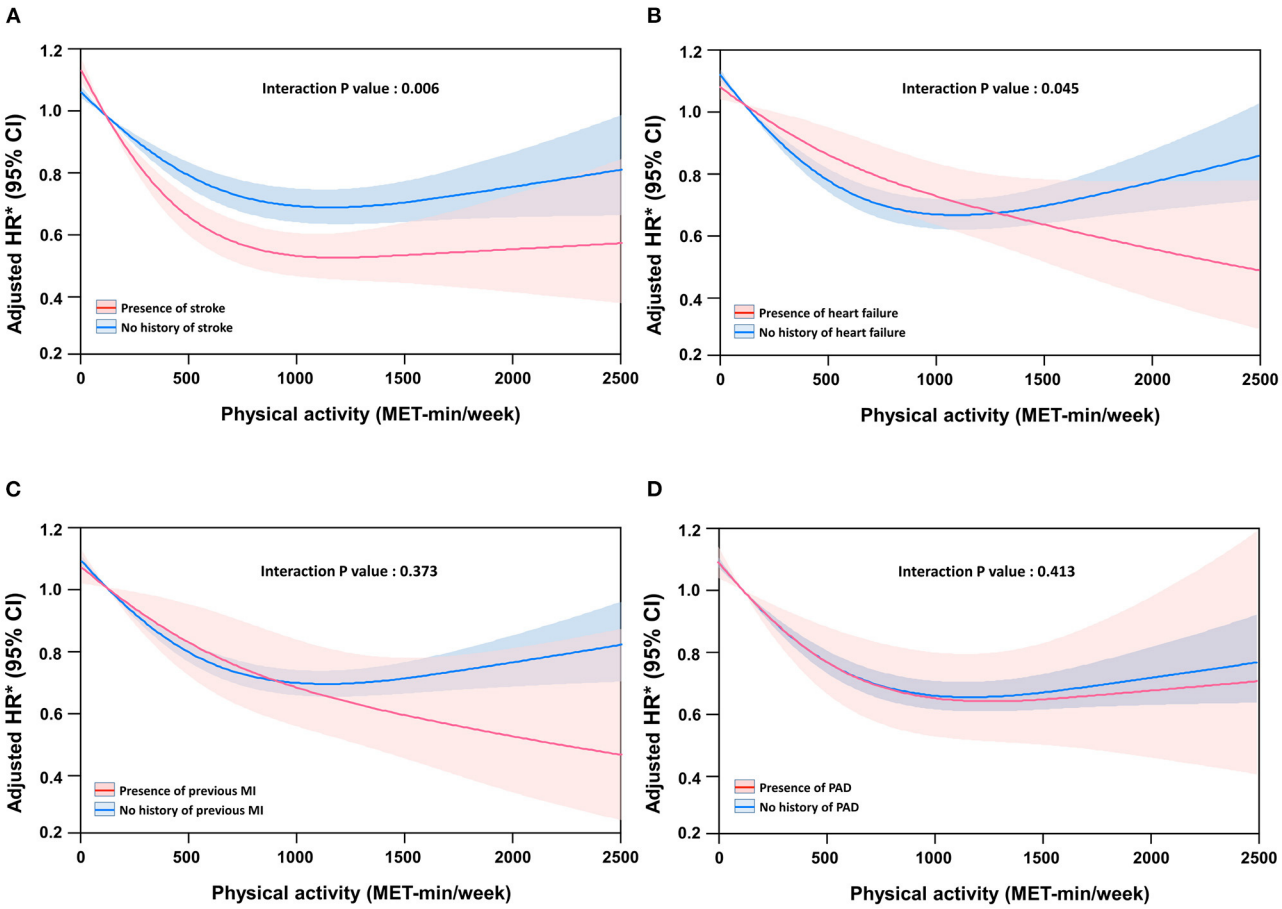

FIGURE 3 | Spline curve of all-cause mortality according to physical activity level in patients with specific cardiovascular disease. **(A)** Stroke, **(B)** heart failure, **(C)** previous myocardial infarction (MI), and **(D)** peripheral artery disease (PAD).

Specific CVD and Physical Activity

Strong evidence supports exercise-based cardiac rehabilitation in patients with coronary heart disease and exercise training in patients with chronic heart failure (26–28). In previous studies on peripheral artery disease, low-intensity exercise was significantly less effective than high-intensity exercise and was not significantly different from the non-exercise control in improving the 6-min walk distance (29). However, recommendations on the level of physical activity for specific CVD groups are not consistent. The European Society of Cardiology guidelines on CVD prevention encourage at least 150–300 min/week of moderate-intensity or 75–150 min/week of vigorous aerobic physical activity (13). Meanwhile, the guidelines for stable ischemic heart disease from the American College of Cardiology Foundation and American Heart Association recommend 30–60 min of moderate-intensity aerobic activity for at least 5 days and preferably 7 days per week (30). The latter states that the recommended level of physical activity is in line with that recommended for healthy adults (31, 32).

In this study, physical activity was associated with a reduced risk of all-cause mortality in older adults irrespective of the specific CVD, but the effect was greater in patients with stroke or heart failure. Notably, the risk of mortality was progressively reduced by increasing physical activity in patients with heart failure or myocardial infarction. The benefits were not significantly different between patients with and without peripheral artery disease. In the case of peripheral artery disease, there is a possibility that the effect of physical activity was not fully elucidated, as peripheral artery disease may have restricted the amount of exercise. However, all data suggest that a physical activity level of 500 MET-min/week should be considered as the minimum requirement for patients with CVD.

Limitations

This study had several limitations. First, this retrospective and non-randomized cohort study cannot prove or disprove causal relationships. Second, we relied on self-reported questionnaires of physical activity collected at specific time points. The questionnaires surveyed lifestyle behaviors during the preceding 1 week. Information obtained from questionnaires may not represent the level of actual physical activity, and behavioral changes that occur during follow-up could be assessed in our study. However, the large sample size of this study reduced the level of potential uncertainty and provided a

reliable approximation of the level of physical activity at the population level. Third, only physical activity during leisure time was analyzed, but various types of physical activity, such as household, occupation, and transportation, that can occur throughout the day were not included or analyzed. Firth, the existence of unadjusted confounders could not be excluded despite strict statistical adjustments. Confounders such as diet habits, changes in medication use, and compliance were not adjusted for in the analysis. Finally, the existence of CVD was determined using claims data, so there is a possibility of errors due to incorrect coding. To minimize this problem, definitions that were verified in previous studies using sample cohorts of the Korean NHIS were applied, and the diagnostic reliability of the cohort data was high (15–24).

CONCLUSION

Physical activity is important for improved outcomes in elderly patients with CVD and should be routinely recommended. Physical activity was associated with a reduced risk of all-cause mortality in older adults with or without CVD. The benefits of physical activity were greater in patients with CVD, especially patients with stroke of heart failure, than those in patients without CVD.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institutional Review Board of the Yonsei University Health System (4-2021-0894). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

M-HK and J-HS contributed to the conception and design of the work, interpretation of data, and drafting of the manuscript. P-SY and BJ are joint senior authors and contributed to the conception and design of the work and critical revision of the manuscript. EJ and P-SY contributed to the acquisition and analysis of data. M-NJ, HY, T-HK, H-NP, M-HL, and GL contributed to the conception and design of the work and revision of the manuscript. All authors read and approved the manuscript before its submission.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.811058/full#supplementary-material

REFERENCES

1. Moore SC, Patel AV, Matthews CE, Berrington de Gonzalez A, Park Y, Katki HA, et al. Leisure time physical activity of moderate to vigorous intensity and mortality: a large pooled cohort analysis. *PLoS Med.* (2012) 9:e1001335. doi: 10.1371/journal.pmed.1001335
2. Arem H, Moore SC, Patel A, Hartge P, Berrington de Gonzalez A, Visvanathan K, et al. Leisure time physical activity and mortality: a detailed pooled analysis of the dose-response relationship. *JAMA Intern Med.* (2015) 175:959–67. doi: 10.1001/jamainternmed.2015.0533
3. World Health Organization. *WHO Guidelines on Physical Activity and Sedentary Behaviour*. Washington, DC: World Health Organization (2020).
4. Piercy KL, Troiano RP, Ballard RM, Carlson SA, Fulton JE, Galuska DA, et al. The Physical Activity Guidelines for Americans. *JAMA.* (2018) 320:2020–8. doi: 10.1001/jama.2018.14854
5. Chou WT, Tomata Y, Watanabe T, Sugawara Y, Kakizaki M, Tsuji I. Relationships between changes in time spent walking since middle age and incident functional disability. *Prev Med.* (2014) 59:68–72. doi: 10.1016/j.ypmed.2013.11.019
6. Rogers NT, Marshall A, Roberts CH, Demakakos P, Steptoe A, Scholes S. Physical activity and trajectories of frailty among older adults: evidence from the English Longitudinal Study of Ageing. *PLoS ONE.* (2017) 12:e0170878. doi: 10.1371/journal.pone.0170878
7. Calle EE, Rodriguez C, Jacobs EJ, Almon ML, Chao A, McCullough ML, et al. The American Cancer Society Cancer Prevention Study II Nutrition Cohort: rationale, study design, and baseline characteristics. *Cancer.* (2002) 94:2490–501. doi: 10.1002/cncr.101970
8. Genkinger JM, Platz EA, Hoffman SC, Comstock GW, Helzlsouer KJ. Fruit, vegetable, and antioxidant intake and all-cause, cancer, and cardiovascular disease mortality in a community-dwelling population in Washington County, Maryland. *Am J Epidemiol.* (2004) 160:1223–33. doi: 10.1093/aje/kwh339
9. Koster A, Harris TB, Moore SC, Schatzkin A, Hollenbeck AR, van Eijk JT, et al. Joint associations of adiposity and physical activity with mortality: the National Institutes of Health-AARP diet and health study. *Am J Epidemiol.* (2009) 169:1344–51. doi: 10.1093/aje/kwp053
10. Vasankari V, Husu P, Vaha-Ypya H, Suni JH, Tokola K, Borodulin K, et al. Subjects with cardiovascular disease or high disease risk are more sedentary and less active than their healthy peers. *BMJ Open Sport Exerc Med.* (2018) 4:e000363. doi: 10.1136/bmjsem-2018-000363
11. Task Force M, Montalescot G, Sechtem U, Achenbach S, Andreotti F, Arden C, et al. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease

of the European Society of Cardiology. *Eur Heart J.* (2013) 34:2949–3003. doi: 10.1093/eurheartj/eht296
12. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J.* (2018) 39:119–77. doi: 10.1093/eurheartj/ehx393
13. Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Back M, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J.* (2021) 42:3227–337. doi: 10.1093/eurheartj/ehab484
14. Jeong SW, Kim SH, Kang SH, Kim HJ, Yoon CH, Youn TJ, et al. Mortality reduction with physical activity in patients with and without cardiovascular disease. *Eur Heart J.* (2019) 40:3547–55. doi: 10.1093/eurheartj/ehz564
15. Kim D, Yang PS Yu HT, Kim TH, Jang E, Sung JH, et al. Risk of dementia in stroke-free patients diagnosed with atrial fibrillation: data from a population-based cohort. *Eur Heart J.* (2019) 40:2313–23. doi: 10.1093/eurheartj/ehz386
16. Yang PS, Jang E, Yu HT, Kim TH, Pak HN, Lee MH, et al. Changes in cardiovascular risk factors and cardiovascular events in the elderly population. *J Am Heart Assoc.* (2021) 10:e019482. doi: 10.1161/JAHA.120.019482
17. Kim D, Yang PS, Jang E, Yu HT, Kim TH, Uhm JS, et al. 10-year nationwide trends of the incidence, prevalence, and adverse outcomes of non-valvular atrial fibrillation nationwide health insurance data covering the entire Korean population. *Am Heart J.* (2018) 202:20–6. doi: 10.1016/j.ahj.2018.04.017
18. Kim D, Yang PS, Jang E, Yu HT, Kim TH, Uhm JS, et al. Increasing trends in hospital care burden of atrial fibrillation in Korea, 2006 through 2015. *Heart.* (2018) 104:2010–7. doi: 10.1136/heartjnl-2017-312930
19. Kim D, Yang PS, Kim TH, Jang E, Shin H, Kim HY, et al. Ideal blood pressure in patients with atrial fibrillation. *J Am Coll Cardiol.* (2018) 72:1233–45. doi: 10.1016/j.jacc.2018.05.076
20. Jin MN, Yang PS, Song C, Yu HT, Kim TH, Uhm JS, et al. Physical activity and risk of atrial fibrillation: a nationwide cohort study in general population. *Sci Rep.* (2019) 9:13270. doi: 10.1038/s41598-019-49686-w
21. Kim TH, Yang PS, Yu HT, Jang E, Shin H, Kim HY, et al. Effect of hypertension duration and blood pressure level on ischaemic stroke risk in atrial fibrillation: nationwide data covering the entire Korean population. *Eur Heart J.* (2019) 40:809–19. doi: 10.1093/eurheartj/ehy877
22. Kim D, Yang PS, Jang E, Tae Yu H, Kim TH, Uhm JS, et al. Blood pressure control and dementia risk in midlife patients with atrial fibrillation. *Hypertension.* (2020) 75:1296–304. doi: 10.1161/HYPERTENSIONAHA.119.14388
23. Kim D, Yang PS, Sung JH, Jang E, Yu HT, Kim TH, et al. Less dementia after catheter ablation for atrial fibrillation: a nationwide cohort study. *Eur Heart J.* (2020) 41:4483–93. doi: 10.1093/eurheartj/ehaa726
24. Kim D, Yang PS, You SC, Sung JH, Jang E, Yu HT, et al. Treatment timing and the effects of rhythm control strategy in patients with atrial fibrillation: nationwide cohort study. *BMJ.* (2021) 373:n991. doi: 10.1136/bmj.n991
25. Chun MY. Validity and reliability of Korean version of international physical activity questionnaire short form in the elderly. *Korean J Fam Med.* (2012) 33:144–51. doi: 10.4082/kjfm.2012.33.3.144
26. Piepoli MF, Davos C, Francis DP, Coats AJ, ExTraMatch Collaborative. Exercise training meta-analysis of trials in patients with chronic heart failure (ExTraMATCH). *BMJ.* (2004) 328:189. doi: 10.1136/bmj.37938.645220.EE
27. O'Connor CM, Whellan DJ, Lee KL, Keteyian SJ, Cooper LS, Ellis SJ, et al. Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial. *JAMA.* (2009) 301:1439–50. doi: 10.1001/jama.2009.454
28. Anderson L, Oldridge N, Thompson DR, Zwisler AD, Rees K, Martin N, et al. Exercise-based cardiac rehabilitation for coronary heart disease: cochrane systematic review and meta-analysis. *J Am Coll Cardiol.* (2016) 67:1–12. doi: 10.1016/j.jacc.2015.10.044
29. McDermott MM, Spring B, Tian L, Treat-Jacobson D, Ferrucci L, Lloyd-Jones D, et al. Effect of low-intensity vs high-intensity home-based walking exercise on walk distance in patients with peripheral artery disease: the LITE randomized clinical trial. *JAMA.* (2021) 325:1266–76. doi: 10.1001/jama.2021.2536
30. Fihn SD, Gardin JM, Abrams J, Berra K, Blankenship JC, Dallas AP, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the diagnosis and management of patients with stable ischemic heart disease: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Am Coll Cardiol.* (2012) 60:2564–603. doi: 10.1016/j.jacc.2012.07.012
31. Haskell WL, Lee IM, Pate RR, Powell KE, Blair SN, Franklin BA, et al. Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. *Med Sci Sports Exerc.* (2007) 39:1423–34. doi: 10.1249/mss.0b013e3180616b27
32. Physical Activity Guidelines Advisory Committee. (2018). *2018 Physical Activity Guidelines Advisory Committee Scientific Report.* Washington, DC: U.S. Department of Health and Human Services.

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Development and Validation of a Prognostic Model to Predict High-Risk Patients for Coronary Heart Disease in Snorers With Uncontrolled Hypertension

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Purpose: Snoring or obstructive sleep apnea, with or without uncontrolled hypertension, is common and significantly increases the risk of coronary heart disease (CHD). The aim of this study was to develop and validate a prognostic model to predict and identify high-risk patients for CHD among snorers with uncontrolled hypertension.

Methods: Records from 1,822 snorers with uncontrolled hypertension were randomly divided into a training set (n = 1,275, 70%) and validation set (n = 547, 30%). Predictors for CHD were extracted to construct a nomogram model based on multivariate Cox regression analysis. We performed a single-split verification and 1,000 bootstraps resampling internal validation to assess the discrimination and consistency of the prediction model using area under the receiver operating characteristic curve (AUC) and calibration plots. Based on the linear predictors, a risk classifier for CHD could be set.

Results: Age, waist circumference (WC), and high- and low-density lipoprotein cholesterol (HDL-C and LDL-C) were extracted as the predictors to generate this nomogram model. The C-index was 0.720 (95% confidence interval 0.663–0.777) in the derivation cohort and 0.703 (0.630–0.776) in the validation cohort. The AUC was 0.757 (0.626–0.887), 0.739 (0.647–0.831), and 0.732 (0.665–0.799) in the training set and 0.689 (0.542–0.837), 0.701 (0.606–0.796), and 0.712 (0.615–0.808) in the validation set at 3, 5, and 8 years, respectively. The calibration plots showed acceptable consistency between the probability of CHD-free survival and the observed CHD-free survival in the training and validation sets. A total of more than 134 points in the nomogram can be used in the identification of high-risk patients for CHD among snorers with uncontrolled hypertension.

Conclusion: We developed a CHD risk prediction model in snorers with uncontrolled hypertension, which includes age, WC, HDL-C, and LDL-C, and can help clinicians with early and quick identification of patients with a high risk for CHD.

Keywords: coronary heart disease, hypertension, snorer, prognosis, nomogram

INTRODUCTION

Coronary heart disease (CHD) is one of the main forms of cardiovascular disease and a leading cause of death and disease burden worldwide (1, 2). From a global perspective, the mean prevalence of CHD in adults older than 18 years is 6.03% [interquartile range (IQR) 3.70–7.60%], and this prevalence increases with age, reaching 19.34% (IQR 11.30–34.30%) among adults older than 65 years (3). Fortunately, CHD is a preventable non-communicable disease; therefore, strategic intervention for high-risk patients can effectively reduce the occurrence of CHD (4).

Snoring is a predictor of sleep apnea and a cardinal symptom of obstructive sleep apnea (OSA) (5), with a prevalence of approximately 7.9–56% in different populations and countries (6–8). Snoring is more common than OSA, accounting for 9–38% of population (9). Both of these conditions involve enhanced upper airway resistance during sleep (10), but OSA can only be distinguished from primary snoring with the evaluation by a physician and objective testing (11). Habitual snoring or the frequency of snoring is associated with the risk of hypertension in all age and sex groups (12), especially in midlife male snorers (13). Epidemiological and pathophysiological studies have revealed clear evidence of a causal relationship between OSA and hypertension (14–16) and also an increase in the hypertension risk with increasing severity of OSA (17). The involvement of snoring or OSA in poorly controlled hypertension may be owing to the activation of the sympathetic nervous system by upper respiratory tract resistance and intermittent hypoxia, subsequently inducing vasoconstriction, systemic vascular resistance, increased cardiac output, and elevated fluid retention, and finally leading to a sustained increase in blood pressure (BP) (12, 18, 19). Snoring or OSA, with or without uncontrolled hypertension, can increase cardiovascular morbidity and mortality (20–23).

An important strategy for primary prevention of CHD is the early identification of high-risk individuals (24). Useful methods for assessing patients' risk of CHD include the use of prediction models, which can estimate a patient's relative risk of outcomes and can help clinicians to decide whether to enhance management in certain individuals. Prediction models may be more effective than risk estimation based on BP level alone (25). Snorers have a 28% increased risk for coronary artery disease (20), and poor BP control has been a traditional predictor of CHD. Snoring and hypertension commonly coexist (15) and are associated with apnea, hypopnea, or hypoxemia, indicators that may be the predictors of CHD. However, population-based prediction models for CHD may not be appropriate or accurate when applied to snorers with uncontrolled hypertension owing to an absence of special parameters (26). Therefore, it is necessary to develop a prediction model to evaluate CHD risk in snorers with uncontrolled hypertension using characteristic predictors.

A variety of risk calculators are available to predict CHD, such as charts, Excel spreadsheets, algorithms, computer programs, and web-based tools. A nomogram is a novel way to present the results of an individualized prediction model because it is visual and can help clinicians better understand and apply prediction models. Therefore, the first aim of this study was to develop and internally validate a prognosis prediction model for CHD, which is displayed as a nomogram that is based on certain clinical features or routine biomedical or simple polysomnography (PSG) parameters. The second aim was to determine a risk classifier cutoff value of this model to identify patients with a high CHD, which can serve as a reference for clinicians in furthering education or strengthening patient management to prevent CHD.

MATERIALS AND METHODS

Study Cohort

Retrospective data with longitudinal follow-up information used in this study were obtained from the database of a single tertiary hospital. We reviewed the records of 2,456 inpatients with uncontrolled hypertension, who were admitted to the Hypertension Center of People's Hospital of Xinjiang Uygur Autonomous Region referred from the community, primary care, or general clinic settings. All patients had undergone hypertension-related evaluation and PSG owing to self-reported or family members' complaints of snoring at the Hypertension Center between January 1, 2010 and December 31, 2013. We excluded patients aged less than 18 years (n = 10), those with known CHD at baseline (n = 348), and those who were missing physician-confirmed outcome information (n = 276). Finally, we analyzed the data from 1,822 snorers with uncontrolled hypertension (**Figure 1**). Follow-up began at least 1 year after discharge and took a variety of forms, such as telephone contact or rehospitalization. The follow-up ended on December 31, 2020. The minimum follow-up was 1 year, and the longest was 10 years. Clinical data were collected and primary endpoints were identified and extracted from the medical records. The Institutional Ethics Committee of People's Hospital of Xinjiang Uygur Autonomous Region approved the study design and data analysis and waived the need for informed consent owing to the retrospective nature of the study and use of anonymized data.

Definitions

Uncontrolled hypertension was defined as systolic BP $\geq$ 140 mmHg and/or diastolic BP $\geq$ 90 mmHg in patients receiving antihypertensive treatment, regardless of the type of drugs. According to the medical records, CHD events were defined as physician-confirmed angina, myocardial infarction, coronary revascularization, and coronary death.

Data Collection

The following clinical variables were collected from the electronic medical records on admission (**Supplementary Table 1**): ethnic, age, sex, smoking status, body mass index (BMI), neck circumference (NC), waist circumference (WC), hypertension duration, history of chronic respiratory diseases, diabetes mellitus (DM) presence, office BP on admission, and biochemical indicators that include fasting plasma glucose (FPG), serum total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), and high-sensitivity C-reactive protein

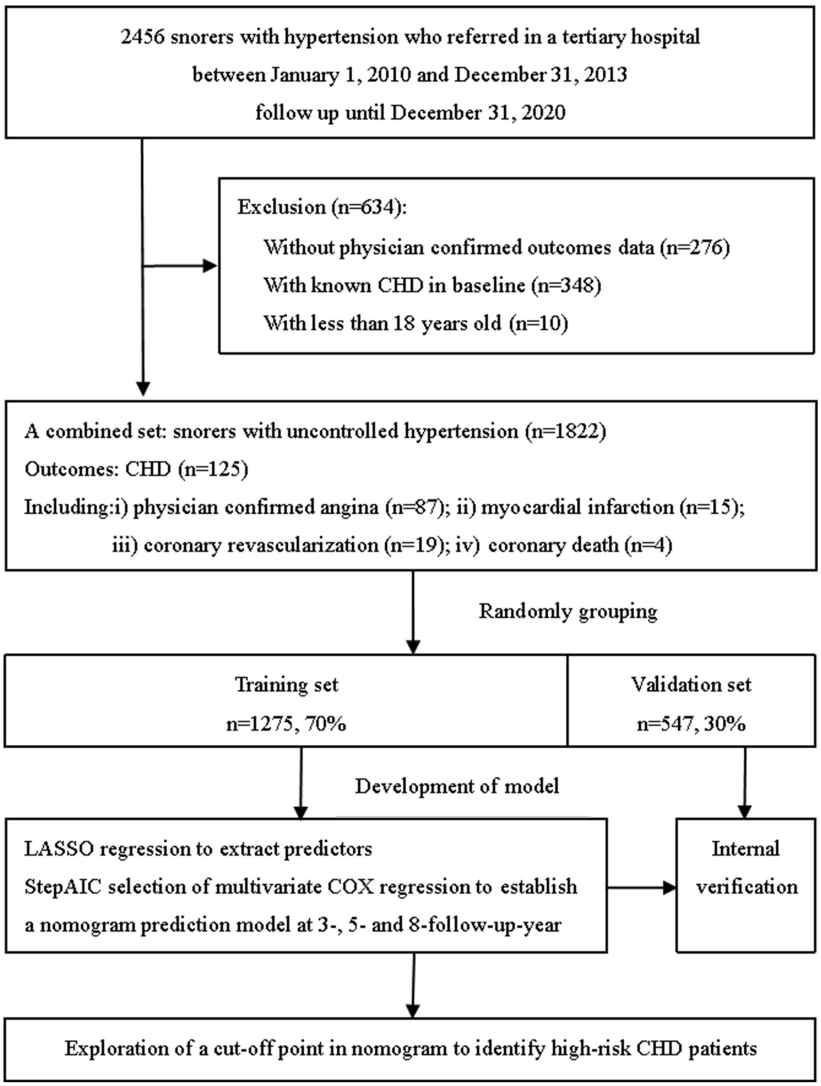

FIGURE 1 | The flowchart of this study design.

(hs-CRP). We also calculated the estimated glomerular filtration rate (eGFR) as follows: $186 \times (\text{serum creatinine})^{-1.154} \times (\text{age in years})^{-0.203} \times (0.742$ if female sex). Biochemical indicators were measured *via* enzymatic methods using an auto-analyzer (7600-010 Automatic Analyzer: Hitachi Medical Systems, Suzhou, China). Some important factors influencing cardiovascular prognosis in hypertensive patients were also collected from the electronic medical records, including target organ damage (TOD) and concomitant clinical diseases (CCDs) (27). Specifically, TOD includes left ventricular hypertrophy, carotid ultrasound, or atherosclerotic plaque or stage 2–3 chronic kidney disease (CKD) (eGFR 30–59 mL/min/1.73 m^2), and CCDs are defined as hemorrhage or ischemic stroke, lacunar infarction, atrial fibrillation, diabetic nephropathy, stage 4–5 CKD (eGFR $<$ 30 mL/min/1.73 m^2), retinal hemorrhage, or papillary edema. We collected sample PSG (Ultrasom, Nicolett, Madison, WI) parameters, including the apnea–hypopnea index (AHI) and lowest oxygen saturation ($LSpO_2$). AHI was calculated using the number of obstructive apneas and hypopneas per hour of sleep. Apnea events were defined as the absence of airflow for >10 s, and hypopnea events were defined as any airflow reduction lasting for >10 s and resulting in arousal or oxygen desaturation $\geq 4\%$, as previously described (28).

Development and Validation Sets

A total of 1,822 patients were randomly divided into two groups: the training set (n = 1,275, 70%) to construct the nomogram model and the validation set (n = 547, 30%).

Statistical Analysis

Continuous variables are presented as mean ± standard deviation or median and interquartile range, and categorical variables are expressed as percentage. In the training set, clinical characteristics were compared between groups with and without CHD using

Student's *t*-test for normally distributed continuous variables, the Wilcoxon rank-sum test for non-normally distributed variables, and the chi-square test for categorical variables. Cox regression analyses were used to estimate the hazard ratio (HR), and the 95% confidence interval (CI), or *p*-value.

For missing data, we used multiple imputations based on the all indicators and CHD events. We created five imputed datasets for missing variables that were then combined across all datasets. Extreme values after interposition (e.g., a negative measured value) were shifted to the lowest line values of those indicators to prevent undue leverage effects.

Univariate Cox regression was used to quantify the association between candidate predictors and CHD in the training set. We used the least absolute shrinkage and selection operator (LASSO) regression model, which is a popular method for removing independent variables that are irrelevant or have multicollinearity to prevent overfitting when selecting the candidates. Before multivariate Cox proportional hazards (PH) regression analysis, variance inflation factors for each predictor were calculated to determine the collinearity, and the PH assumption was tested to verify that the HR did not change over time with $p > 0.05$. Backward stepwise selection (stepAIC) was used to obtain a simplified model in multivariate Cox regression analysis to help to determine the predictors from candidates. Based on this single-split verification, we performed another 1,000 bootstrap internal samples in the combined set, and the split ratio was still 7:3. Adding the original single-split verification, there were 1,001 splits in total. In the backward stepwise selection of multivariate Cox regression analyses, those variables more frequently included in the final model were predictors. According to a comparison of integrated discrimination improvement (IDI) and continuous net reclassification improvement (NRI) between before (model 1) and after (model 2) stepwise selection analysis in multivariable Cox regression, we determined a final prediction model to establish the nomogram. The number of events per variable (EPV) was also used to evaluate the sample size, according to CHD events per number of candidate predictors.

Model discrimination was quantified using Harrell's c-statistic and area under the receiver 158 operating characteristic (ROC) curve (AUC) values, and 1,000 bootstrap resampling was used for unbiased evaluation of the nomogram. An AUC of 0.60–0.75 indicates possibly helpful discrimination, and an AUC greater than 0.75 indicates clearly useful discrimination (29). Calibration curves were plotted to describe the consistency between nomogram-predicted probability and actual CHD-free survival at 3, 5, and 8 years in the training and validation sets, respectively.

Once the nomogram model was successfully established, both the total points and linear predictor (lp) could be obtained, which is a relatively fixed part of the semiparametric model in the Cox regression formula:

$$S(t) = S0(t)^{\wedge}\exp(\mathrm{lp})$$

In the above formula, S0(t) is the baseline survival function estimated from the data, and S(t) is the cumulative survival; then, cumulative incidence is equal to 1 − S(t). The total points corresponding to lp = 0 were set as the cutoff in risk stratification to determine the nomogram-predicted patients with a relatively low or high risk of developing CHD. After stratification, we compared the frequency of CHD occurrence between low-risk and high-risk groups and also calculated the 10-year cumulative incidence of CHD using different total risk scoring. Because Kaplan–Meier analysis may overestimate the outcome risk, competitive risk bias should be addressed, mainly considering non-CHD death as a competing event.

This article was prepared in accordance with the TRIPOD reporting checklist (30), and the methods were assessed with PROBAST (31). Tests were two-sided and 0.05 was set as the *p*-value for statistical significance. The statistical analyses were performed using IBM SPSS version 25.0 (IBM Corp., Armonk, NY, United States) or R version 4.1.0 (The R Project for Statistical Computing, Vienna, Austria).

RESULTS

Clinical Characteristics of Snorers With Uncontrolled Hypertension

According to the available data, among 2,456 snorers with uncontrolled hypertension, 473 can be diagnosed with CHD (19.3%), with a mean follow-up of 7.0 (7.0–8.0) years. Of the 1,822 included patients, the median age at baseline was 46.7 years (range 18–83 years), data were analyzed, and no significant difference was found between the training and validation cohort for all characteristics and follow-up times (**Table 1**). In the group with 10-year follow-up, 125 cases of new-onset CHD occurred, accounting for 6.8%. In total, there are 23 candidate predictors; therefore, the EPV was equal to 5.43 (125/23). Our cohort had missing information on NC (n = 146, 8.0%), TC (n = 42, 2.3%), TG (n = 47, 2.6%), HDL-C (n = 46, 2.5%), LDL-C (n = 44, 2.4%), FPG (n = 64, 3.5%), and hs-CRP (n = 58, 3.2%); the interpolated data are shown in **Supplementary Table 2**.

Predictors and Construction of the Nomogram Model

In the training set, patients with CHD were less ethic Han (p = 0.006), older ($p < 0.001$) and had higher values of BMI (p = 0.006), NC (p = 0.004), WC ($p < 0.001$), more hypertensive with TOD (p = 0.039) and DM (p = 0.038), AHI (p = 0.024), and LSpO2 (p = 0.027) than patients without CHD (**Supplementary Table 3**). We performed LASSO regression analysis and identified ten candidate predictors without multicollinearity in the training set: age, male, BMI, NC, WC, hypertension with TOD, DM, HDL-C, LDL-C, and AHI (**Table 2**, **Supplementary Table 4**, and **Supplementary Figure 1**). In the PH assumption test conducted prior to performing Cox regression analysis, the *p*-values of all predictors were >0.05 (**Supplementary Table 5**). After backward stepwise selection in multivariate Cox regression analysis, we obtained two models. Model 1 retained all predictors from the LASSO analysis; the AUC (95% CI) was 0.727 (0.670–0.783) at 8 years. In model 2, five predictors were extracted owing to the weaker association with CHD, including male, BMI, NC, DM and AHI, with AUC (95% CI) 0.720 (0.662–0.774) at 8 years. Comparisons

TABLE 1 | Comparison of characteristics between training and validation sets.

Variables	Combined set (*N* = 1822)		
	Training (*n* = 1,275)	Validation (*n* = 547)	*P* value
Ethnic Han (%)	816 (64.2)	350 (64.1)	0.968
Sex [male (%)]	869 (68.2)	352 (64.4)	0.113
Age (years)	46.5 ± 10.0	47.0 ± 9.9	0.327
BMI (kg/m^2)	28.1 ± 3.8	28.1 ± 3.7	0.892
NC (cm)	40.0 ± 3.6	40.1 ± 3.5	0.523
WC (cm)	99.4 ± 10.4	99.3 ± 10.2	0.896
Current smoking [*n* (%)]	385 (30.2)	168 (30.7)	0.826
Hypertensive duration (years)	3.0 (1.0, 7.0)	3.0 (1.0, 7.0)	0.959
Single hypertension [*n* (%)]	444 (34.8)	186 (34.0)	0.736
Hypertension with TOD [*n* (%)]	436 (34.2)	176 (32.2)	0.403
Hypertension with CCD [*n* (%)]	395 (31.0)	185 (33.8)	0.233
DM presence [*n* (%)]	179 (14.0)	74 (13.5)	0.773
Chronic respiratory diseases [*n* (%)]	33 (2.6)	10 (1.8)	0.327
eGFR (ml/min/1.73 m^2)	97.8 ± 21.1	98.3 ± 21.3	0.634
Office SBP in admission (mmHg)	146.2 ± 17.0	146.9 ± 16.3	0.397
Office DBP in admission (mmHg)	97.8 ± 11.5	97.4 ± 11.5	0.487
FPG (mmol/L)	5.2 ± 1.3	5.2 ± 1.6	0.311
Serum TC (mmol/L)	4.6 ± 1.2	4.5 ± 1.2	0.596
Serum TG (mmol/L)	2.3 (1.8, 2.9)	2.2 (1.8, 2.9)	0.447
Serum HDL-C (mmol/L)	1.1 ± 0.3	1.1 ± 0.3	0.795
Serum LDL-C (mmol/L)	2.6 ± 0.8	2.6 ± 0.8	0.215
Serum hs-CRP (mmol/L)	2.0 (0.9, 3.7)	1.9 (0.9, 3.7)	0.263
AHI (events/hour)	13.2 (5.2, 27.9)	13.0 (5.6, 26.8)	0.830
$LSpO_2$ (%)	82.0 (77.0, 86.5)	82.0 (77.0, 86.0)	0.842
Coronary heart disease [*n* (%)]	83 (6.5)	42 (7.7)	0.825
Confirmed angina [*n* (%)]	56 (4.4)	31 (5.7)	
Myocardial infarction [*n* (%)]	3 (0.2)	1 (0.2)	
Coronary revascularization [*n* (%)]	11 (0.9)	4 (0.7)	
Coronary death [*n* (%)]	13 (1.0)	6 (1.1)	
Follow-up time (years)	7.0 (7.0, 8.0)	7.0 (7.0, 8.0)	0.873

AHI, apnea hypopnea index; BMI, body mass index; CCD, concomitant clinical diseases; CHD, coronary heart disease; DBP, diastolic blood pressure; eGFR, glomerular filtration rate; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; $LSpO_2$, lowest oxygen saturation; NC, neck circumference; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides; TOD, target organ damage; WC, waist circumference. Continuous variables are presented as mean ± standard deviation or medians and interquartile spacing and categorical variables are expressed as percentages. Student's t-test (continuous variables) and Pearson's chi-square test (categorical variables) were performed to compare between training and validation sets.

TABLE 2 | Univariable Cox regression analysis and least absolute shrinkage and selection operator (LASSO) regression analysis to extract the potential predictors in the training set.

Variables	Univariable cox regression		LASSO regression
	HR (95% CI)	*p*-value	Lambda (log) = 0.006 (−5.1193)
Age	1.05 (1.03, 1.07)	<0.0001	0.0473702184965897
Male	1.18 (0.73, 1.90)	0.4966	0.0000000000000001
BMI	1.07 (1.02, 1.13)	0.0047	0.0081677379934463
NC	1.08 (1.01, 1.15)	0.0185	0.0148402550539110
WC	1.04 (1.02, 1.06)	0.0002	0.0188237783613461
Current smoking	0.91 (0.57, 1.47)	0.7044	0
Hypertensive duration	1.04 (1.01, 1.07)	0.0136	0
Single hypertension	0.58 (0.35, 0.96)	0.0323	0
Hypertension with TOD	1.52 (0.98, 2.34)	0.0600	0.0055683324443603
Hypertension with CCD	1.08 (0.67, 1.73)	0.7502	0
DM presence	2.33 (1.38, 3.93)	0.0015	0.0027472424787100
Chronic respiratory diseases	1.53 (0.48, 4.85)	0.4701	0
eGFR	1.00 (0.99, 1.01)	0.5128	0
Office SBP	1.01 (0.99, 1.02)	0.3401	0
Office DBP	0.98 (0.96, 1.00)	0.0764	0
FPG	1.13 (0.98, 1.30)	0.1055	0
Serum TC	1.03 (0.86, 1.24)	0.7169	0
Serum TG	0.93 (0.77, 1.12)	0.4507	0
Serum HDL-C	0.49 (0.22, 1.10)	0.0856	−0.4454591060154290
Serum LDL-C	1.32 (1.01, 1.72)	0.0411	0.1889524482600690
Serum hsCRP	1.03 (0.97, 1.10)	0.3084	0
AHI	1.01 (1.00, 1.02)	0.0225	0.0007788607916679
$LSpO_2$	0.99 (0.97, 1.00)	0.0542	0

AHI, apnea hypopnea index; BMI, body mass index; CCD, concomitant clinical diseases; CHD, coronary heart disease; CI, confidence interval; DBP, diastolic blood pressure; eGFR, lomerular filtration rate; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; hsCRP, high-sensitivity C-reactive protein; LASSO, least absolute shrinkage and selection operator; LDL-C, low-density lipoprotein cholesterol; $LSpO_2$, lowest oxygen saturation; NC, neck circumference; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides; TOD, target organ damage; WC, waist circumference. Tuning parameter (lambda) selection in the LASSO model used 10-fold crossvalidation.

of the AUC between the two models revealed no significant difference (**Supplementary Figure 2**). Continuous NRI and IDI revealed a slightly negative improvement from models 1 to 2 (-0.175 and -0.007, $p > 0.05$; **Table 3**). Model 1 maintains the characteristics of the specific group studied, such as larger NC and elevated AHI; however, as a practical predictive tool, model 2 is simpler and easier to use because it only involves five predictors, including age, WC, hypertension with TOD, HDL-C, and LDL-C (**Table 3**), as similar as that from the 1,000 bootstrap analyses. There were few differences in their coefficients between the two internal validation forms (**Supplementary Table 6**). Of these five predictors, CHD is weakly associated with hypertension with TOD [HR (95% CI): 1.51 (0.96–2.36), $p = 0.073$] in the COX regression analysis (**Table 3**). Then, we performed a further exploring analysis (**Supplementary Figure 3**). The results suggested that it is almost negligible about the median improvement of the model in risk score with or without hypertension with TOD (AUC: 0.720 vs. 0.717, $p = 0.432$). Therefore, the four predictors, including age, WC, HDL-C, and LDL-C, were selected to establish the final nomogram model (**Figure 2A**). The processes and methods of modeling, including ROC curve and optimal threshold analysis of prediction model, are shown in **Supplementary Table 7**.

Assessment of Nomogram Model Accuracy

The C-index was 0.720 (95% CI 0.663–0.777) in the derivation cohort and 0.703 (95% CI 0.630–0.776) in the validation cohort. In the training cohort, the AUC for the established

TABLE 3 | Multivariate cox regression analysis to construct a nomogram model from randomly grouped data for prediction CHD in the training set.

Variables	Model 1			Model 2[#]		
	β	HR (95% CI)	*p*-value	β	HR (95% CI)	*p*-value
Age	0.063	1.06 (1.04, 1.09)	<0.0001	0.057	1.06 (1.04, 1.08)	<0.0001
Male	0.259	1.30 (0.67, 2.44)	0.423	–		
BMI	0.031	1.03 (0.93, 1.14)	0.541	–		
NC	0.016	1.01 (0.93, 1.11)	0.718	–		
WC	0.014	1.01 (0.98, 1.05)	0.467	0.032	1.03 (1.01, 1.05)	0.0013
Hypertension with TOD	0.347	1.41 (0.89, 2.25)	0.143	0.410	1.51 (0.96, 2.36)	0.0731
DM presence	0.227	1.25 (0.71, 2.22)	0.436	–		
Serum HDL-C	−0.796	0.45 (0.19, 1.10)	0.080	−0.949	0.39 (0.16, 0.93)	0.0330
Serum LDL-C	0.312	1.37 (1.04, 1.79)	0.023	0.291	1.34 (1.02, 1.75)	0.0323
AHI	0.003	1.00 (0.99, 1.01)	0.627	–		
*AUC (95% CI)	0.727 (0.670, 0.783)			0.720 (0.662, 0.778)		
[†]IDI (95% CI)				−0.007 (−0.049, 0.001), *p = 0.066*		
[†]Continuous NRI (95% CI)				−0.175 (−0.300, 0.009), *p = 0.060*		

*AHI, apnea hypopnea index; AIC, Akaike information criterion; AUC, area under the curve for receiver operating characteristic curves; CHD, coronary heart disease; CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; IDI, integrated discrimination improvement; NC, neck circumference; NRI, net reclassification improvement; TOD, target organ damage; WC, waist circumference. [#]Stepwise (stepAIC) selected model. *AUC at 8-year. [†]Model 1 as a reference.*

nomogram was 0.757 (95% CI 0.626–0.887), 0.739 (95% CI 0.647–0.831), and 0.732 (95% CI 0.665–0.799) for 3-, 5-, and 8-year CHD-free survival (**Figure 2B**); these AUC values were 0.689 (95% CI 0.542–0.837), 0.701 (95% CI 0.606–0.796), and 0.712 (95% CI 0.615–0.808) in the validation cohort (**Figure 2C**), respectively. Time-dependent AUC and C-index of the nomogram model from 1,000 bootstraps were shown in **Supplementary Figures 4, 5**, respectively. With the extension of follow-up time from 3 to 8 years, the nomogram model's AUC values of both training and validation sets were always above 0.68 (**Supplementary Table 7**). The calibration plots for 3-, 5-, and 8-year CHD-free survival showed acceptable consistency in the training (**Figure 2D**) and validation cohorts (**Figure 2E**) between the nomogram-predicted probability of CHD-free survival and the observed CHD-free survival.

Risk Classifier for Coronary Heart Disease and Utility of Model

Based on the lp in the nomogram model, we calculated the total points for every patient and set a risk classifier according to a cutoff of lp = 0 in the training and validation sets.

The total points were calculated as follows (all formulas about nomogram model in **Supplementary Table 8**):

$$(1.429 \times \text{ age} - 21.429) + (0.800 \times \text{ WC} - 48.016) + (-24.468 \times \text{HDL-C} + 68.511) + (7.800 \times \text{LDL-C} - 3.900).$$

In the training set, if the lp was 0, the total was 134 points based on the nomogram. Patients with more than 134 total points were assigned to the group with a high risk of CHD. For further convenience of application, based on the above formula, the nomogram was converted to a score sheet for screening high-risk patients and evaluating total points and CHD probability (**Figure 3A**); the quantization table is provided in the **Supplementary Excel algorithm**. Regardless of which calculation method was used, patients with a total score of more than 134 points were predicted to be at high risk for CHD, thus requiring special attention and active management by clinicians.

Cumulative Incidence

The actual CHD occurrence was significantly more frequent in the nomogram-predicted high-risk than the low-risk groups not only in the training set (9.76%, 62/635 vs. 3.28%, 21/640; $\chi^2 = 20.009$, $p < 0.001$; **Supplementary Excel 1**) but also in the validation set (10.84%, 31/286 vs. 4.21%, 11/261; $\chi^2 = 8.448$, $p = 0.004$; **Supplementary Excel 2**). Although we considered that competitive risk bias may influence estimates of CHD risk, after careful checking, only 2 of 1,822 patients died from non-CHD. Therefore, the result of competitive risk bias was insufficient to lead to the cumulative incidence misestimation of CHD events. The observed 10-year cumulative incidence of CHD in the nomogram-predicted high-risk group was also higher than that in the low-risk group in the training set ($p < 0.0001$; **Figure 3B**) and the validation set ($p < 0.001$; **Figure 3C**).

Self-Assessment of Writing and Methodology Quality

Based on the PROBAST checklist, the overall risk assessment of the methodology was "high risk of bias" because of the retrospective cohort, small sample (EPV = 5.43), and the absence of mediating effect tests, crossvalidation, or external validation (**Supplementary Table 9**). According to the TRIPOD reporting checklist, writing quality self-assessment of this article is shown in **Supplementary Table 10**.

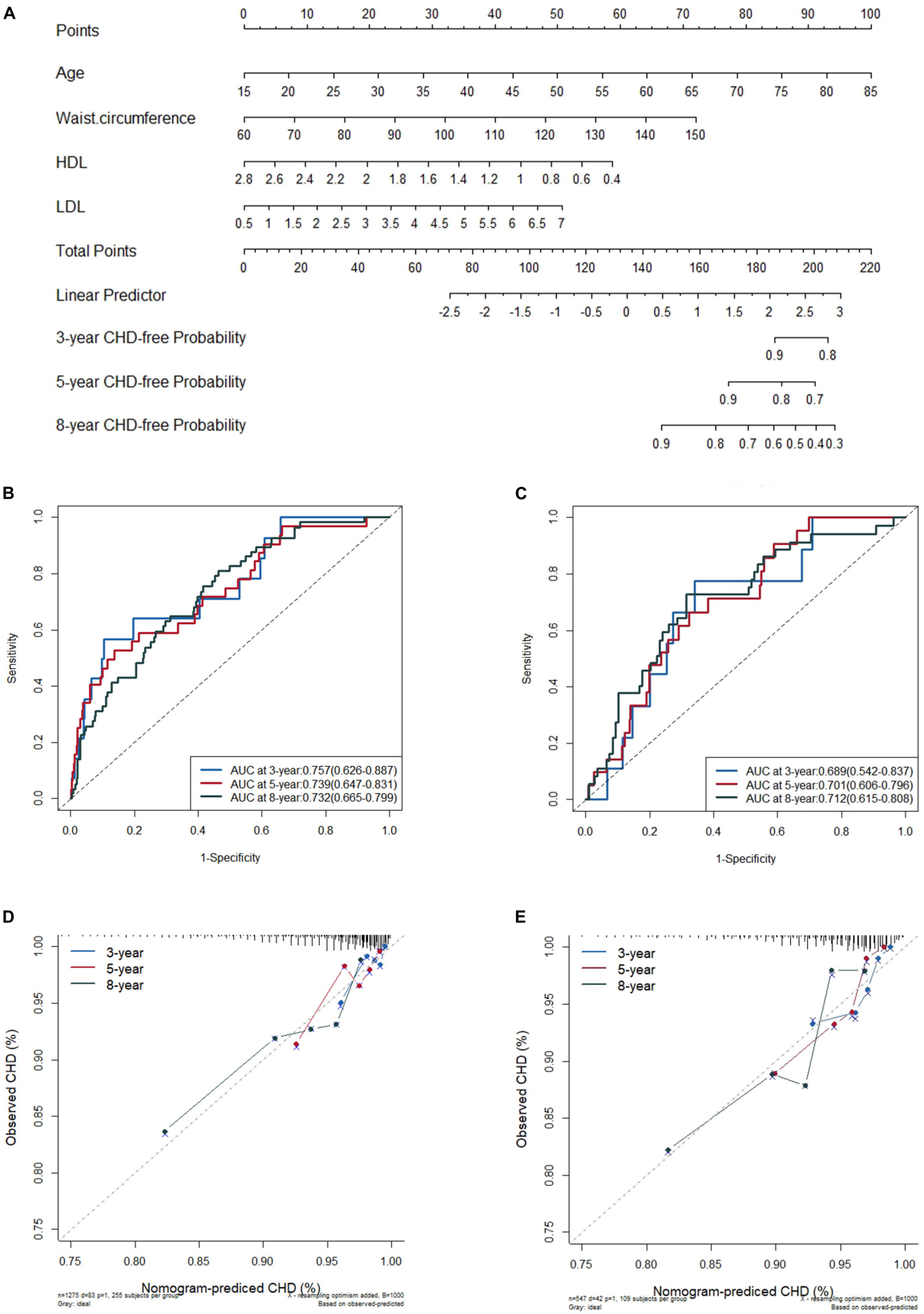

FIGURE 2 | Nomogram for predicting new onset coronary heart disease (CHD) in the training set **(A)**, the receiver operating characteristic (ROC) curves of the model in training set **(B)** and in validation set **(C)**, and the calibration plots in the training set **(D)** and in the validation set **(E)** at 3, 5, and 8 years.

A

Age		WC		HDL-C		LDL-C	
(years)	Points	(cm)	Points	(mmol/L)	Points	(mmol/L)	Points
15	0	60	0	2.8	0	0.5	0
20	7	70	8	2.6	5	1.0	4
25	14	80	16	2.4	10	1.5	8
30	21	90	24	2.2	15	2.0	12
35	29	100	32	2.0	20	2.5	16
40	36	110	40	1.8	24	3.0	20
45	43	120	48	1.6	29	3.5	23
50	50	130	56	1.4	34	4.0	27
55	57	140	64	1.2	39	4.5	31
60	64	150	72	1.0	44	5.0	35
65	71			0.8	49	5.5	39
70	79			0.6	54	6.0	43
75	86			0.4	59	6.5	47
80	93					7.0	51
85	100						

Add up points to look up 3-, 5- and 8-year CHD probability and to identify high-risk individuals

Linear predictor	Total-Points	CHD probability (%)			Risk classifier
		3-year	5-year	8-year	
-2.5	72	<0	<0	<0	Low risk for CHD
-2.0	85	<0	<0	<0	
-1.5	97	<0	<0	<0	
-1.0	109	<0	<0	<0	
-0.5	122	<0	<0	<0	
0	134	<0	<0	8.7	Cut-off of CHD risk
0.5	147	<0	6.4	10.1	High risk for CHD
1.0	159	<0	7.1	15.4	
1.5	172	2.5	10.6	25.2	
2.0	184	8.9	16.6	37.7	
2.5	197	15.8	26.5	54.4	
3.0	209	22.2	39.1	72.5	

Recommend some strategies to educate or intervene for high-risk patients

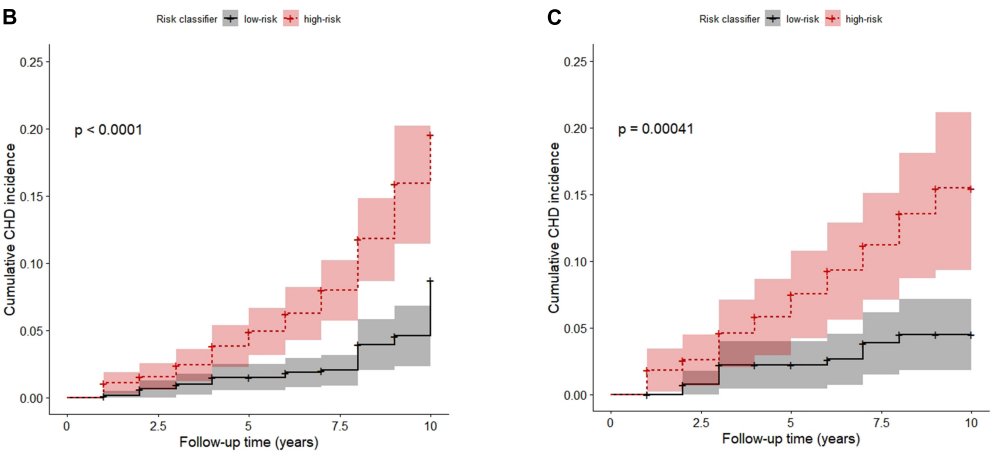

FIGURE 3 | A score sheet and risk classifier to identify high-risk patients for CHD in snorers with uncontrolled hypertension **(A)**, and the cumulative incidences after risk stratification in the training set and **(B)** in the validation set **(C)**.

DISCUSSION

According to the published literature, the global prevalence of CHD ranges from 3.45 to 19.88% (3). In this study of snorers with uncontrolled hypertension, the total incidence rate of CHD was 19.3%, and the 10-year new-onset cumulative incidence was 6.86%. It should be noted that all patients with hypertension in this study had taken at least one antihypertensive drug, were hospitalized owing to concern for their health, and had good adherence to treatment. The incidence of CHD in patients with common snoring and hypertension may be much greater than the above rate. Therefore, this group is at high risk of CHD and requires greater attention from clinicians. Individualized management strategies should be developed according to the patients' specific indicators. The prognosis model presented in this report involved only four commonly used indicators (age, WC, HDL-C, and LDL-C) to predict the risk of developing CHD within the subsequent decade among snorers with uncontrolled hypertension. This model offers a visual presentation that can help clinicians to better understand the results and apply the prediction model. The nomogram model had similar predictive accuracy in both training and validation cohorts, with AUCs of more than 0.7 and tolerable calibration. Using total points $\geq$ 134 in the nomogram, patients with a high risk of CHD can be identified and actively managed.

In the nomogram model, apart from WC, age, HDL-C, and LDL-C are known as traditional predictors for CHD (24). According to epidemiological data, the proportion of snorers with abdominal obesity is significantly higher (12) and the WC was positively correlated with the AHI (32). In a recent Mendelian randomization study, the results revealed that WC was causally associated with CHD, and a 12.5-cm increase in WC predicted more than a 1.5-fold increased risk of CHD (33). Therefore, WC is a powerful predictor of CHD that is reflected in the physical characteristics of snorers and can easily be measured (34). NC is also a user-friendly indicator of a relationship with CHD (35); unfortunately, NC was eliminated in the model after performing backward stepwise selection. Although we included AHI in our analysis, which can represent snoring or OSA severity (11), the AHI may contribute less to CHD than traditional predictors of CHD. In addition, the results based on the Cox regression analysis revealed that hypertension with TOD is more weakly associated with CHD than the other four predictors. Moreover, given that information on hypertension in association with organ damage is not readily available without a comprehensive assessment of the patient, the model's generalizability and applicability will be limited. To prioritize simplicity of the risk model, only four easily obtainable indexes were retained in the final nomogram model. According to NRI and IDI assessments, the results showed that the accuracy of this simplified model in predicting CHD did not decrease significantly.

Although the nomogram is intuitive, its calculation requires measuring the points of each predictor, which is time-consuming in the clinic. Therefore, based on the known formula, the nomogram model can be translated into a score sheet and an Excel spreadsheet for clinicians to quickly obtain a rough determination of whether a patient is at high risk for CHD. Formulae to calculate the total points of the nomogram and probability of CHD occurrence are provided in **Supplementary Material**, which can help researchers evaluate patient data in batches or validate our model.

A difficulty in this study was determining cutoff points to distinguish high-risk patients for CHD. If ROC curves were used to identify these cutoff points, we could obtain multiple different cutoff values for different follow-up years. The non-uniformity among cutoff values makes this model difficult to use and affects the users' understanding. Therefore, we used the semiparametric characteristic of the Cox regression model to solve this issue because the estimation of the lp value is a relatively stable part of this equation. Once the Cox model is established, the partial regression coefficients for each predictor can be determined, and the patient's lp can be calculated according to the sum of weighted observations for each predictor, which corresponds to the total points in the nomogram. The total points estimated from baseline data at follow-up initiation will not change over time. Additionally, according to the principle that combined predictors increase hazards when lp is greater than 0, we suggest that the total points (n = 134) corresponding to lp = 0 are the cutoff values for identifying high-risk patients. This is consistent with what we predicted, that is, that the incidence of actual CHD was significantly increased among high-risk patients with lp $>$ 0 in comparison with low-risk ones.

The strength of this study is that, for snorers with uncontrolled hypertension, patients with a high risk for CHD can be identified early and quickly according to the individuals' age, WC, HDL-C, and LDL-C values. We maintained the continuous nature of each predictor to minimize the loss of patient's information. To illustrate how this model can be applied, we can use a clinical example. A 40-year-old (36 points) man has failed to lower his BP to below 149/90 mmHg after regularly taking two antihypertensive drugs; he has self-reported snoring, WC 110 cm (40 points), HDL-C 0.8 mmol/L (49 points), and LDL-C 3.3 mmol/L (22 points). According to our nomogram, score sheet, or Excel algorithm, his total points are 147 (n $>$ 134); this patient would therefore be identified as a patient with a high risk for CHD. Clinicians can then target this patient's abnormal indicators, such as central obesity and hyperlipidemia, with reasonable use of antihypertensive drugs, informing the patient of the high risk of CHD and providing suggestions and a diet and exercise prescription and also lipid-lowering therapy. Establishment of health records and a follow-up schedule are needed to properly manage this patient. Adherence should be evaluated, and the patient should be reminded to see a doctor and undergo cardiac examinations to prevent irreversible ischemic heart disease if the patient experiences any chest discomfort.

This study includes several limitations. (i) According to PROBAST, the overall risk assessment of the methods used showed a "high risk of bias" owing to the use of a retrospective cohort, small sample (EPV $<$ 10) and the absence of external validation. (ii) We must acknowledge that the nomogram's ability to correctly distinguish CHD is limited because the AUC was less than 0.75. (iii) This was a single-center study with data from a tertiary hospital. Although many patients were

referred from primary hospitals for uncontrolled hypertension, extensive use of the model in the general patient population is limited. (iv) Selection bias is inevitable in retrospective studies, especially when excluding some patients without baseline or follow-up outcome data. (v) Xinjiang province is a multiethnic region. Although we had complete data on all patients' ethnicity, it was not included in the candidate predictors, considering from a non-population cohort and the hospitalization bias. (vi) OSA mainly increases nighttime systolic and 24-h diastolic BP variability in patients with hypertension, which may be a major risk determinant of cardiovascular diseases (36). Although ambulatory-monitored blood pressure (ABPM) data may provide a more precise prediction model for OSA patients, the ABPM is not yet an easily accessible measurement, involving which may limit the scope of this nomogram model application. Whereas office BP at admission is more random without being adjusted by hypertensive specialists, and thus results can be generalized more. And last but not least, DM presence, as a recognized predictor of CHD, was not included in the final nomogram model. The possible reason is that some patients have not developed diabetes at baseline but may gradually become diabetic during the 10-year follow-up. Therefore, the use of baseline data analysis may underestimate the impact of diabetes on CHD outcomes. In addition, besides DM and FPG, we also considered postprandial blood glucose or glycosylated hemoglobin as representative indicators of hyperglycemia, whereas there were a lot of missing data on these parameters, which unfortunately limited our analysis.

In summary, we developed a risk prediction model of CHD including age, WC, HDL-C, and LDL-C, for snorers with uncontrolled hypertension, which may help clinicians to identify patients with a high risk of CHD. Given that snoring and uncontrolled hypertension are both common, this risk-scoring system is useful for application in clinical practice in primary healthcare clinics. The accuracy and applicability of the model should be verified in further cohort studies.

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

N-FL and M-HW conceptualized the study. M-HW, MH, and X-GY contributed to methodology. JH, YM, RW, LS, Y-LR, and NY contributed to the resources and data curation. M-HW and MH contributed to writing – original draft preparation. QL and M-YL contributed to software. N-FL contributed to project administration and funding acquisition. All authors have read and agreed to the final version of the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.777946/full#supplementary-material

REFERENCES

1. Dalen JE, Alpert JS, Goldberg RJ, Weinstein RS. The epidemic of the 20(th) century: coronary heart disease. *Am J Med.* (2014) 127:807–12. doi: 10.1016/j.amjmed.2014.04.015
2. Weiwei C, Runlin G, Lisheng L, Manlu Z, Wen W, Yongjun W, et al. Outline of the report on cardiovascular diseases in China, 2014. *Eur Heart J Suppl.* (2016) 18(Suppl. F):F2–11. doi: 10.1093/eurheartj/suw030
3. Zhu KF, Wang YM, Zhu JZ, Zhou QY, Wang NF. National prevalence of coronary heart disease and its relationship with human development index: a systematic review. *Eur J Prev Cardiol.* (2016) 23:530–43. doi: 10.1177/2047487315587402
4. Houston M. The role of noninvasive cardiovascular testing, applied clinical nutrition and nutritional supplements in the prevention and treatment of coronary heart disease. *Ther Adv Cardiovasc Dis.* (2018) 12:85–108. doi: 10.1177/1753944717743920
5. Sowho M, Sgambati F, Guzman M, Schneider H, Schwartz A. Snoring: a source of noise pollution and sleep apnea predictor. *Sleep.* (2020) 43:zsz305. doi: 10.1093/sleep/zsz305
6. Appleton SL, Gill TK, Lang CJ, Taylor AW, McEvoy RD, Stocks NP, et al. Prevalence and comorbidity of sleep conditions in Australian adults: 2016 sleep health foundation national survey. *Sleep Health.* (2018) 4:13–9. doi: 10.1016/j.sleh.2017.10.006
7. Yang KI, Kim JH, Hwangbo Y, Koo DL, Kim D, Hwang KJ, et al. Prevalence of self-perceived snoring and apnea and their association with daytime sleepiness in korean high school students. *J Clin Neurol.* (2017) 13:265–72.
8. Patel M, Tran D, Chakrabarti A, Vasquez A, Gilbert P, Davidson T. Prevalence of snoring in college students. *J Am Coll Health.* (2008) 57:45–52. doi: 10.3200/JACH.57.1.45-52
9. Senaratna CV, Perret JL, Lodge CJ, Lowe AJ, Campbell BE, Matheson MC, et al. Prevalence of obstructive sleep apnea in the general population: a systematic review. *Sleep Med Rev.* (2017) 34:70–81. doi: 10.1016/j.smrv.2016.07.002
10. Lugaresi E, Plazzi G. Heavy snorer disease: from snoring to the sleep apnea syndrome–an overview. *Respiration.* (1997) 64(Suppl. 1):11–4. doi: 10.1159/000196730
11. Kapur VK, Auckley DH, Chowdhuri S, Kuhlmann DC, Mehra R, Ramar K, et al. Clinical practice guideline for diagnostic testing for adult obstructive sleep apnea: an american academy of sleep medicine clinical practice guideline. *J Clin Sleep Med.* (2017) 13:479–504.

12. Xiao M, Tang X, Zhang F, Zhou L, Bu X, Liu X, et al. Association between self-reported snoring and hypertension among Chinese Han population aged 30-79 in Chongqing, China. *Environ Health Prev Med.* (2020) 25:78. doi: 10.1186/s12199-020-00908-y
13. Lee SK, Choi K, Chang YH, Kim J, Shin C. Increased risk for new-onset hypertension in midlife male snorers: The 14-year follow-up study. *J Sleep Res.* (2019) 28:e12757. doi: 10.1111/jsr.12757
14. Salman LA, Shulman R, Cohen JB. Obstructive sleep apnea, hypertension, and cardiovascular risk: epidemiology, pathophysiology, and management. *Curr Cardiol Rep.* (2020) 22:6. doi: 10.1007/s11886-020-1257-y
15. Postrzech-Adamczyk K, Nahorecki A, Zatońska K, Lawson J, Wołyniec M, Skomro R, et al. Prevalence and risk of obstructive sleep apnea and arterial hypertension in the adult population in poland: an observational subset of the international prospective urban rural epidemiology (PURE) study. *Adv Exp Med Biol.* (2019) 1222:37–42. doi: 10.1007/5584_2019_419
16. Wang L, Li N, Yao X, Chang G, Zhang D, Heizhati M, et al. Detection of secondary causes and coexisting diseases in hypertensive patients: OSA and PA are the common causes associated with hypertension. *Biomed Res Int.* (2017) 2017:8295010. doi: 10.1155/2017/8295010
17. Hou H, Zhao Y, Yu W, Dong H, Xue X, Ding J, et al. Association of obstructive sleep apnea with hypertension: a systematic review and meta-analysis. *J Glob Health.* (2018) 8:010405. doi: 10.7189/jogh.08.010405
18. Oliveras A, Schmieder RE. Clinical situations associated with difficult-to-control hypertension. *J Hypertens.* (2013) 31(Suppl. 1):S3–8. doi: 10.1097/HJH.0b013e32835d2af0
19. Wu Y, Hu G, Pan F, Liu J, Mo X, Xie Y, et al. Obstructive sleep apnea hypopnea syndrome was a risk factor for uncontrolled hypertension in adult snorers in South China. *Clin Exp Hypertens.* (2016) 38:429–34. doi: 10.3109/10641963.2016.1151525
20. Liu J, Shao Y, Bai J, Shen Y, Chen Y, Liu D, et al. Snoring increases the development of coronary artery disease: a systematic review with meta-analysis of observational studies. *Sleep Breath.* (2021) 25:2073–81. doi: 10.1007/s11325-021-02345-9
21. Xie C, Zhu R, Tian Y, Wang K. Association of obstructive sleep apnoea with the risk of vascular outcomes and all-cause mortality: a meta-analysis. *BMJ Open.* (2017) 7:e013983. doi: 10.1136/bmjopen-2016-013983
22. Arnaud C, Bochaton T, Pépin JL, Belaidi E. Obstructive sleep apnoea and cardiovascular consequences: pathophysiological mechanisms. *Arch Cardiovasc Dis.* (2020) 113:350–8. doi: 10.1016/j.acvd.2020.01.003
23. Amare F, Hagos B, Sisay M, Molla B. Uncontrolled hypertension in Ethiopia: a systematic review and meta-analysis of institution-based observational studies. *BMC Cardiovasc Disord.* (2020) 20:129. doi: 10.1186/s12872-020-01414-3
24. Zhao D, Liu J, Xie W, Qi Y. Cardiovascular risk assessment: a global perspective. *Nat Rev Cardiol.* (2015) 12:301–11. doi: 10.1038/nrcardio.2015.28
25. Damen JA, Pajouheshnia R, Heus P, Moons K, Reitsma JB, Scholten R, et al. Performance of the Framingham risk models and pooled cohort equations for predicting 10-year risk of cardiovascular disease: a systematic review and meta-analysis. *BMC Med.* (2019) 17:109. doi: 10.1186/s12916-019-1340-7
26. Jean-Louis G, Zizi F, Clark LT, Brown CD, McFarlane SI. Obstructive sleep apnea and cardiovascular disease: role of the metabolic syndrome and its components. *J Clin Sleep Med.* (2008) 4:261–72.
27. Joint Committee for Guideline Revision. 2018 chinese guidelines for prevention and treatment of hypertension – a report of the revision committee of chinese guidelines for prevention and treatment of hypertension. J *Geriatr Cardiol.* (2019) 16:182–241. doi: 10.11909/j.issn.1671-5411.2019.03.014
28. Heizhati M, Zhang Y, Shao L, Wang Y, Yao X, Abulikemu S, et al. Decreased serum potassium may disturb sleep homeostasis in essential hypertensives. *Hypertens Res.* (2019) 42:174–81. doi: 10.1038/s41440-018-0131-4
29. Alba AC, Agoritsas T, Walsh M, Hanna S, Iorio A, Devereaux PJ, et al. Discrimination and calibration of clinical prediction models: users' guides to the medical literature. *JAMA.* (2017) 318:1377–84. doi: 10.1001/jama.2017.12126
30. Moons KG, Altman DG, Reitsma JB, Ioannidis JP, Macaskill P, Steyerberg EW, et al. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): explanation and elaboration. *Ann Intern Med.* (2015) 162:W1–73. doi: 10.7326/M14-0698
31. Moons K, Wolff RF, Riley RD, Whiting PF, Westwood M, Collins GS, et al. PROBAST: a tool to assess risk of bias and applicability of prediction model studies: explanation and elaboration. *Ann Intern Med.* (2019) 170:W1–33. doi: 10.7326/M18-1377
32. Shao C, Jiang JB, Wu HC, Wu SB, Yu BY, Tang YD. Clinical assessment and polysomnographic study of sleep apnea in a Chinese population of snorers. *J Zhejiang Univ Sci B.* (2015) 16:215–23. doi: 10.1631/jzus.B1400236
33. Chen Q, Li L, Yi J, Huang K, Shen R, Wu R, et al. Waist circumference increases risk of coronary heart disease: evidence from a Mendelian randomization study. *Mol Genet Genomic Med.* (2020) 8:e1186. doi: 10.1002/mgg3.1186
34. Wei Y, Zheng B, Fan J, Lv J, Guo Y, Bian Z, et al. Habitual snoring, adiposity measures and risk of type 2 diabetes in 0.5 million Chinese adults: a 10-year cohort. *BMJ Open Diabetes Res Care.* (2020) 8:e001015. doi: 10.1136/bmjdrc-2019-001015
35. Yang GR, Dye TD, Zand MS, Fogg TT, Yuan SY, Yang JK, et al. Association between neck circumference and coronary heart disease: a meta- analysis. *Asian Pac Isl Nurs J.* (2019) 4:34–46. doi: 10.31372/20190401.1031
36. Shi J, Piao J, Liu B, Pan Y, Gong Y, Deng X, et al. Obstructive sleep apnea increases systolic and diastolic blood pressure variability in hypertensive patients. *Blood Press Monit.* (2017) 22:208–12. doi: 10.1097/MBP.0000000000000259

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