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Sports cardiology

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Sports cardiology

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Cardiac and Pulmonary Vascular Remodeling in Endurance Open Water Swimmers Assessed by Cardiac Magnetic Resonance: Impact of Sex and Sport Discipline

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Background: The cardiac response to endurance exercise has been studied previously, and recent reports have described the extension of this remodeling to the pulmonary vasculature. However, these reports have focused primarily on land-based sports and few data are available on exercise-induced cardio-pulmonary adaptation in swimming. Nor has the impact of sex on this exercise-induced cardio-pulmonary remodeling been studied in depth. The main aim of our study was to evaluate cardiac and pulmonary circulation remodeling in endurance swimmers. Among the secondary objectives, we evaluate the impact of sex and endurance sport discipline on this cardio-pulmonary remodeling promoted by exercise training.

Methods: Resting cardiovascular magnetic resonance imaging was performed in 30 healthy well-trained endurance swimmers (83.3% male) and in 19 terrestrial endurance athletes (79% male) to assess biventricular dimensions and function. Pulmonary artery dimensions and flow as well as estimates of pulmonary vascular resistance (PVR) were also evaluated.

Results: In relation to the reference parameters for the non-athletic population, male endurance swimmers had larger biventricular and pulmonary artery size (7.4 ± 1.0 vs. 5.9 ± 1.1 cm^2, $p < 0.001$) with lower biventricular ejection fraction (EF) (left ventricular (LV) EF: 58 ± 4.4 vs. 67 ± 4.5 %, $p < 0.001$; right ventricular (RV) EF: 60 ± 4 vs. 66 ± 6 %, $p < 0.001$), LV end-diastolic volume (EDV): 106 ± 11 vs. 80 ± 9 ml/m^2, $p < 0.001$; RV EDV: 101 ± 14 vs. 83 ± 12 ml/m^2, $p < 0.001$). Significantly larger LV volume and lower LV EF were also observed in female swimmers (LV EF: 60 ± 5.3 vs. 67 ± 4.6 %, $p = 0.003$; LV EDV: 90 ± 17.6 vs. 75± 8.7 ml/m^2, $p = 0.002$). Compared to terrestrial endurance athletes, swimmers showed increased LV indexed mass (75.0 ± 12.8 vs. 61.5 ± 10.0 g/m^2, $p < 0.001$). The two groups of endurance athletes had similar pulmonary artery remodeling.

Conclusions: Cardiac response to endurance swimming training implies an adaptation of both ventricular and pulmonary vasculature, as in the case of terrestrial endurance athletes. Cardio-pulmonary remodeling seems to be less extensive in female than in male swimmers.

Keywords: athletes' heart, endurance swimmers, pulmonary circulation, right ventricle, cardiac remodeling

INTRODUCTION

Long-lasting endurance exercise training induces structural and functional remodeling of all four cardiac chambers (1, 2), affecting mainly the right ventricle (RV) rather than the left ventricle (LV) (3, 4). It has also been suggested that exercise-induced remodeling not only involves cardiac chambers but also pulmonary circulation, increasing pulmonary artery dimensions, reducing pulmonary artery flow velocity, and finally increasing the estimated pulmonary vascular resistance (PVR) (5).

Different patterns of cardiac adaptation to endurance exercise have been observed between athletes of different disciplines (6–8). In this regard, previous studies have compared upper- and lower-body endurance training and have shown specific differences in ventricular and atrial remodeling (9, 10). Nevertheless, most of the evidence comparing endurance disciplines involving different muscle groups comes from echocardiographic studies and has focused on LV. Cardiac magnetic resonance (CMR) is considered the gold standard imaging modality for the quantification of biventricular morphology and function (11); additionally, it is also regarded as a non-invasive alternative for evaluating pulmonary circulation hemodynamics and for estimating PVR (12). To our knowledge, most of the CMR studies carried out in male athletes have been performed on subjects practicing terrestrial sports (13–15), and little is known about the hemodynamic effects of swimming on cardiac performance and pulmonary circulation. The effects of swimming on cardiac and pulmonary circulation remodeling may differ from those observed in other sports, given the predominant use of the upper-body and also, presumably, the differential impact of gravitational forces due to the horizontal position and the intermittent respiratory pattern while exercising (16–18).

Consequently, this study had three aims: (1) by means of CMR imaging, to analyze cardiac and pulmonary circulation remodeling in a series of endurance open-water swimmers; (2) to evaluate the impact of the endurance sport discipline, by comparing the remodeling observed in swimmers to that observed in a cohort of terrestrial endurance athletes; and (3) to analyze the impact of sex on this exercise-induced cardio-pulmonary remodeling.

METHODS

Study Population

Thirty non-elite endurance-trained swimmers taking part in the open water swimming race "Oceanman Palamós 9.5 Km" in Catalonia, Spain, and currently engaged in endurance open-water swimming competitions of distances between 3 and 10 km, volunteered to participate in the study. All athletes were trained primarily using the front stroke technique.

Additionally, data on 19 healthy age and sex-matched non-elite endurance athletes trained in terrestrial sports (cycling and running) were obtained retrospectively from a pre-analyzed CMR data base managed by our working group.

A cardiovascular evaluation including a comprehensive personal and family history, resting 12-lead electrocardiogram, treadmill stress test and transthoracic echocardiography at rest was performed prior to the study in order to rule out cardiovascular disease.

All participants filled out a questionnaire providing details of their training history. Exclusion criteria included any history of cardiopulmonary disease and standard contraindications for CMR imaging. To assess training load, a standardized form based on the IPAQ questionnaire (19) was used and the data collected were presented as MET/min/week. The competitive experience was also recorded.

The study protocol was approved by the ethics committee of our institution and complied with the Declaration of Helsinki.

Cardiovascular Magnetic Resonance Protocol

The CMR studies in the swimming group were carried out by an experienced cardiologist on a 1.5 Tesla scanner (MAGNETOM Essenza, Siemens Healthcare) using standard steady-state, free precession ECG-gated breath-hold cines in three long-axis planes and sequential short axis slices from the atrioventricular ring to the apex. Additional cross-sectional cine images of main pulmonary artery and ascending aorta at level of right pulmonary artery were acquired. For flow measurements, standard breath-hold velocity-encoded phase-contrast MR sequences were used with slices positioned perpendicular to the long axis of the ascending aorta where the flow is parallel to the long-axis of the body, and perpendicular to the long axis of the main pulmonary artery. The CMR studies in the group of terrestrial athletes were conducted previously using the same acquisition protocol, and the images were also analyzed beforehand by the same cardiologist.

Quantitative image data analysis was performed on a separate workstation using software from the vendor (*syngo.via, Siemens Healthcare, Erlangen, Germany*). Global LV and RV function were assessed by manually contouring the endocardial borders of end-diastolic and end-systolic short-axis images. For the computation of LV mass, the epicardial borders were additionally contoured at end diastole. LV and RV volumes and EF

and left ventricular mass were automatically calculated by the software. Measurements were indexed for body surface area. For the assessment of ascending aorta and pulmonary artery flow, the cross-sectional area of these vessels was defined and manually corrected, and flow parameters were then automatically provided by the software (**Figure 1**). The following parameters were obtained: peak velocity, average velocity during the complete cardiac cycle, minimum and maximum areas, and pulmonary artery net forward volume. Pulmonary artery pulsatility was calculated as: (maximal pulmonary artery area-minimal pulmonary artery area)/minimal pulmonary artery area x 100. PVR was estimated by a formula that was developed from a cohort of patients with diagnosis or suspicion of pulmonary hypertension and validated in an independent cohort of patients (12). Late gadolinium enhancement sequences were not performed because of the need for contrast in healthy volunteer athletes.

Inter-observer intra-class correlations for CMR measurements were performed in 10 endurance swimmers and presented the following results: 0.970 for LV EF, 0.872 for indexed LV EDV, 0.976 for RVEF, 0.916 for indexed RV EDV, 0.960 for pulmonary flow, 0.986 for mean pulmonary flow velocity, 0.983 for indexed maximal pulmonary area and 0.972 for PVR. Regarding terrestrial athletes, concordance was high between the two observers for ejection fraction, EDV and pulmonary artery and average flow velocities (intraclass correlation coefficient-absolute agreement was >0.85 for all five parameters) (5).

Statistical Analysis

Statistical analysis was carried out using the SPSS Software version 22.0 *(SPSS Inc., Chicago, Illinois, USA)*. All continuous variables were analyzed for normality of distribution using the Kolmogorov-Smirnov test. Subsequently, the Student's *t* test was used to compare baseline data. If normality was not confirmed, the Mann–Whitney-*U* test was applied. Bivariate correlational analysis was used for RV EF, indexed RV EDV, and RVP to determine any possible relationship. The intraclass correlation coefficient (ICC) for the two-way mixed effect models and for absolute agreement ICC (A,2) was calculated to assess the inter-rater reliability of the CMR parameters. The alpha value was set at 0.003 to account for Bonferroni correction.

RESULTS

Clinical and functional characteristics of both groups and according to sex are shown in **Table 1**. Irrespective of sex, endurance swimmers and terrestrial athletes had similar training loads and there were no significant differences in mean age. The proportion of women was also similar between the groups (16.7% in swimmers vs. 21.1% in control group, $p = 0.706$). No significant differences were found between male and female swimmers, except for BSA, which was higher in men.

CMR results in endurance swimmers are summarized in **Table 2**. Compared to the reference parameters reported for the general population (20, 21), male athletes had lower biventricular EF, with larger LV and RV volumes as well as pulmonary artery size (22), and a trend toward higher estimated PVR (5).

Similar to the men, female swimmers showed significantly lower values of LV EF with larger LV volumes. Conversely,

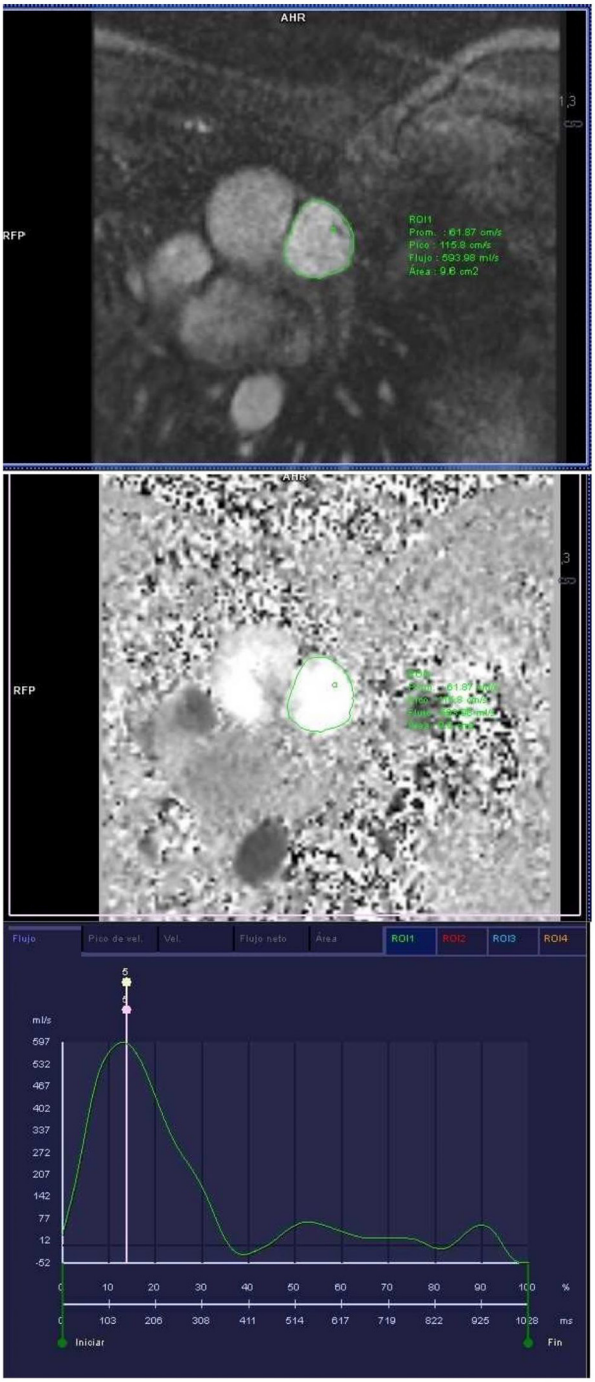

FIGURE 1 | Phase contrast sequence at the level of the main pulmonary artery for the study of pulmonary artery velocities and volumes and subsequent calculation of PVR.

TABLE 1 | Clinical and functional characteristics.

Parameters	Swimmers (men) ($n = 25$)	Terrestrial endurance athletes (men) ($n = 15$)	*p*-value	Swimmers (women) ($n = 5$)	Terrestrial endurance athletes (women) ($n = 4$)	*p*-value
Age (years)	42.2 ± 7.0	39.0 ± 5.4	0.130	37 ± 7.5	35.6±7.6	0.813
BSA (m^2)	1.9 ± 0.1	1.9 ± 0.2	0.420	1.7 ± 0.1*	1.7±0.1	0.909
Training load (MET's/min/week)	5,769 ± 1,584	6,624 ± 1,944	0.138	5,688 ± 864	5,328 ± 720	0.527
Training load (years)	10.6 ± 6.1	13.3 ± 4.2	0.110	10.2 ± 4.4	8.3 ± 1.1	0.154

BSA, body surface area.
**, p<0.05 for the sex-comparison in swimmers.*

TABLE 2 | Cardiac magnetic resonance parameters in endurance swimmers according to sex.

Parameters	Swimmers (men) ($n = 25$)	Reference value*	*p*-value	Swimmers (women) ($n = 5$)	Reference value*	*p*-value
LV EF (%)	58 ± 4.4	67 ± 4.5	**<0.001**	60 ± 5.3†	67 ± 4.6	**0.003**
LV EDV (ml/m^2)	106 ± 11	80 ± 9	**<0.001**	90 ± 17.6	75 ± 8.7	**0.002**
LV SV (ml/m^2)	62 ± 8	53 ± 6	**<0.001**	55± 15.5	50 ± 6.2	0.163
LV Mass (g/m^2)	78 ± 10.8	74 ± 8.5	0.06	59 ± 10.2†	63 ± 7.5	0.257
RV EF	60 ± 4	66 ± 6	**<0.001**	66 ± 4†	66 ± 6	0.971
RV EDV (ml/m^2)	101 ± 14	83 ± 12	**<0.001**	75 ± 15†	73 ± 9	0.619
RV SV (ml/m^2)	60 ± 8	54 ± 8	**0.001**	50 ± 13	48 ± 6	0.498
Pulmonary artery area (cm^2)	7.4 ± 1.0	3.7 ± 0.7	**<0.001**	5.7 ± 0.5	3.9 ± 0.6	0.128
PVR (Wood Units)	2.3 ± 0.8	1.8 ± 1.2‡	0.068	1.3 ± 0.4†	1.6 ± 1.1‡	0.554

Values expressed as mean ± SD.
LV, left ventricle; EF, ejection fraction; EDV, end-diastolic volume; SV, stroke volume; RV, right ventricle; PVR, pulmonary vascular resistance.
**: reference value for the non-athletic population (20, 21).*
†, p<0.05 for the comparison between male and females.
‡, reference values obtained from Domenech-Ximenos et al. (5).
Values in bold indicate significant differences between groups.

RV dimensions and EF, as well as pulmonary artery size and estimated PVR, were within reference values for the healthy non-athletic population.

Compared to male swimmers, females had higher biventricular EF, smaller LV mass and RV end-diastolic volume (RV EDV) and lower estimated PVR.

Comparison Between Swimmers and Terrestrial Endurance Athletes

The comparison of CMR parameters between swimmers and controls is shown in **Table 3**. Swimmers had larger LV mass than terrestrial athletes. Despite a trend toward lesser RV remodeling in swimmers (with smaller RV volumes) than in controls, no significant differences were observed in biventricular dimensions or function. Nor were significant differences found between sport disciplines with regard to pulmonary artery remodeling.

Figures 2A,B show the relationship between RV EF and RV EDV respectively with PVR. Swimmers with higher PVR presented more RV remodeling, as indicated by lower RV EF and RV EDV. No significant correlations were observed in terrestrial athletes.

DISCUSSION

The current study presents a comprehensive CMR evaluation of the impact of endurance swimming on ventricular and pulmonary circulation structure and function. To our knowledge, the effects of endurance swimming training on cardiac and pulmonary vasculature remodeling have not been previously evaluated in CMR studies.

The key findings of our study were: (1) endurance swimming promoted a significant remodeling of both ventricles, characterized by greater biventricular volumes and lower biventricular function as well as significant remodeling of the pulmonary vasculature (PV) with greater pulmonary artery size and increased PVR; (2) sex has a strong impact on the RV and PV remodeling induced by endurance swimming, with female athletes exhibiting smaller RV cavities, higher RV function and lower PVR; (3) endurance sport discipline did not influence the

TABLE 3 | Cardiac magnetic resonance parameters comparation between swimmers and terrestrial endurance athletes.

Parameters	Swimmers ($n = 30$)	Terrestrial endurance athletes ($n = 19$)	*p*-value
LV EF (%)	56.0 ± 4.6	56.7 ± 5.4	0.918
LV EDV (ml/m^2)	98.0 ± 12.6	102.8 ± 13.8	0.219
LV SV (ml/ m^2)	55.0 ± 8.3	58.2 ± 8.1	0.182
LV Mass (g/m^2)	75.0 ± 12.8	61.5 ± 10.0	**<0.001**
RV EF	56.5 ± 6.6	53.5± 6.8	0.242
RV EDV (ml/m^2)	96.8 ± 15.4	103.7 ± 18.2	0.164
RV SV (ml/m^2)	54.3 ± 7.8	55.6 ± 10.9	0.640
Pulmonary artery pulsatility (%)	46.9 ± 12.0	54.9 ± 25.0	0.137
Pulmonary artery area (cm^2/m^2)	3.8 ± 0.4	4.0 ± 0.6	0.131
Mean pulmonary velocity (cm/s)	16.0 ± 2.8	16.3 ± 2.4	0.646
PVR (Wood Units)	2.2 ± 0.9	2.2 ± 0.8	0.800

Values expressed as mean ± SD.
LV, left ventricle; EF, ejection fraction; EDV, end-diastolic volume; SV, stroke volume. RV, right ventricle; PVR, pulmonary vascular resistance.
Values in bold indicate significant differences between groups.

PV remodeling promoted by long-lasting exercise training, as similar pulmonary artery size, and equivalent estimated PVR were observed in swimmers and terrestrial endurance athletes. However, a trend toward lower exercise-induced RV remodeling was shown in swimmers.

Previous studies have evaluated cardiac adaptation to endurance exercise using CMR imaging, showing enlarged LV and RV dimensions with no differences in biventricular EF between endurance athletes and non-athletic populations (11, 23, 24). Nevertheless, most of these studies were performed in athletes practicing terrestrial sports (running and cycling) or triathletes. As expected, our results showed that male endurance swimmers presented significantly larger biventricular volumes than the general population.

We have recently reported that the response to endurance chronic training involves not only the four cardiac chambers but also the pulmonary circulation, since endurance athletes showed greater pulmonary artery dimensions with reduced pulmonary artery flow velocity and a higher estimated PVR than non-athletes (5). In the present study, endurance swimming was also shown to induce pulmonary artery remodeling at least in male swimmers who presented a larger pulmonary artery size and a trend toward higher estimated PVR values than the general population. The increase in pulmonary artery pressure (PAP) during exertion has been established as a potential mechanism for the acute RV impairment observed after bouts of intense exercise (25). If these increases in PAP occur repeatedly over time, they may induce a chronic remodeling of the pulmonary circulation and the right heart. Related to this, **Figure 1A** shows that individuals with greater PAP remodeling have lower RV function. Our results highlight the importance of including CMR evaluation of pulmonary circulation in endurance athletes in order to assess another aspect of remodeling induced by endurance training: the potentially excessive remodeling of the pulmonary circulation, resulting also in excessive RV remodeling.

However, the cardiopulmonary adaptation differed slightly in female and male swimmers. In females, with respect to the reference population, only enlarged LV and reduced LV EF were observed. Compared to male swimmers, women had smaller LV and RV volumes, higher LV and RV EF, and lower pulmonary artery size and estimated PVR. Thus, the results of the present study show that male swimmers present more extensive biventricular and pulmonary circulation remodeling than their female counterparts. The reason for this difference is not entirely clear, but the finding is in agreement with previous studies performed in idiopathic pulmonary arterial hypertension patients, which have demonstrated a poorer adaptation of RV to increased overload in male subjects (26, 27). This disease is more frequent in women; however, once affected, women present a better prognosis than men. This "estrogen paradox" has been associated with a better hemodynamic profile, more distensible pulmonary circulation and better RV performance (28). Sex hormones seem to play an important role explaining this sex bias, although experimental studies in animal models and clinical observations have yielded conflicting results (29–33).

Using CMR parameters established for the general population as a reference may have induced errors in the athletes' heart evaluations, given that exercise-induced increases in ventricular dimensions may overlap with those observed in patients with pathological conditions, such as dilated cardiomyopathy and RV arrhythmogenic cardiomyopathy. In this connection, a recent meta-analysis defined the normal limits of biventricular size and function in competitive male athletes, which represent a useful tool for athletes' heart evaluations (34). Our results showed ventricular dimensions and function within the reference range reported for competitive athletes. However, we observed a lower remodeling of the RV in swimmers, with RV volumes below, and RV EF above, these limits of reference (34). Additionally, female swimmers showed lower LV remodeling, with LV volumes and LV indexed mass below the reference range.

It has been established that functional and structural cardiac remodeling induced by exercise is influenced by the specific sport discipline; cardiac response to endurance training differs according to the muscle group predominantly involved during exercise (upper- vs. lower-body) (9, 18). The hemodynamic response to sport training may be an important determinant of this ventricular adaptation (35). A recent echocardiographic study comparing cardiac remodeling between endurance swimmers and a cohort of long-distance runners found that swimmers presented lesser RV remodeling (8). So the hemodynamic impact of swimming on cardiac remodeling may differ with regard to other sports, given that swimmers predominantly use the upper-body muscle groups. Additionally, swimming is performed in water, and in a horizontal position, which implies a different impact of gravitational forces on the RV pre-load (16–18). Finally, during swimming, the breath is held for prolonged periods, leading to intermittent hypoxia which

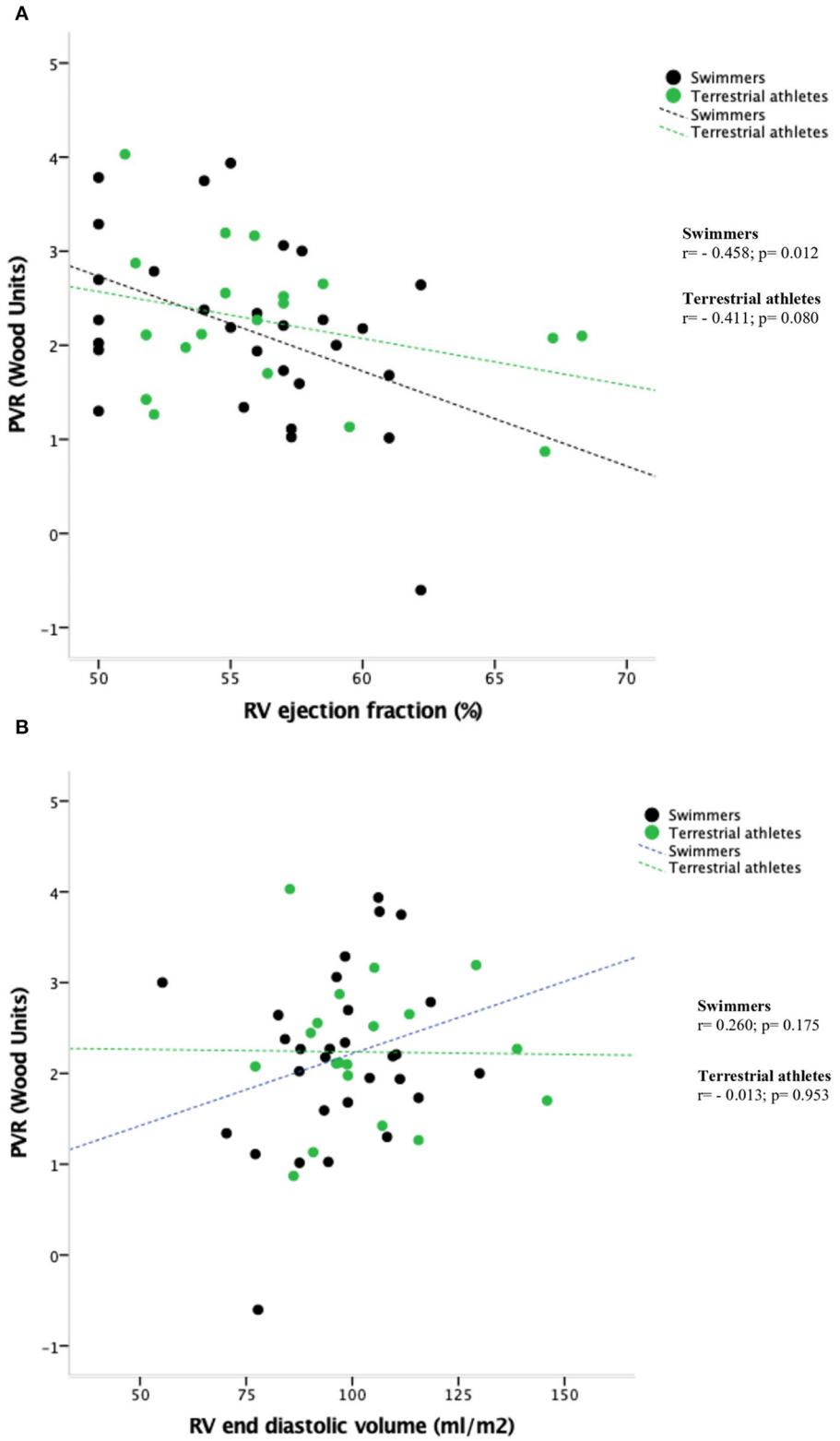

FIGURE 2 | (A) Relationship between RV ejection fraction and cardiac-magnetic resonance-estimated pulmonary resistance (PVR) values. **(B)** Relationship between RV end diastolic volume and cardiac-magnetic resonance-estimated pulmonary resistance (PVR) values.

in turn induces alveolar hyperplasia; similarly, ventilation is restricted under water and the respiratory muscles have to work under greater load. It has been observed that swimmers have larger lung volume and better pulmonary function than other athletes, with higher values of vital capacity, forced vital capacity (FVC), forced expiratory volume for 1 s (FEV1) and FEV1/FVC), unrelated to anthropometric features or to training history (36, 37). Considering all these aspects, the pulmonary circulatory response in swimmers may differ from that found in other athletes, and this may account for the different right ventricular adaptation to endurance training. In the present study, we only observed a trend toward less extensive RV remodeling (with smaller RV dimensions and function) compared to the control group probably due to the small sample size in both groups and the resulting low statistical power.

Finally, the beneficial effect of exercise in terms of cardiovascular health is well established, and greater benefits are obtained with moderate exercise. The athlete's heart is a result of a series of adaptive mechanisms of the heart to cope with the overload involved in intense long-lasting athletic training. However, the amount of this remodeling can make it difficult to distinguish between physiological and pathological cardiac changes. Additionally, emerging data suggest the existence of a syndrome of exercise-induced arrhythmogenic RV cardiomyopathy (38) which may be related to chronic intense-training in genetically predisposed individuals (39). Thus, distinction between physiological and pathological cardiac remodeling is essential in order to detect individuals who are potentially susceptible to present adverse cardiac events. In this context, previous authors have underlined the importance of the use of advanced echocardiographic methods such as the tissue Doppler and two-dimensional strain to help cardiologists in their study of the diagnostic overlaps in sports cardiology, also known as "gray zones" (40). Taking into account that CMR is considered the gold standard imaging modality for the quantification of biventricular morphology and function, it should be considered a complementary tool in the study of athletes included in these "gray zones".

LIMITATIONS

The small sample size of this exploratory observational study limits the statistical power and generalizability of the results. Given the low number of women in both groups of endurance athletes, the conclusions drawn from the sex comparison should be considered exploratory. Further studies with larger athlete populations including women are needed to better understand the influence of sex on cardiac remodeling. PVR values were not obtained invasively with right heart catheterization, and the method used to estimate PVR has not been validated in healthy population. However, a previous study by our group (5) found a high concordance in healthy athletes between PVR data obtained by CMR model and direct and indirect echocardiographic estimates of pulmonary pressure at rest and after exercise (5).

As peak oxygen consumption (VO2) was not measured, we cannot rule out a possible effect of VO2 on cardiac remodeling and, therefore, on the results obtained.

We did not perform delayed gadolinium enhancement sequences, thus limiting the analysis of fibrosis induced by chronic endurance swimming.

CONCLUSIONS

Endurance chronic swimming training induces biventricular and pulmonary vascular adaptation which is more pronounced in males. As compared to other endurance athletes, swimmers seem to present a less extensive remodeling of the RV. These findings may be due to a differential hemodynamic impact of swimming on the pulmonary circulation and the right heart.

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 Fundació Catalana Hospitals, approval number CEIC 15/28. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

VM conceived and designed the study, analyzed the data, and interpreted the results. VM, CF, and CY performed the cardiac magnetic resonance studies. MSG, BD-X, AG-A, SP-G, and MS contributed to the interpretation of the results. VM wrote the manuscript and MS supervised the study. All authors contributed to manuscript revision, read and approved the final manuscript.

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Sex-Specific Exposure–Effect Relationship Between Physical Activity and Incident Atrial Fibrillation in the General Population: A Dose–Response Meta-Analysis of 16 Prospective Studies

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Background: Since evidence regarding the relationship between physical activity (PA) and atrial fibrillation (AF) incidence is inconsistent among studies, we performed a dose–response meta-analysis to comprehensively evaluate the exposure–effect association between PA and incident AF and the potential sex difference in the general population.

Methods: The PubMed and Embase databases were searched for eligible studies published up to July 2020 (PROSPERO: CRD42018091692). The non-linear or linear exposure–effect relationship between PA and AF was examined using the robust error meta-regression method.

Results: A total of 16 prospective studies involving 1,449,017 individuals and 39,884 AF cases were included. We observed an inverse non-linear association between PA level and incident AF ($I^2 = 0\%$, $p_{non-linearity} < 0.001$). In the linear model, a 5 metabolic equivalent of task (MET)-h/week increase in PA was associated with a decreased risk of AF [risk ratio (RR) = 0.992, 95% confidence interval (CI): 0.988–0.996, $I^2 = 0\%$]. In the sex-stratified analysis, we observed an inverse non-linear relationship between PA level and AF risk in females ($I^2 = 90\%$, $p_{non-linearity} < 0.0001$) but not in males ($I^2 = 0\%$, $p_{non-linearity} = 0.40$). In the linear model, a 5 MET-h/week increase in PA was associated with a reduced risk of AF in females (RR = 0.982, 95% CI: 0.975–0.989, $I^2 = 71\%$) but not in males (RR = 0.998, 95% CI: 0.994–1.002, $I^2 = 0\%$), with a significant interaction observed between the two groups ($p_{interaction} < 0.0001$).

Conclusion: There was an inverse non-linear relationship between PA level and incident AF in the general population. The beneficial effect of PA in reducing AF risk might be predominantly observed in females.

Keywords: atrial fibrillation, physical activity, risk factor, dose-response, meta-analysis

INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia encountered in clinical practice, and it is associated with increased risks of stroke or systemic thromboembolism, mortality, and disability. Although the etiology of AF is still not fully understood, several modifiable risk factors, such as obesity, smoking, hypertension, alcohol abuse, and excessive exercise, have been identified (1, 2). Physical activity (PA) is defined as any movement that is produced by skeletal muscular action and results in energy consumption. Whether interventions targeting volumes of PA could be an effective strategy in the management of AF needs further investigation.

Previously, a series of studies examined the association of PA with AF risk in the general population but yielded conflicting results. Valenzuela et al. concluded that long-term endurance exercise was associated with an increased risk of AF among competitive athletes, whereas in non-athletes, either total PA or intense PA did not influence AF incidence (3). The neutral results observed in non-athletes could be partly explained by the sex difference: increased PA is associated with a decreased risk of AF in females but not in males (4). In addition, the association between PA and AF risk should be interpreted with caution because of the methodological limitations of existing studies (3). Moreover, a recent study by Elliott et al. examined a large prospective cohort of 402,406 adults and found an inverse association between total PA volume and AF risk (5), inconsistent with previous reports of a U-shaped or J-shaped association of PA with AF risk. Considering the emerging evidence and controversial findings (5–8), the association of PA level with AF risk warrants further evaluation. Furthermore, given our previous findings regarding discrepant effects of physical activity among males and females (4). We performed a dose–response meta-analysis to comprehensively investigate the exposure–effect association of PA levels with AF incidence in the general population, as well as potential sex-dependent effects.

METHODS

This meta-analysis was performed in accordance with the guidance from the Cochrane Handbook for Systematic Reviews. The results are presented in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (**Supplementary Table 1**). We did not obtain ethical approval because only previously published studies were included in this analysis. The data that support the findings of our study are available from the corresponding author upon reasonable request. The protocol of this meta-analysis has been registered with the PROSPERO International Prospective Register of Systematic Reviews (CRD42018091692).

Literature Search

The PubMed and Embase electronic databases were systematically searched for eligible studies that reported the relationship between PA and incident AF in the general population until July 2020. Two kinds of keywords and their similar terms were applied in the search: (1) "*physical activity*" OR "*exercise*," AND (2) "*atrial fibrillation*" OR "*atrial flutter*." To reduce the possibility of missing retrievals, we checked the reference lists of our included studies as well as that of a newly published umbrella review (3). We applied no language restrictions in the search.

Inclusion and Exclusion Criteria

Studies were considered eligible if they (1) performed a *post-hoc* analysis of randomized clinical trials (RCTs) or observational prospective cohort studies; (2) reported the relationship between leisure-time PA or total PA and incident AF in the general population; (3) provided adjusted risk estimates [risk ratios (RRs) and corresponding 95% confidence intervals (CIs)]; and (4) reported the PA dose in units of metabolic equivalent of task (MET)-h/week or other measures that could be used to calculate the values for analysis.

We excluded studies that assessed the effect of PA on AF risk in competitive athletes (long-term endurance exercise) who compete at different levels. We also excluded studies that focused on work-related PA. Since PA and physical fitness have different definitions and prognostic effects, studies that determined the association between physical fitness and AF were excluded. Abstracts, reviews, editorials, letters, animal studies, and studies with insufficient data were excluded. In cases of multiple reports based on the same data source, we used the risk estimates from the study with the longest follow-up or the largest sample size.

Data Extraction

Two investigators independently reviewed the titles and abstracts of the search records to identify potential studies according to the predefined inclusion criteria. We obtained more detail by screening the full texts of the retrieved studies. Disagreements were resolved by consensus or discussion with a third investigator. Relevant data were collected, including baseline characteristics of the population (e.g., study design, data source, participant age, participant sex, and sample size), diagnosis of AF, AF cases, follow-up duration, measurement of PA, unit of PA assessment (e.g., kilocalories per week, MET-hours per week, minutes per week, and kilometers per hour), covariates in the multivariable models, and adjusted RRs and 95% CIs in each category of PA. If two or more adjusted RRs were reported in a study, the most complete RR was collected.

Quality Assessment

The Newcastle-Ottawa Scale (NOS) (9) was used to evaluate the quality of the observational cohort studies. In *post-hoc* analyses, RCTs can be treated as cohorts when assessing study quality (10). This scale has three domains with a maximum possible score of 9 points: the selection of cohorts (0–4 points), the comparability of cohorts (0 to 2 points), and the assessment of outcome (0–3 points). An NOS score of $\geq$6 was considered to indicate moderate to high quality; otherwise, it was considered to indicate low quality (11, 12).

Abbreviations: PA, physical activity; AF, atrial fibrillation; MET, metabolic equivalent of task; RR, relative risk.

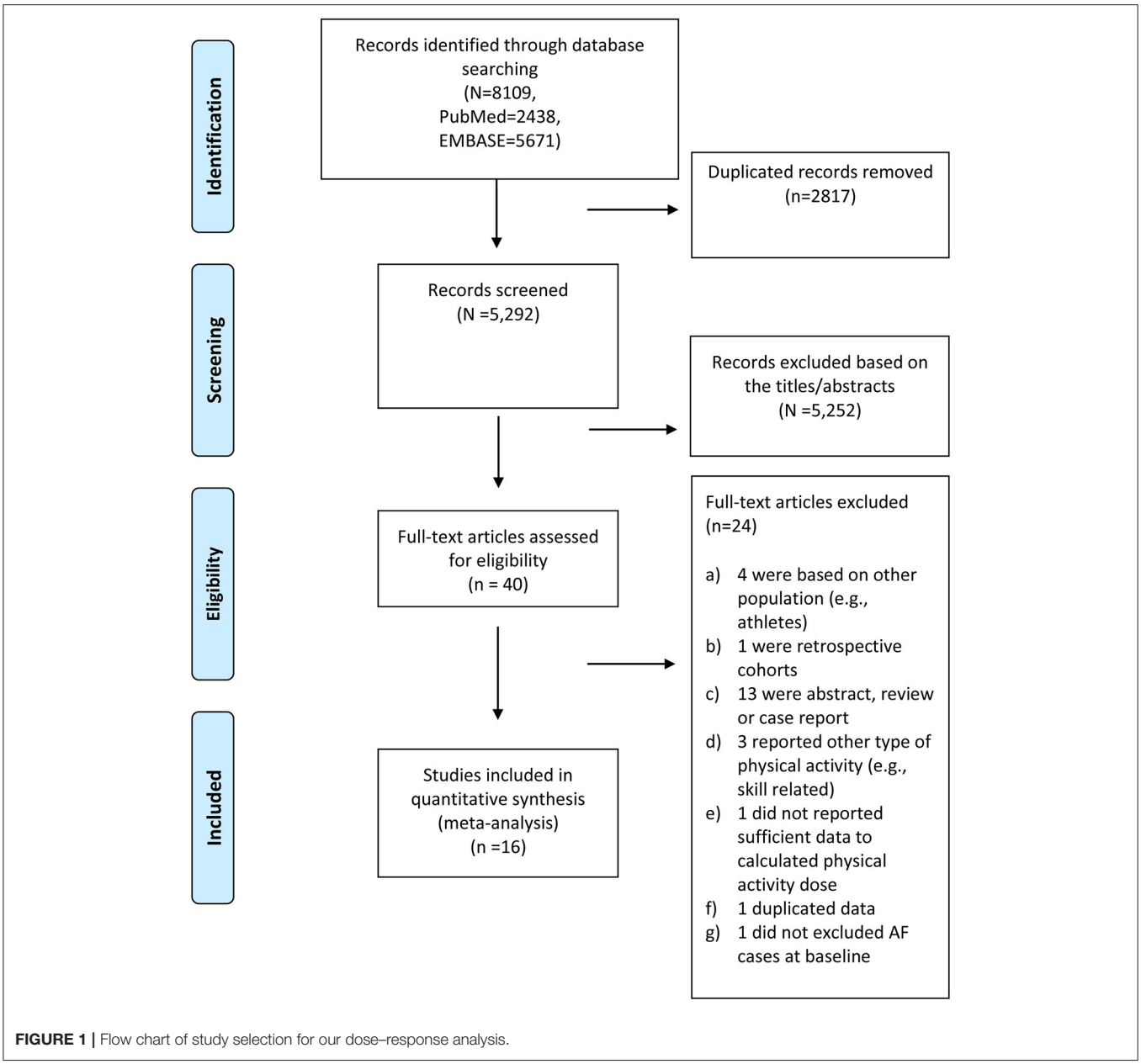

FIGURE 1 | Flow chart of study selection for our dose–response analysis.

Exposure Quantification

Considering that the PA units varied across the included studies, we quantified the group-level exposure estimates using the common unit of METs (h/week), allowing for the integration of different intensities or durations of PA exposure. To assign specific intensity to PA exposure, we regarded 3, 4, 4.5, and 8 METs as the mean intensity for light PA, moderate PA, moderate to vigorous PA, and vigorous PA, respectively (13) (https://www.who.int/dietphysicalactivity/physical_activity_intensity/en/). The intensity of the marginalized PA dose (MET-h/week) was considered in the sensitivity analysis by subtracting the resting metabolic rate of 1 MET from the raw mean PA intensity (2, 3, 3.5, and 7 METs for light PA, moderate PA, moderate to vigorous PA, and vigorous PA, respectively) (14, 15). In addition, we conducted transformations between kcal/week (Y) and MET-h/week (X) using the following formula (16):

$$\frac{\text{X [Met}*\text{h]}}{\text{Y [kcal]}} = \frac{4.5\ \text{[Met]} * 2.5\ \text{[h]}}{550\ \text{[kcal]}}$$

When the PA dose (MET-h/week) was not directly reported in some included studies, we multiplied the median or midpoint duration of the reported category by its assigned MET value. If PA was reported only as a frequency (sessions/week), a single session was assumed to be the estimated mean duration (45 min) in the primary analysis (14, 15). An assumed duration of 30 min

per session was used in the sensitivity analysis (14, 15). An overview of the MET-h/week dose-assignment calculations (both in the primary analysis and sensitivity analysis) is presented in **Supplementary Tables 2, 3**. For studies that reported PA levels at different ages, we only used PA exposure at the latest time.

Statistical Analyses

The heterogeneity across the included studies was assessed using I^2 statistics, where 25–50%, 50–75%, and >75% indicated low, moderate, and high heterogeneity, respectively (17). A random effects model was used to pool the risk estimates. Robust error meta-regression methods were used to fit the possible non-linear or linear relationships (18). The methods required at least two levels of PA and the corresponding RRs with variance estimates. If a study did not use the lowest PA group as the reference, the data were transformed using the methods of Hamling et al. (19). In this situation, the number of AF cases and participants in each category of PA were required. If a study did not provide the median or mean PA in each category of PA, we estimated the midpoint of each category by averaging the lower and upper boundaries of that category (12). If the highest or lowest category was open-ended, we assumed that the open-ended interval length was the same as that of the adjacent interval (12). We used 5 MET-h/week in our linear analysis, defined according to the baseline dose PA levels recommended by WHO (150–300 min of moderate-intensity PA, range ≈5–111.5 MET-h/week). Subgroup analyses were performed based on age, measurement of PA, region, follow-up duration, sample size, and AF diagnosis. Publication bias was investigated by funnel plots for a visual inspection of asymmetry and statistically assessed by Egger's and Begg's tests.

Statistical analyses were performed using Review Manager software (version 5.3, the Cochrane Collaboration 2014; Nordic Cochrane Center Copenhagen, Denmark) and Stata software (Version 14.0, Stata Corp. LP, College Station, Texas, USA).

RESULTS

Study Selection

The process of study selection is shown in **Figure 1**. We initially identified 8,109 records in the electronic PubMed and Embase databases. After reviewing the titles and abstracts of the search records, the full texts of 40 retrieved studies were reviewed for detailed evaluation. We excluded 24 studies because they (1) assessed the association of PA with AF in competitive athletes (long-term endurance exercise); (2) were designed as retrospective cohorts or case–control studies; (3) were conference abstracts, reviews, or case reports; or (4) focused on duplicate populations. Finally, we included a total of 16 prospective studies [1 *post-hoc* analysis of RCTs (20) and 15 prospective cohorts (5–8, 21–31)] representing a total sample size of 1,449,017 individuals and 39,884 AF cases.

Study Characteristics

A summary of the study characteristics is provided in **Table 1** and **Supplementary Table 4**. Among the included studies, the sample size ranged from 5,446 to 501,690, and the cumulative AF incidence ranged from 0.14 to 19.48%. The mean age of the study population ranged from 38.0 to 72.8 years. The duration of follow-up ranged from 3.7 to 22 years. Nine studies (5, 7, 8, 22, 25, 26, 29–31) and 11 studies (5, 7, 8, 20, 21, 23, 25, 26, 29–31) reported the association between PA and AF in males and females, respectively. Apart from the study by O'Neal et al. (8), the studies relied on self-reported PA collected by questionnaire or interview. Regarding AF measures, those of 13 studies were based on electrocardiogram or codes of the International Classification of Diseases; 2 studies (8, 31) used electrocardiogram and/or self-reported medical history, and 1 study (29) applied the prescription of flecainide or sotalol. Each of the included studies was moderate-to-high quality, as indicated by their NOS quality scores of >7 (**Supplementary Table 5**).

Dose–Response Association Between PA and AF

The reference PA dose varied widely (from 0 to 68 MET-h/week) across the included studies, limiting the direct synthesis of all included studies in the dose–response analysis. Therefore, we first regarded low or sedentary activity (0–1.5 MET-h/week) as the reference (5–8, 20–30) to investigate AF risk of moderate PA dose compared with low or sedentary activity. As shown in **Figure 2A** and **Supplementary Table 6**, we found a significant non-linear relationship between PA in the range of 0–80 MET-h/week and AF risk ($I^2 = 0$; $p_{\text{non-linearity}} = 0.0016$). The linear model applied to investigate the average relationship between PA and AF suggested that every 5 MET-h/week increment in PA was associated with a significantly decreased risk of AF (RR = 0.992, 95% CI: 0.988–0.996; $I^2 = 0$; **Figure 2B**). In the sensitivity analyses, conducted by changing the assumptions of intensity or duration of PA exposure, the corresponding shapes of the dose–response curves were similar to that observed in the abovementioned primary analysis (**Supplementary Figures 1, 2**).

Subsequently, we included three studies (25, 30, 31) that regarded a moderate dose of PA (ranging from 38.5 to 63.5 MET-h/week) as the reference to investigate AF risk of a high PA dose (up to 250 MET-h/week) compared with a moderate PA dose. As shown in **Figure 2C**, there was a non-significant non-linear relationship between a high PA dose and AF risk ($I^2 = 0$; $p_{\text{non-linearity}} = 0.22$). In the linear model, a 5 MET-h/week increase in PA was not associated with a change in AF risk (RR = 0.989, 95% CI: 0.964–1.014, $I^2 = 0$, **Figure 2D**). Due to the small number of included studies in this part, the results should be interpreted with caution.

In the sex-stratified analysis, using low or sedentary activity as the reference, we found an inverse non-linear relationship between PA dose and AF risk in females ($I^2 = 90\%$, $p_{\text{non-linearity}} < 0.0001$, **Figure 3A**). The linear model showed that a 5 MET-h/week increase in PA (13) was associated with a 2.8% decrease in the risk of AF in females (RR = 0.982, 95% CI: 0.975–0.989, $I^2 = 71\%$, **Figure 3B**). In males, there was a non-significant non-linear relationship between PA dose and AF risk ($I^2 = 0\%$, $p_{\text{non-linearity}} = 0.40$, **Figure 3C**). The linear model showed that a 5 MET-h/week increase in PA was not associated with a change in AF

TABLE 1 | A summary of basic characteristics of the included studies.

References, country	Source of individuals	Follow-up (years)	Sex	Mean age (years)	AF diagnosis	Case/size AF prevalence (%)	Measurement of PA	Adjusted covariates
Lee et al. (6), Korea	Kangbuk Samsung Health Study	5.6	M/W	44.7	ECG	304/211,992 (0.14%)	Questionnaire	Age, sex, center, year of screening examination, smoking status, alcohol intake, and education level. BMI, DM, hypertension, cardiovascular disease, and hs-CRP
Choi et al. (31), Korea	Korean Genome and Epidemiology Study	12.0	M/W	50.0	ECG or self-reported history of physician-determined diagnosis	167/8,811 (1.89%)	Questionnaire	Age, sex, residence, education, BMI, comorbidity, alcohol, and smoking, and RHR
Jin et al. (7), Korea	NHIS cohort of Korean	4.0	M/W	47.6	ICD	3,443 /501,690 (0.68%)	Questionnaire	Age, sex, BMI, HF, hypertension, DM, previous MI, prior stroke or transient ischemic attack, chronic kidney disease, smoking, and alcohol drinking
Elliott et al. (5), UK	UK Biobank cohort	7.0	M/W	56.0	ICD	8,640/402,406 (2.14%)	Questionnaire	Age, BMI, smoking, alcohol intake, hypertension, Type 2 DM, sleep apnea, HF, valvar disease, and coronary artery disease
Albrecht et al. (30), USA	Rotterdam Study	16.9	M/W	69.4	ECG	800/7,018 (11.39%)	Questionnaire	Age, sex, all other PA types, smoking, previous CVDs, alcohol consumption, diet, education, BMI, total and HDL, DM, lipid reducing agents, SBP, DBP, anti-thrombotic agents, and ACE-inhibitor use.
O'Neal et al. (8), USA	REGARDS Study	3.5	M/W	63.0	ECG and self-reported medical history	439/5,147 (8.52%)	Objectively Measured	Age, gender, race, education, income, and geographic region, with the addition of SBP, HDL, total cholesterol, BMI, smoking, DM, antihypertensive medications, LVH, and previous cardiovascular disease
Mokhayeri et al. (25), USA	MESA Study	11.0	M/W	62.3	ICD	242/6,487 (3.73%)	Questionnaire	Race, income, pack-years of smoking, BMI, alcohol, HP, lipids (total cholesterol, HDL), and diabetes
Morseth et al. (26), Norway	Tromsø Study survey	20.0	W/M	38.0	ECG	750/20,484 (3.66%)	Questionnaire	Age, sex, BMI, height, daily smoking, CVD, SBP, DBP, DM, hypertension treatment, RHR, and use of heart medication
Skielboe et al. (28), Denmark	Copenhagen City Heart Study	20.3	M/W	48.0	ECG or ICD	1,192/17,196 (6.93%)	Questionnaire	Age, height, BMI, sex, smoking, drinking habits, school education, BP, RHR, spirometry, cardiac medication, DM, ischemic heart disease, and enrolment number
Drca et al. (23), Sweden	Swedish Mammography Cohort	12.0	W	60.0	ICD	2,915/36,513 (7.98%)	Questionnaire	Age, education, smoking status, pack years of smoking, BMI, DM, history of hypertension, history of CHD or HF, family history of MI, aspirin use, and alcohol consumption
Azarbal et al. (21), USA	WHI Observational Study	11.5	W	64.5	ICD	9,792/81,317 (12.04%)	Questionnaire	Age, race, education, BMI, hypertension, DM, hyperlipidemia, CHD, HF, PAD, and smoking
Drca et al. (22), Sweden	People in Västmanland and Örebro	12.0	M	60.0	ICD	4,568/44,410 (10.28%)	Questionnaire	Age, education, smoking status, pack years of smoking, BMI, diabetes, history of hypertension, history of CHD or HF, family history of MI, aspirin use, and alcohol consumption
Huxley et al. (24), USA	ARIC Study	22.0	M/W	54.2	ECG	1,775/14,219 (12.48%)	Questionnaire	Age, race, study site, education, income, prior CVDs, cigarette smoking, height, and alcohol consumption

(Continued)

TABLE 1 | Continued

References, country	Source of individuals	Follow-up (years)	Sex	Mean age (years)	AF diagnosis	Case/size AF prevalence (%)	Measurement of PA	Adjusted covariates
Thelle et al. (29), Norway	People in Norwegian	5.0	M/W	42.5	Prescription of flecainide or sotalol	863/309,540 (0.27%)	Questionnaire	Age, year of screening, education, BMI, height, daily smoking, self-reported CVDs at screening, and dispensed CVDs drug
Everett et al. (20), USA	Women's Health Study	14.4	W	54.6	ECG	968/34,759 (2.78%)	Questionnaire	Age, randomized treatment, cholesterol, current smoking, past smoking, alcohol, DM, race, hypertension, and BMI
Mozaffarianet et al. (27), USA	CHS Study	12.0	M/W	72.8	ECG	1,061/5,446 (19.48%)	Questionnaire	Age, sex, race, enrollment site, education, smoking status, pack-year of smoking, CHD, chronic pulmonary disease, DM, alcohol use, and β-blocker use

PA, physical activity; AF, atrial fibrillation; CI, confidence interval; MET-h/wk, the metabolic equivalent of task-h/week; M, men; W, women; ECG, electrocardiogram: relative risk; ICD, International Classification of Diseases; BMI, body mass index; CVD, cardiovascular disease; CHD, Coronary heart diseases; RHR, resting heart rate; DM, diabetes mellitus; CHD, coronary heart disease; HF, heart failure; MI, myocardial infarction; PAD, peripheral artery disease; BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high-density lipoprotein cholesterol; LVH, left ventricular hypertrophy; hs-CRP, high sensitivity C-reactive protein; MESA, Multi-Ethnic Study of Atherosclerosis; CHS, Cardiovascular health study; ARIC, Atherosclerosis Risk In Communities; WHI, Women's Health Initiative; SCHPPM, Seirei Center for Health Promotion and Preventive Medicine; Korean National Health Insurance Service (NHIS); REGARDS, Reasons for Geographic and Racial Differences in Stroke.

risk (RR = 0.998, 95% CI: 0.994–1.002, $I^2 = 0$, **Figure 3D**). There was a significant interaction between the two groups ($p_{\text{interaction}} < 0.0001$, **Supplementary Figure 2**).

We further examined the sex-stratified effect of PA level recommended by international institutions (32). In females, compared with sedentary activity, both the recommended basic PA level (150–300 min of moderate-intensity PA ≈ 11.25 MET-h/week; RR = 0.90; 95% CI: 0.88–0.92) and the strongly recommended PA level (>300 min of moderate-intensity PA ≈ >22.5 MET-h/week; RR = 0.86; 95% CI: 0.84–0.88) were associated with a decreased risk of AF. In males, decreased AF risk was not observed in the groups with recommended basic PA levels (RR = 0.96; 95% CI: 0.90–1.01) and strongly recommended PA levels (RR = 0.95; 95% CI: 0.88–1.02).

Subgroup Analyses

In the age-stratified analysis, a 5 MET-h/week increase in PA was not associated with a change in AF risk (RR = 1.02, 95% CI: 0.95–1.09, $I^2 = 0$) in the ≤50 years group, while a 5 MET-h/week increase in PA was associated with a decreased risk of AF (RR = 0.99, 95% CI: 0.98–0.99, $I^2 = 16\%$) in the >50 years subgroup (**Table 2**). Nevertheless, we observed no significant interaction between the two groups ($p_{\text{interaction}} = 0.32$). The exposure–effect analysis of the non-linear model yielded similar results to the linear model (**Supplementary Figure 4**).

In addition, we found no interactions in the other subgroup analyses based on the measurement of PA, region, follow-up duration, sample size, or AF diagnosis (all $p_{\text{interaction}} > 0.05$).

Publication Bias

As shown in **Supplementary Figure 5**, there was no indication of publication bias according to Egger's test ($p = 0.35$), Begg's test ($p = 0.42$), or the funnel plot.

DISCUSSION

In the present study, our findings based on data from 16 prospective studies involving 1,449,017 individuals and 39,884 AF included the following: (1) an inverse non-linear association was found between PA level and incident AF in the general population, (2) a 5 MET-h/week increase in PA was associated with a reduced risk of AF in the linear model, and (3) the sex-stratified analysis indicated that the benefit of PA in reducing AF risk was predominantly in females.

Several studies regarding PA and the risk of AF have been published but have yielded inconsistent findings. Prior meta-analyses have reported that long-term endurance exercise is associated with an increased risk of AF among competitive athletes, whereas either total PA or intense PA has no impact on AF incidence in the general population. Neilson et al. (33) defined a "U"-shaped association of PA with AF risk. Subsequently, a J-shaped association was confirmed by a non-linear exposure–effect meta-regression analysis (34). Nevertheless, as proposed by Valenzuela et al. (3), the association between exercise and AF should be interpreted with caution because of the methodological limitations of existing evidence (4). On the one hand, some prior meta-analyses showed considerable heterogeneity in their

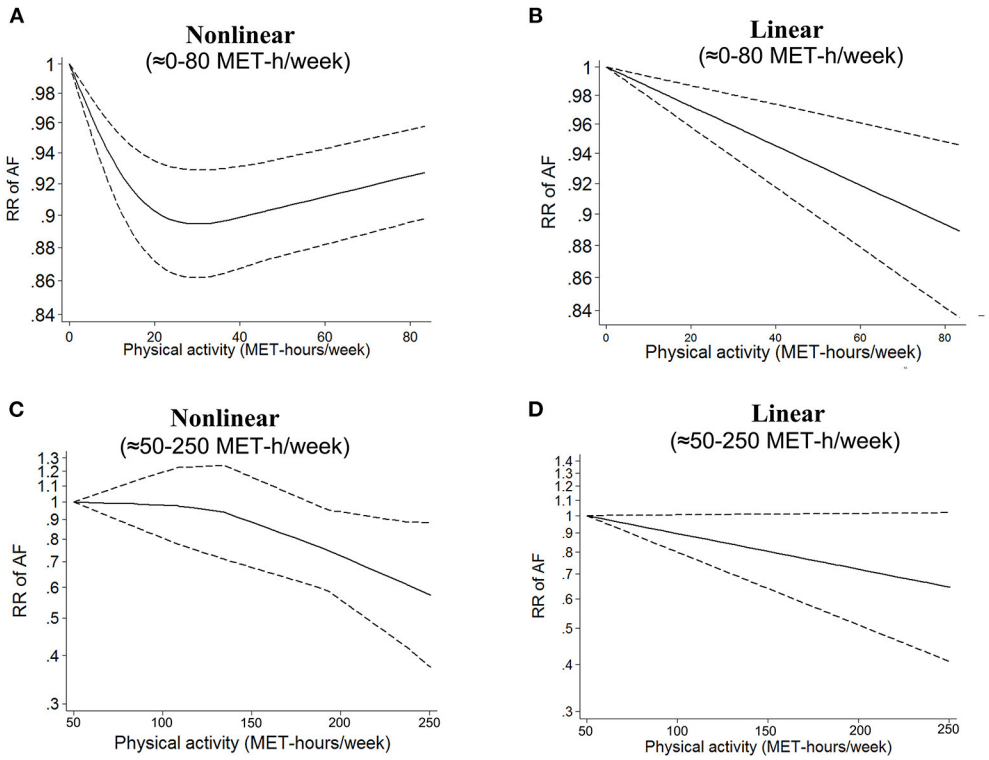

FIGURE 2 | Dose–response analysis of physical activity and atrial fibrillation in the total population. **(A,B)** Non-linear and linear models of PA and AF in the range of 0–80 MET-h/week. **(C,D)** Non-linear and linear models of PA and AF at the high level of PA. The bold and dashed lines represent the estimated RR and 95% CI, respectively. The non-linear models were fit by using a restricted cubic spline. PA, physical activity; AF, atrial fibrillation; RR, risk ratio; CI, confidence interval.

study population because athletes were not excluded (35–37). As a result of cardiac adaptations to long-term endurance exercise, athletes often have a lower resting heart rate, larger diameter of the left atrium, elevated fibrosis level, and imbalance of autonomic function, potentially increasing susceptibility to AF (38). As such, sports-related AF among athletes should be disregarded when examining the relationship between PA and AF in the general population. On the other hand, given the different impacts of occupational PA and leisure-time PA on AF (38), it might not be reasonable to combine different types of PA for analysis in some meta-analyses (34, 39). Moreover, a newly published prospective cohort study by Elliott et al. found an inverse association between total PA (>500 MET-min/week) and AF risk in the general population (5). Considering the methodological limitations of previous studies and novel emerging evidence, the association of PA with AF risk warrants reevaluation. Unlike previous studies reporting a J-shaped association (34, 40), our current meta-analysis revealed an inverse relationship between PA level and AF risk in the general population. Notably, cardiorespiratory fitness is inversely associated with AF risk (41). Since PA, as one of the primary determinants of cardiorespiratory fitness, could improve fitness (42), the finding of similar benefits of PA and cardiorespiratory fitness in reducing AF risk is not unexpected.

A prior meta-analysis by Mohanty et al. revealed that moderate exercise was protective against AF regardless of sex (39). Our previous meta-analysis by Zhu et al. suggested that increasing PA was associated with a decreased risk of AF in females but an increased AF risk in males (3). In the newly published study by Elliott et al., PA was found to be associated with a reduced risk of incident AF across PA levels (from 500 to 5,000 MET-min/week) in females, whereas in males, a decreased risk of AF was observed for PA levels ranging from 500 to 1,500 MET-min/week, but a detrimental effect, enhancement of AF risk, was observed for PA levels of >5,000 MET-min/week (5). Elliott et al. further found that, in males, there was no association of vigorous PA at low to moderate doses with AF risk, but vigorous PA at extreme doses resulted in a 12% increased risk of AF; in contrast, a reduced incidence of AF across PA levels was observed in female participants (5). Therefore, whether such sex differences in the association between PA and AF risk exist in the general population remains unclear. To our knowledge, we are the first to assess the sex difference in the dose–response association between PA and AF risk in the general population, and we revealed a significant benefit of PA in decreasing AF risk in females. Consistent with this finding, a reduced risk of AF in females at recommended PA levels has been reported by international institutions (32). However, in males, we did not

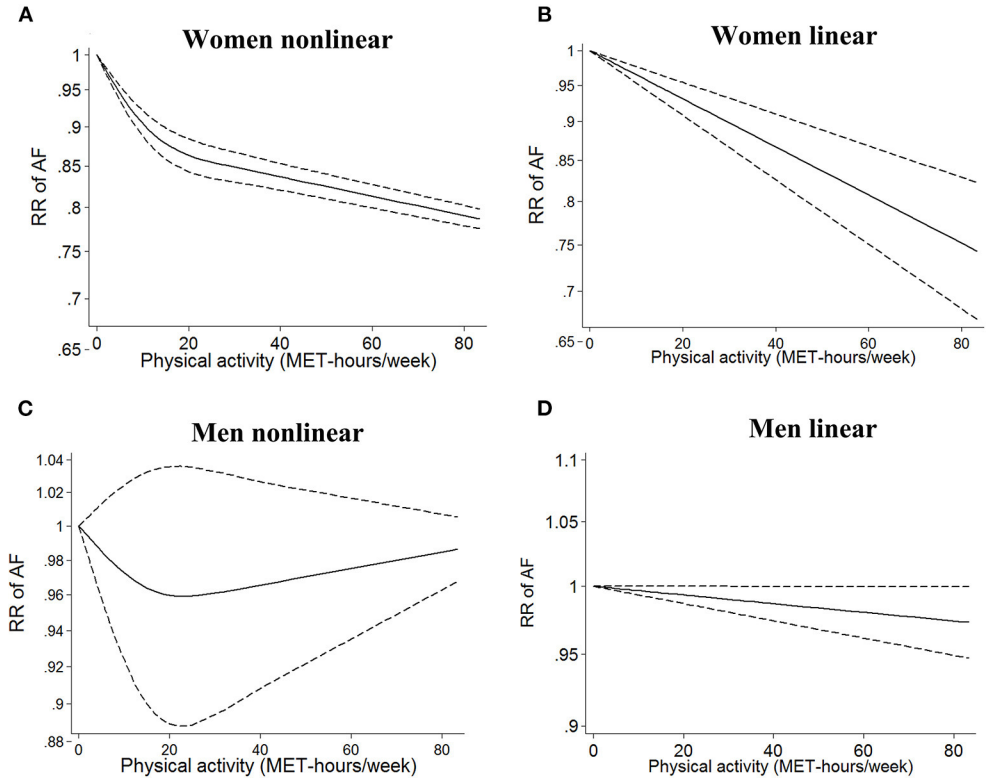

FIGURE 3 | Dose–response analysis of physical activity and atrial fibrillation in the sex-stratified analysis. **(A,B)** Non-linear and linear models of PA and AF in females. **(C,D)** Non-linear and linear models of PA and AF in males. The bold and dashed lines represent the estimated RR and 95% CI, respectively. The non-linear models were fit by using a restricted cubic spline. PA, physical activity; AF, atrial fibrillation; RR, risk ratio; CI, confidence interval.

find a benefit of moderate or high levels of PA in AF. This result should be interpreted with caution. In the non-linear relationship shown in **Figure 2C**, a non-significant trend was found for the moderate level of PA, suggesting that moderate exercise might have some benefit. On the other hand, there was a trend of increased AF risk at high levels. This phenomenon does not surprise us, as it is consistent with some of our previous findings. It has long been suspected that the AF-promoting effects of exercise are predominantly expressed in males. The study of Elliott et al. (5) is the clearest and most definitive demonstration to date regarding potential sex differences. They showed that among women, only a protective effect of exercise was evident, expressed across the entire range of exercise levels. Among men, a clearly decreased AF risk was observed only with moderate PA; men became more AF prone with regular vigorous exercise.

The potential mechanism underlying the positive association between a high level of PA and AF in males in the general population is difficult to interpret. In endurance training athletes, compared with females, males exhibit more atrial electrophysiological changes (e.g., a larger atrial volume and left ventricle mass index, a greater relative wall thickness, and a longer p-wave duration) in response to rapid atrial pacing (43). Furthermore, in a frequency domain analysis of heart rate variability, male athletes were found to have a greater low-/high-frequency power ratio than females, suggesting greater sympathovagal balance in males. As several excellent reviews pointed out, multiple pathophysiological mechanisms might be responsible for the development of AF in athletes, such as atrial enlargement and fibrosis, atrial ectopic triggers, increased vagal tone, increased inflammation, and atrial function response to exercise (44–46). However, it remains unknown whether the discrepancy in atrial electrophysiological remodeling between the sexes could be responsible for the sex-specific exposure–effect relationship between PA and AF in the generally healthy population. The mechanistic basis of this phenomenon merits further investigation.

There is compelling evidence that individuals who have higher PA levels benefit from reduced incidences of all-cause mortality, diabetes, and cardiovascular diseases (32). Several international guidelines support the preventive effect of regular PA against non-communicable diseases such as cardiovascular diseases and diabetes (32). Among patients with established heart failure, the advancement of PA could reduce the risks of hospitalization and cardiovascular mortality and improve cardiorespiratory function and quality of life (47). In addition, a higher PA level is associated with a lower risk of AF in patients with heart failure (48). In patients with AF, a higher PA is associated with lower risks of all-cause mortality and cardiovascular mortality (49). Our current analysis extends the findings of previous studies, revealing an inverse association between PA and AF occurrence in the general

TABLE 2 | Subgroup analysis of physical activity and atrial fibrillation, exposure-effect analysis, per 5 MET h/week increment[#] (8 MET-h/week is equivalent to 30 min of regular walking a day for 3 days a week).

Items		Number of studies	RR (95% CI)	I^2 within each subgroup	*P* for subgroup difference
Result of primary analysis PA		15	0.992 (0.988–0.996)	0	–
Sex※	Females	9	0.982 (0.975–0.989)	71	<0.0001
	Males	9	0.998 (0.994–1.002)	0	
Age※	≤50 years	5	1.020 (0.950–1.090)	0	0.32
	>50 years	10	0.992 (0.98–0.997)	16	
Measurement of PA	Questionnaire	14	0.992 (0.988–0.996)	0	–
	Objectively Measured	1	NA*	–	–
Region	Northern America	7	0.96 (0.93–0.99)	47	0.44
	Europe	6	0.994 (0.992–0.997)	73	
	Asia	2	NA*		
Follow-up duration	≤10 years	5	0.995 (0.991–0.998)	48	0.23
	>10 years	10	0.977 (0.957–0.997)	0	
AF Diagnosis	ECG or ICD	14	0.991 (0.986–0.997)	0	NA
	Others	1	NA*		
Sample size	<100 000	11	0.97 (0.95–0.99)	0	0.31
	>100 000	4	0.994 (0.992–0.996)	94	

[#]*Subgroup of results that used the low or sedentary activity as a reference; the subgroup analysis that used moderate exercise as reference were not available due to the limited studies (N = 3).*

[*]*Not available for dose-response analysis due to the limited data.*

※*Multi-subgroup (age and sex) data were reported in some cohorts.*

The number of studies is not always equal because the subgroup analyses were not available in several included studies.

AF, atrial fibrillation; PA, physical activity; NA, not available.

population. In contrast, studies of long-term endurance exercise athletes have shown that high volumes of high-intensity PA are associated with an increased AF risk, thus indicating that "more is not always better" when referring to the association between PA and AF (50).

A previous meta-analysis showed that higher PA levels could increase AF risk in males (3). However, our current data showed that, in males, moderate-intensity PA of 150–300 min or >300 min did not significantly increase the risk of AF. We cannot exclude the possibility that if more patients are included in future studies, significant benefits of PA in reducing AF risk in males may be found. Collectively, our current evidence indicated that exercise at a dose in accordance with the recommended PA guidelines played a protective role in females, reducing AF risk among females, and was at least not harmful in males. The harmful dose of exercise was higher than the recommended PA levels. Therefore, both males and females could undergo an adequate amount of PA and maintain fitness with no fear of an increased AF risk.

Strengths and Limitations

In this meta-analysis, we included high-quality studies with a large sample size of participants. We also excluded studies that enrolled athletes to focus on PA in the general population. A robust error meta-regression method was employed in the dose–response analysis to enhance the robustness of our results. In addition, we performed sensitivity analyses by changing assumptions regarding the intensity or duration of PA exposure; the results were similar to those of the primary analysis, suggesting the robustness of our findings. Nevertheless, our study has several limitations, as follows: First, although the included studies adjusted for several hybrid variables, residual confounding factors could not be excluded. Second, we calculated the PA dose based on assumptions regarding intensity or duration of PA exposure, which might have impacted our results. Third, nearly all the included studies assessed self-reported PA exposure, which might be prone to recall bias and overestimation. However, a recently published article showed an inverse association between PA and AF by using accelerometer measurements (51), which confirms our main results. Specifically, they found a weak correlation between accelerometer assessment and self-reported PA and a non-significant AF benefit from self-reported exercise. However, their results regarding self-reported PA were not consistent with previous studies based on the same dataset from the UK Biobank. Both Elliott et al. (5) and Said et al. (52) showed that greater self-reported activity may be beneficial with respect to AF risk. The discrepancy might derive from the small sample sizes and study differences in the methods of statistical analysis. As our results are based on a large sample, they may be reliable regardless of the form of assessment of PA. Fourth, studies investigating the effect of long-term endurance exercise on the risk of AF in athletes were excluded from our study. Further research could focus on the association of long-term endurance exercise with AF risk. Finally, although PA is the greatest determinant of fitness, PA and physical fitness have different definitions, and they may

have independent associations with AF risk (42). Whether the relationship between PA and AF is independent of physical fitness needs further examination.

Conclusions

The results from our dose–response meta-analysis revealed an inverse non-linear relationship between PA and AF risk in the general population. The beneficial effect of PA in reducing AF incidence was predominantly present in females.

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

WZ and XL performed the study design. QW and XL performed the selection, extraction, statistical analysis, and interpretation of the data. QW, YZ, and XL wrote and revised the manuscript. 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.2021.710071/full#supplementary-material

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Circulating Vascular Cell Adhesion Molecule-1 (sVCAM-1) Is Associated With Left Atrial Remodeling in Long-Distance Runners

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Introduction: An increased risk of atrial fibrillation (AF) has been demonstrated in high-performance athletes. Soluble vascular adhesion molecule-1 (sVCAM-1), a biomarker involved in inflammation and cardiac remodeling, is associated with the development of AF in the general population. However, the relationship between sVCAM-1 and left atrial (LA) remodeling has been poorly investigated in long-distance runners (LDR).

Aim: To determine the association between LA remodeling and sVCAM-1 levels in LDR during the training period before a marathon race.

Methods: Thirty-six healthy male LDR (37.0 ± 5.3 years; 174.0 ± 7.0 height; BMI: 23.8 ± 2.8; $\dot{V}O_2$-peak: 56.5 ± 7.3 mL·kg^{-1}·min^{-1}) were evaluated in this single-blind and cross-sectional study. The LDR were separated into two groups according to previous training levels: high-training (HT) (n = 18) ≥100 km·week^{-1} and low-training (LT) (n = 18) ≥70 and <100 km·week^{-1}. Also, 18 healthy non-active subjects were included as a control group (CTR). In all participants, transthoracic echocardiography was performed. sVCAM-1 blood levels were measured baseline and immediately finished the marathon race in LDR.

Results: HT showed increased basal levels of sVCAM-1 (651 ± 350 vs. 440 ± 98 ng·mL^{-1} CTR, p = 0.002; and vs. 533 ± 133 ng·mL^{-1} LT; p = 0.003) and a post-marathon increase (ΔsVCAM-1) (651 ± 350 to 905 ± 373 ng·mL^{-1}; p = 0.002), that did not occur in LT (533 ± 133 to 651 ± 138 ng·mL^{-1}; p = 0.117). In LDR was a moderate correlation between LA volume and sVCAM-1 level (rho = 0.510; p = 0.001).

Conclusions: In male long-distance runners, sVCAM-1 levels are directly associated with LA remodeling. Also, the training level is associated with basal sVCAM-1 levels and changes after an intense and prolonged exercise (42.2 km). Whether sVCAM-1 levels predict the risk of AF in runners remains to be established.

Keywords: arrhythmias, cardiac remodeling, exercise, sports cardiology, athletes heart

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INTRODUCTION

Moderate aerobic exercise is considered an essential element in maintaining cardiovascular health (1). However, when performed regularly at high intensity, it can have deleterious effects (2). In this regard, there is a growing group of athletes who perform several hours of intense exercise a week and are developing cardiac level changes, a phenomenon called *"athlete's heart"* (3). These structural modifications are characterized by increases in the size and thickness of both ventricular cavities, hypertrabeculation of the left ventricular (LV) walls (4–6), and increases in left atrial (LA) size and changes in its function (6). These physiological adaptations enable the achievement of greater cardiac output during exercise with the consequential increase in the maximum oxygen consumption ($\dot{V}O_2$-max) and improvement in sports performance (7). However, in some athletes, intense and prolonged exercise can induce unexpected changes in response to physical exercise, the long-term impact of which is not yet clear (8–12). These changes are characterized by exaggerated cardiac remodeling, a phenomenon called *"Phidippides cardiomyopathy"* (3), that it is currently a hypothesis supported by evidence of potentially adverse cardiac remodeling in some endurance athletes (10). In that regard, evidence has shown that intense exercise can generate potentially adverse cardiac remodeling (11), fibrosis of the myocardial tissue (12), and a higher incidence of atrial fibrillation (AF) (13).

Soluble vascular cell adhesion molecule-1 (sVCAM-1), a possible biomarker of the process of fibrosis and cardiac remodeling as a consequence of physical exercise (14), plays a key role in the adhesion of inflammatory molecules and transmigration of leukocytes to the vascular intima (15); it can cause endothelial dysfunction, thus affecting the regulation of cardiac blood flow. In this regard, aerobic exercise has been shown to increase its expression and induce cellular infiltration and inflammation of the heart tissue in untrained subjects (16) as well as patients with peripheral vascular disease (17). On the other hand, both atrial fibrillation (AF) and rapid atrial stimulation are associated with increases in the endocardial expression of VCAM-1 (18); even its elevated plasma levels have been considered a predictor of postoperative AF (19).

The association between sVCAM-1 and cardiac structural changes has not been studied in long-distance runners, who are accustomed to intense and prolonged training. Thus, the present study determined the plasma levels of sVCAM-1 in long-distance runners at different training levels before and immediately after intense and prolonged exercise (42.2 km marathon race) and evaluated the association with LA remodeling on echocardiography. The study aimed to evaluate the role of sVCAM-1 as a possible biomarker of exaggerated atrial remodeling and subsequent development of AF in high-performance athletes.

MATERIALS AND METHODS

This prospective single-blind cohort study evaluated 36 Caucasian male competitive long-distance runners. The inclusion criterion was prior participation in at least 3–5 marathon competitions in the last 5 years. The exclusion criteria were as follows: arterial hypertension (resting blood pressure >140/90 mmHg in two separate measurements); dyslipidemia (total cholesterol >200 $mg{\cdot}dL^{-1}$, low-density lipoprotein cholesterol >100 $mg{\cdot}dL^{-1}$, high-density lipoprotein cholesterol <40 mg/dL, triglycerides >150 $mg{\cdot}dL^{-1}$); diabetes mellitus; insulin resistance (homeostatic model assessment >2.5); any degree of smoking; previous cerebrovascular disease (self-reported clinical history); alcohol consumption >40 g per day; drug use; nutritional supplement use; impaired renal function (glomerular filtration rate <60 $mL{\cdot}min^{-1}$ Modification of Diet in Renal Disease); family history of sudden death; liver damage; autoimmune disease; active neoplasm; chronic obstructive pulmonary disease; diseases that alter the studied biomarker levels (acute inflammation or infectious disease in the month before the marathon); and the use of any antihypertensive, anorectic, antidepressant, and/or antibiotic.

The runners were divided into two groups according to previous training levels: high-training (HT; >100 km per week; $n = 18$) and low-training (LT; >70 and <100 km per week; $n = 18$). Eighteen age- and body surface area—matched healthy and non-active men were included as a control group (CTR). This study adhered to the principles outlined in the Declaration of Helsinki and was approved by the Ethics Committee for Human Research at the Faculty of Medicine of the Pontificia Universidad Católica de Chile (project no. 16082603). Written informed consent was obtained from all participants prior to any procedure. The **Figure 1** shows the protocol design.

Cardiopulmonary Test (Peak Oxygen Consumption ($\dot{V}O_2$-Peak)

To evaluate the performance of runners, the peak aerobic capacity test ($\dot{V}O_2$-peak) was performed at the end of the "optimal phase" training period. All runners were instructed not to perform physical activity for 24 h prior to the measurement and to avoid intakes of alcohol, caffeine, or other stimulants and food for at least 3 h before. The $\dot{V}O_2$-peak test was measured on a treadmill ergometer (HP Cosmos, Traunstein, Germany) until voluntary exhaustion, despite oral breathing (respiratory quotient, 1.20 ± 0.05). The exercise protocol consisted of a 3-min rest, 5-min warm-up (8 $km{\cdot}h^{-1}$), and subsequent increase of 2 $km{\cdot}h^{-1}$ every 150 s, until all criteria for stopping the test were met. The exhaled gases were measured continuously using a metabolic detector (Masterscreen-CPX, Jaeger, Traunstein, Germany) equipped with O_2 and CO_2 analyzers.

Echocardiographic Assessment

Standard transthoracic echocardiography (TTE) was performed in all subjects according to international standards of the American Society for Echocardiography (ASE) (20). The baseline TTE was obtained the week before the marathon. The examination was performed by trained expert personnel and included parasternal and apical views on a 1.5/3.5 MHz cardiac transducer and a Vivid I portable computer (GE, Healthcare, Horton, Norway). Parietal wall thickness, cavitary volumes, and LV mass were evaluated in accordance with ASE recommendations (20). The LV mass was calculated using the

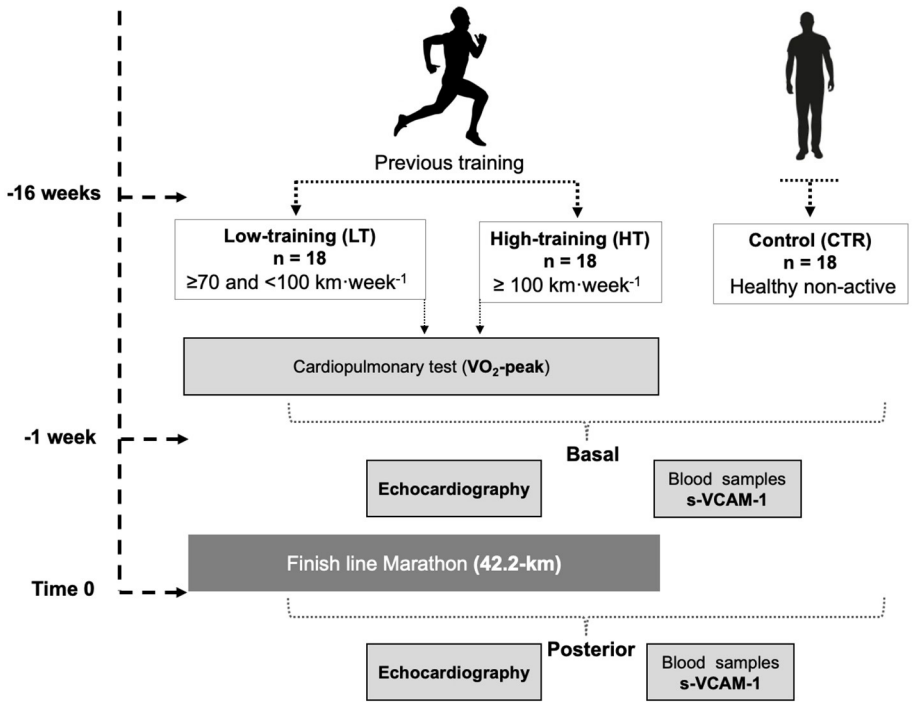

FIGURE 1 | Study scheme design.

linear method (21). To LA volume assessment, the biplane (two and four chamber view) disk summation technique were used, and for RA volume, the single plane disk summation technique in apical four chamber view was used (21). Image quality was optimized for at least 60 frames per second and digitally stored for further analysis using EchoPAC BT 12 software (GE Healthcare, Horton, Norway).

Assessment of sVCAM-1

A venous blood sample was taken from all subjects. A commercially available immunoenzymatic assay (ELISA sVCAM-1, R&D Systems, Minneapolis, MN, USA) was used to determine the sVCAM-1 plasma levels. Each sample was analyzed twice, and the mean value was obtained using the standard curve method. Blood cell count, liver function, renal function, and plasma electrolytes were also measured using standard methods.

Statistical Analysis

The data distribution was assessed using the Shapiro-Wilk test. Variables were evaluated using the Mann-Whitney U-test and Kruskal-Wallis test. The associations between variables were evaluated using the Spearman correlation test. To evaluate independent association between LA remodeling with sVCAM-1 levels and training degree parameters, a binary logistic regression was performed; the dependent (categorical) variable for regression was defined as: LA volume $\leq$41 mL·m^{-2} or LA volume >41 mL·m^{-2} (the cut-off of moderate LA dilatation) (21). Values of $p < 0.05$ were considered significant. The statistical software used was GraphPad PRISM v.8.0 (GraphPad Software Inc., San Diego, CA, USA).

RESULTS

The participants' characteristics are shown in **Table 1**. All athletes ended the race without symptoms or signs of adverse events. The groups were similar in age, and no differences were noted in the blood and biochemical parameters. The CTR group subjects had a higher mean heart rate than the athletes ($p < 0.001$ vs. HT and LT). The mean $\dot{V}O_2$-peak was higher in the HT group ($p = 0.020$ vs. LT).

Exercise and Cardiac Remodeling

Significant structural changes were observed in the HT group than in the LT and CTR groups, specifically greater interventricular septum ($p < 0.001$) and posterior wall ($p < 0.005$) thickness and a higher LV mass index ($p < 0.001$) and LA volume index ($p < 0.001$). Also, RA volume index was higher in HT group as compared to CTR group ($p = 0.030$) (**Table 2**).

Pre- and Post-marathon sVCAM-1 Plasma Levels

The mean resting sVCAM-1 plasma levels were higher in the HT vs. LT and CTR groups (651 ± 350 vs. 566 ± 133 and 440 ± 98 ng·mL^{-1}, respectively; $p < 0.05$). After the

TABLE 1 | Characteristics of the participants.

	Groups			*p*-value
	CTR	HT	LT	
Age (years)	36 ± 4	37 ± 6	38 ± 5	0.373
Height (cm)	175 ± 6	174 ± 6	172 ± 7	0.470
Weight (kg)	72 ± 9	71 ± 8	69 ± 8	0.090
Body superficial area (m^2)	1.9 ± 0.1	1.8 ± 0.1	1.8 ± 0.1	0.075
Heart rate at rest (bpm)	69 ± 6*	53 ± 8	55 ± 7	***<0.001***
Na^+ ($mEq{\cdot}L^{-1}$)	142 ± 2	142 ± 3	142 ± 2	0.440
Creatinine ($mg{\cdot}dL^{-1}$)	0.99 ± 0.11	0.98 ± 0.09	0.97 ± 0.10	0.630
Aspartate aminotransferase ($U{\cdot}L^{-1}$)	26 ± 7	29 ± 9	28 ± 8	0.670
Hematocrit (%)	42 ± 3	43 ± 2	43 ± 3	0.870
Uric acid ($mg{\cdot}dL^{-1}$)	5.2 ± 0.8	5.6 ± 0.9	5.0 ± 0.9	0.170
$\dot{V}O_2$-peak ($ml{\cdot}kg^{-1}{\cdot}min^{-1}$)	––	58.5 ± 5.3#	52.5 ± 8.1	***0.020***
Running experience (years)	––	17 ± 3	16 ± 3	0.810
Time training per week (hours)	––	19 ± 2#	15 ± 2	***0.018***
Training intensity (%HR máx., 220-age)	––	81 ± 3	80 ± 2	0.780

*Data are expressed as mean and standard deviation. *P < 0.05 control vs. other groups; Kruskal-Wallis test. #P < 0.05 HT vs. LT; Mann-Whitney U-test. CTR, Control; HT, High-training group (≥100 km by week); LT, Low-training group (≥70 and <100 km by week); $\dot{V}O_2$-peak, Peak oxygen consumption. The meaning of numbers in bold and italic are related to difference statistically (p-value less than 0.05).*

TABLE 2 | Echocardiographic characteristics of participants.

Heart chambers quantification	Groups			*p*-value
	CTR	HT	LT	
Diastolic diameter LV (mm)	46 ± 4	49 ± 5	48 ± 5	0.404
Systolic diameter LV (mm)	30 ± 4	29 ± 5	30 ± 5	0.879
Posterior wall (mm)	8.1 ± 0.8	9.1 ± 1.2*	8.2 ± 1.1	***<0.005***
Interventricular septum (mm)	7.6 ± 0.8	9.3 ± 2.1*	8.5 ± 1.2	***<0.001***
Ejection fraction (%)	57 ± 4	55 ± 3	55 ± 6	0.110
LV mass index ($gr{\cdot}m^{-2}$)	58 ± 11	106 ± 27*	78 ± 18	***<0.001***
LA volume index ($mL{\cdot}m^{-2}$)	25 ± 9	42 ± 8*	30 ± 11	***<0.001***
LA diameter (mm)	33 ± 4	36 ± 4	34 ± 3	0.220
E wave ($cm{\cdot}s^{-1}$)	77 ± 15	78 ± 13	84 ± 12	0.217
A wave ($cm{\cdot}s^{-1}$)	48 ± 16	50 ± 12	53 ± 10	0.438
Deceleration time (ms)	221 ± 66	233 ± 65	229 ± 65	0.184
RA volume index ($mL{\cdot}m^{-2}$)	21 ± 9	43 ± 11#	33 ± 10	***0.030***

*Data are expressed as mean and standard deviation. *P < 0.05 HT vs. other groups. #P < 0.05 HT vs. CTR. Kruskal-Wallis test.*
CTR, Control; HT, High-training group (≥100 km by week); LT, Low-training group (≥70 and <100 km by week); LV, left ventricular; LA, left atrial; RA, right atrial.
The meaning of numbers in bold and italic are related to difference statistically (p-value less than 0.05).

exercise was completed, an increase in the HT group was observed (from 651 ± 350 to 905 ± 373 $ng{\cdot}mL^{-1}$, $p = 0.002$). The LT group showed a similar trend, although non-significant. The comparison between HT vs. LT groups of changes in sVCAM-1 plasma levels (ΔsVCAM-1 = post–pre-marathon) was significant (254 ± 48 vs. 118 ± 34, respectively; $p = 0.015$) (**Figure 2**).

Multivariate Analysis for LA Remodeling in Athletes

In the multivariate analysis for LA volume (as a categorical variable previously described), the following variables were assessed: sVCAM-1 at baseline, age, running experience (years), time training per week (hours), training intensity (%HR máx. 220-age) and $\dot{V}O_2$-peak. In the final model the significant variables were: sVCAM-1 (OR: 2.85; $p < 0.010$) and $\dot{V}O_2$-peak (OR: 1.75; $p = 0.02$).

Correlation Between Atrial Size and Baseline sVCAM-1 Levels

In long-distance runners, there was a moderate correlation between LA volume and baseline plasma sVCAM-1 levels (rho = 0.510, $p = 0.001$) (**Figure 3**), showing that the LA remodeling process is related at least in part to sVCAM-1 levels. No significant correlation between RA volume and sVCAM-1 was found.

DISCUSSION

The main finding of this study is that runners in the HT group had elevated sVCAM-1 plasma values compared to runners in the LT group and the healthy physically non-active subjects (CTR group). In addition, in both runner groups, there was an increase in sVCAM-1 after intense and prolonged exercise (42.2 km marathon), most significantly in the HT group. The sVCAM-1 plasma values were directly correlated with the LA volume evaluated by echocardiography.

Moderate exercise is considered a key element in maintaining cardiovascular health (1) and an important tool in cardiovascular

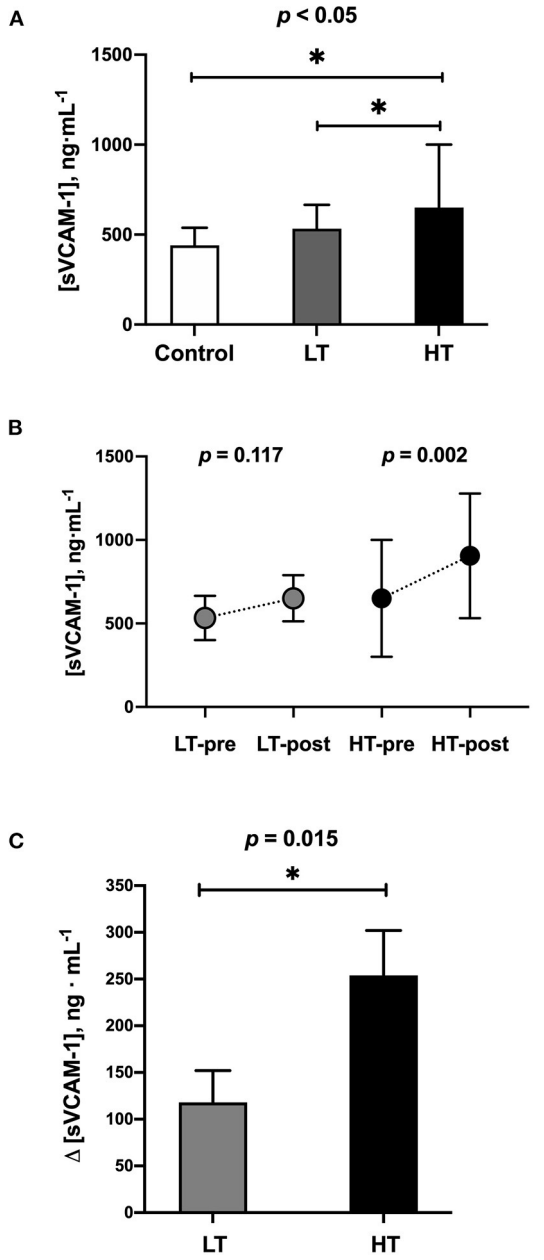

FIGURE 2 | Blood samples levels of sVCAM-1. **(A)** At baseline conditions (1 week before marathon race). **(B)** Exercise-induced changes after marathon race (42.2 km). **(C)** Comparison of changes (ΔsVCAM-1 = post–pre-marathon) between runners' groups. LT, low training (≥70 and <100 km·week^{-1}) ($n = 18$); HT, high training (≥100 km·week^{-1}) ($n = 18$). * = p-value < 0.05.

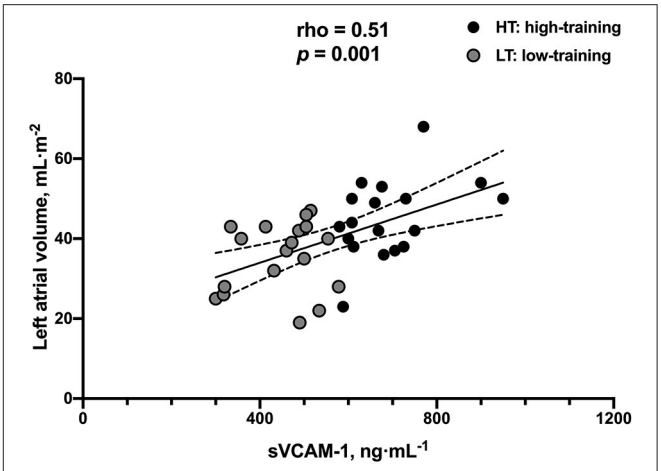

FIGURE 3 | Correlation between sVCAM-1 blood sample levels and left atrial volume in long-distance runners ($n = 36$).

rehabilitation programs for patients with coronary heart disease (22) and chronic heart failure (23). International guidelines suggest 150 min per week of moderate exercise or 75 min per week of vigorous exercise for the general adult population (24). However, a growing group of people performs 20 or more hours of intense exercise per week. These people demonstrate multiple adaptive cardiac changes, a condition called "athlete's heart" (25, 26). This cardiac remodeling process is an adaptation to the volume overload inherent to aerobic physical training; in most cases, it is considered a reversible and benign condition (27).

In this study, we found that only HT athletes, not LT athletes, have significant changes in LV cardiac remodeling and LA volume. This result is concordant with previous data showing that intense training induces significant changes in the size and function of the atrial syncytium (6). Pellicia et al. showed 20% mild atrial dilation and 2% severe LA dilation in a group of 1,777 competitive athletes (25). Our group included professional handball players (26) and marathon runners (9, 28) with significant right atrial dilation; however, in this study, the parameters of atrial deformation were preserved, unlike other pathological conditions with similar atrial dilation (29, 30). On the other hand, our results show that although the most trained runners had a higher-volume LA and thicker ventricular walls, they had a normal ejection fraction similar to the other study participants.

This study did not specifically evaluate LA function, which constitutes a limitation; however, we previously described that this function is particularly stressed during the performance of aerobic resistance exercise in trained athletes with characteristics similar to the runners studied here (8), a finding that is directly associated with $\dot{V}O_2$-peak and sports performance (31). Our findings suggest that athletes with high-performance aerobic resistance develop right atrial and LA dilation, a condition that is associated with less atrial deformation during contraction at rest (31). Our research group previously reported that this condition enables greater functional reserve but causes greater atrial wall stress (26). We also describe that a subgroup of athletes showed severe atrial dilation associated with a lower capacity to increase atrial deformation during exercise contraction, possibly resulting in early atrial dysfunction (8).

Although risk prediction models for AF that incorporate clinical and genetic factors have been developed for the general population, their discriminatory ability remains moderate (29,

30). To our knowledge, there are no prediction models in high-performance athletes that stratify the risk of AF; only a few articles report some key factors to consider, such as training history (32), body height, and atrial size (33). Thus, new research is necessary to clarify which characteristics are associated with an increased risk of AF in highly trained athletes, and the measurement of biomarkers associated with AF in athletes seems to be an interesting study topic.

In different clinical scenarios, LA dilation and deformation properties are related to the risk of AF (32–36), a phenomenon that could be extrapolated to the sports setting. In addition to LA dilation, other potentially arrhythmogenic changes can occur in the athlete's atrium, including fibrosis that promotes conduction heterogeneity (36), changes in autonomic equilibrium toward parasympathetic activation and a decrease in sympathetic tone shortening of the atrial refractory period (37), and activation of ectopic foci facilitated by autonomous changes (38). These electrical and structural changes within the atrium facilitate the re-entry mechanism and AF that still require confirmation with new studies in high-performance athletes (38). However, it is challenging to identify the athletes with the highest risk of developing the arrhythmia because the absolute risk of AF among them is relatively low for any subject (3% among endurance athletes) (39). Risk prediction models for AF in the general population have been developed, however they show only a moderate discriminatory capacity (29, 30). Currently there are no prediction models to stratify the risk of AF in endurance athletes, with only few reports considering individual life time training history (32), atrial dilatation and body stature (33), but without a clear threshold beyond which the risk of AF increases.

From a clinical point of view, sVCAM-1 is a biomarker significantly associated with the risk of AF in the general population (40, 41) as well as postoperative AF (22, 42). In fact, sVCAM-1 was the only biomarker that was significantly associated with long-term risk of AF, independent of a large number of clinical and laboratory measurements (43). Willeit et al. in a population-based cohort study with a 20-year follow-up described that sVCAM-1, but not other inflammation markers, are significantly associated with new-onset AF in the general community (40).

Our results show that the more trained runners showed higher baseline sVCAM-1 levels than the moderately trained and physically active healthy subjects (**Figure 2A**). Although VCAM-1 levels are low in the endothelium and the resting endocardium, its expression may increase under multiple stress conditions, including high-intensity aerobic exercise (14). The increase of this biomarker leads to cell infiltration and inflammation of the entire heart, stimulating the process of fibrosis and cardiac remodeling. This has also been seen in experimental models in which both AF and rapid atrial stimulation increase the endocardial expression of VCAM-1 (18). Accordingly, increased ventricular tissue VCAM-1 have been associated with cardiac remodeling due to hemodynamic stress (44).

Therefore, an association among strenuous exercise, cardiac remodeling, sVCAM-1 and AF is proposed. However, we do not know whether elevated sVCAM-1 values at rest in more trained runners are predictors of future AF. For that purpose, it will be necessary to perform new studies with clinical follow-up in this population.

Another important finding was that highly trained runners significantly increased sVCAM-1 levels at the end of the marathon (**Figure 2B**), which was higher than low trained runners (**Figure 2C**). A previous investigation reported that after brisk exercises (similar to high-intensity interval exercises), the levels of VCAMs increase in trained subjects (45), returning to basal levels promptly (48-h post-exercise); and recently, an interesting review reported that the low-to-moderate intensity aerobic exercise favorably decreases VCAMs levels in a variety of subject populations, while VCAMs levels momentarily increase immediately following high-intensity aerobic exercise, returning pre-exercise levels within several hours post-exercise. On the other hand, regardless of its intensity, resistance exercise does not significantly change the VCAMs levels (46). To our knowledge, there are no previous studies in runners chronically accustomed to that type of stimulus that has evaluated the changes in sVCAM-1 levels after an intense and prolonged exercise, such as a marathon race. In the clinical context, there has been a ventricular level increase of VCAM-1 associated with hemodynamic stress in patients with rheumatoid arthritis (44) or intermittent claudication (47). In skeletal muscle tissue, an increase has been seen in post-prolonged exercise (48) associated with muscle remodeling (49).

Another interesting finding is the moderate correlation found between LA volume and sVCAM-1 levels in this group of athletes (**Figure 3**) since it can be inferred that VCAM-1 blood levels may have a role as a biomarker for LA remodeling link to AF risk in aerobic resistance athletes, which should be explored in future studies involving both a greater number of participants and both sexes. Also, the evaluation of LA function (contractile, conduit, and reservoir) and its relationship with sVCAM-1 could contribute to a better characterization of these athletes. Considering that multiple factors linked to the degree of training, like duration, volume, the intensity of exercises, and oxygen consumption, could be implicated in the changes induced by exercise in cardiac chambers in our participants; besides the simple associations showed, we did a multivariate analysis to find associations between these variables and sVCAM-1 levels and LA remodeling. This analysis showed that sVCAM-1 levels and $\dot{V}O_2$-peak were independent predictors of LA volume; this finding corroborates that LA remodeling in athletes is a complex phenomenon probably related to the degree of training and individual predisposition but at least in part linked to sVCAM-1 levels. Regarding the right atrial volume, we found a higher volume in the more trained subjects compared to the controls, but with a greater dispersion, these findings being consistent with previous studies (9–11).

In conclusion, high-intensity physical exercise is associated with an increase in sVCAM-1 plasma levels in Caucasian male runners. Because sVCAM-1 levels were positively correlated with higher LA volume, sVCAM-1 could be a potential biomarker that could be used to assess potential adverse consequences for LA structure and function in high-performance athletes.

In addition, since sVCAM-1 has been established as a predictor of postoperative AF and AF in the general population, we propose that this biomarker could be used to predict the risk of AF in athletes, which requires further prospective studies to validate our findings.

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 Ethics Committee of Pontificia Universidad Católica de Chile (Chile) (project no. 16082603). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

FC-B, LG, JV-A, MC, PC, and SL substantially contributed to the concept and design of the study. MO and LG contributed to assay setup. JV-A, SH, and MS contributed to data acquisition, analysis, and interpretation. FC-B, LG, MO, MC, PC, JJ, and SL contributed to the data interpretation, discussion, and manuscript preparation. FC-B, LG, JJ, PC, and SL wrote the manuscript. All authors critically revised the manuscript for important intellectual content and contributed to the article and approved the submitted version.

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Exercise-Induced Cardiac Fatigue in Soldiers Assessed by Echocardiography

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Background: Echocardiographic signs of exercise-induced cardiac fatigue (EICF) have been described after strenuous endurance exercise. Nevertheless, few data are available on the effects of repeated strenuous exercise, especially when associated with other constraints as sleep deprivation or mental stress which occur during military selection boot camps. Furthermore, we aimed to study the influence of experience and training level on potential EICF signs.

Methods: Two groups of trained soldiers were included, elite soldiers from the French Navy Special Forces (elite; $n = 20$) and non-elite officer cadets from a French military academy (non-elite; $n = 38$). All underwent echocardiography before and immediately after exposure to several days of uninterrupted intense exercise during their selection boot camps. Changes in myocardial morphology and function of the 4 cardiac chambers were assessed.

Results: Exercise-induced decrease in right and left atrial and ventricular functions were demonstrated with 2D-strain parameters in both groups. Indeed, both atrial reservoir strain, RV and LV longitudinal strain and LV global constructive work were altered. Increase in LV mechanical dispersion assessed by 2D-strain and alteration of conventional parameters of diastolic function (increase in E/e' and decrease in e') were solely observed in the non-elite group. Conventional parameters of LV and RV systolic function (LVEF, RVFAC, TAPSE, s mitral, and tricuspid waves) were not modified.

Conclusions: Alterations of myocardial functions are observed in soldiers after uninterrupted prolonged intense exercise performed during selection boot camps. These alterations occur both in elite and non-elite soldiers. 2D-strain is more sensitive to detect EICF than conventional echocardiographic parameters.

Keywords: cardiac fatigue, exercise, soldiers, speckle tracking echocardiography, myocardial work

INTRODUCTION

Despite the evident cardio-protective effect of moderate regular aerobic exercise, several studies have questioned the possible deleterious cardiac consequences induced by strenuous long-duration exercise (1–3). Indeed, a transient alteration of ventricular systolic or diastolic function following such exercise has frequently been reported, which is often called exercise-induced cardiac fatigue (EICF) (4–6).

EICF is commonly evaluated with cardiac biomarkers or imaging methods, especially echocardiography. Two-dimensional speckle-tracking echocardiography offers quantitative assessment of myocardial mechanical function and is a more sensitive measure of contractile function than conventional echocardiographic parameters. Transient reductions in left and right ventricular strain (7, 8), and left atrial strain (9) have already been documented after acute endurance exercise. Left ventricular myocardial work (LV MW), analyzed by pressure-strain loops, allows the estimation of myocardial performance. Previous publications demonstrate a relationship between LV MW and LV contractility (10–12) and remodeling (13). Data on this topic are scarce in athletes, and to our knowledge no specific study has addressed the evaluation of LV MW by pressure-strain loops analysis among this population after a prolonged endurance exercise.

Furthermore, most of the studies focused on the acute cardiac effects of a single strenuous long-duration endurance exercise, and less data are available on consequences of repeated bouts of strenuous exercise over several days (5), especially when associated with other constraints as sleep deprivation or mental stress which are an integral part of military selection boot camps.

Lastly, to our knowledge, as most of the studies included well-trained endurance athletes no study has evaluated the potential occurrence of EICF in population presenting with different experience and training.

The aim of the present study was to identify and to quantify the cardiac effects of a several days of uninterrupted strenuous exercise during military selection boot camps, and to study the influence of prior experience and training level.

MATERIALS AND METHODS

Study Population

Two populations of French soldiers were prospectively included:

- A group of non-elite soldiers: second-year officer cadets from a French military academy ($n = 39$), the Special Military School of Saint-Cyr, located in Coëtquidan, Brittany. This was their first selection boot camp, their previous selection was solely based on their academic skills. Their regular physical training included 3 weekly 2 h sessions combining endurance and resistance activities.
- A group of elite soldiers: French Navy Special Forces soldiers ($n = 20$), located in Lorient, Brittany. This group was more experienced, as they had already been selected during previous boot camps to be able to join this elite unit. This unit is considered one of the world's references in the field of Special Forces and counterterrorism units. Therefore, their selection is extremely tough, and they all have a very high level of physical training and a great individual's ability to adapt to a hostile environment.

All participants gave written informed consent to participate in this study, which received the approval of the local Rennes University Hospital and regional Ethics Committee (Number 35RC13_8801) and was conducted in accordance with the "Good Clinical Practice" Guidelines as laid down in the Declaration of Helsinki.

Experimental Procedure

Boot Camp

All subjects participated in a winter boot camp, which consisted of intense and continuous outdoor endurance and resistance physical practice. The boot camps were part of the usual military preparation, we were therefore not able to change them. The soldiers had to undergo several timed orienteering marches, abseiling, crossing, and swimming exercises. This was associated with difficult outdoor living conditions, sleep deprivation (only a few hours of sleep during the boot camp), and mental stress. In both groups the goal of the boot camp was to push the soldiers to their very limit, in order to perform a selection of the soldiers. As the experience and training level of both groups of soldiers were completely different, the level of difficulty and duration of the boot camp were also different (respectively, 36 and 96 h). The programs were specific to each Army corps and adapted to the performance level of the subjects by experienced military instructors, which kept the soldier constantly under pressure.

All subjects were healthy, this was confirmed prior to inclusion by a pre-participation health screening, including clinical examination and resting ECG. Height, weight, resting heart rate, and blood pressure were recorded. They all were non-smokers, with no cardiovascular risk factor, no history of cardiopulmonary, no metabolic, nor neuromuscular disorders, and were not taking any chronic medication.

Echocardiography

Echocardiographies were recorded the day before and immediately following the end of the boot camp, using a Vivid Q (GE Healthcare, Horten, Norway). Offline analysis was performed on a dedicated workstation (EchoPAC Version 202, GE Vingmed Ultrasound, Norway).

LV cardiac chamber size, LV systolic and diastolic function were assessed as recommended (14, 15). LV global longitudinal strain (GLS) was assessed on the 18 segments obtained from two-dimensional grayscale images acquired in the apical 4, 3, and 2 chamber views at a frame rate $\geq$60 frames/s (16). LV Mechanical dispersion was calculated as the standard deviation of the time to maximal myocardial shortening, measured from the electrocardiographic onset Q/onset R- wave in the 18 LV segments (**Figure 1**) (17).

Right ventricular (RV) morphological parameters were assessed as recommended, using RV end diastolic (ED) basal and mid cavity diameter, RVED, and RVES area (13). RV conventional parameters of systolic function were assessed using

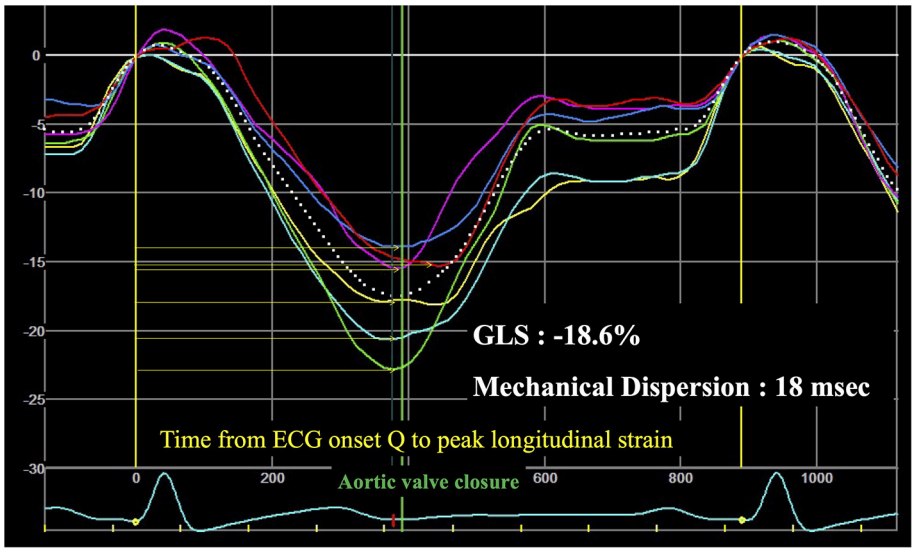

FIGURE 1 | Example of speckle-tracking strain analysis of left ventricular mechanical dispersion. GLS, global longitudinal strain; Mechanical Dispersion, assessed by the standard deviation of the 18 segments (for the clarity of the figure only 6 segments are shown).

TAPSE, s' tricuspid wave and RV fractional area change (RV FAC). RV GLS was determined as the average of the 3 RV free wall segments, from an apical four-chamber image focused on the RV (18).

Left atrial (LA) and right atrial (RA) volumes were measured using the modified Simpson's method from the 4 and 2 chamber views for the LA and 4 chamber views for the RA. Atrial longitudinal strain was assessed for left atrium on the 12 segments of the 4- and 2-chamber views, and for right atrium on the six segments of apical four-chamber view as recommended (18).

LV MW and related indices were estimated by the combination of LV strain data and the non-invasive estimation of the LV pressure curve as previously described (19). Briefly, the peak systolic LV pressure was assumed equal to the peak arterial pressure recorded from the brachial cuff systolic pressure. A patient-specific LV pressure curve was then constructed by the software (EchoPAC, GE Vingmed Ultrasound, Norway), adjusting LV pressure curve to the duration of the isovolumic and ejection phases, defined by valvular timing events. Strain and pressure data were synchronized using the R wave on ECG as common time reference. The area within the peak segmental longitudinal strain provided an index of LV MW for each myocardial segment. During the isovolumic contraction and LV ejection period, segmental shortening contributes to the final LV ejection, whereas segmental stretch or lengthening does not contribute to LV ejection. As a result, the work performed by the myocardium during segmental shortening represents constructive work (CW), whereas the work performed by the myocardium during stretch or segmental lengthening represents energy loss, defined as wasted work (WW). So, the CW was defined as MW during segmental shortening in systole, and segmental lengthening during the isovolumic relaxation time. The WW was defined as the work performed during lengthening in systole and shortening in isovolumic relaxation, associated with energy loss. By averaging segmental CW and WW for each segment, LV global constructive work (LV GCW) and LV global wasted work (LV GWW) were estimated for the entire LV (19) (**Figure 2**).

Both inter-observer and intra-observer concordances for the estimation of CW and WW work have already been evaluated in a previous study from our research group (20).

Statistical Analyses

Normal distribution of all continuous variables was confirmed by a Kolmogorov-Smirnov test. All data were expressed as means and standard deviations. Quantitative data were compared using Student's *t*-test. Paired student's *t*-tests were used to determine differences between pre- and post-exercise values for the various echocardiographic parameters. Student's *t*-tests were used to determine differences between non-elite and elite groups. The response from pre-to-post-exercise in the different groups was compared using repeated measures ANOVA with time of echocardiography (pre- vs. post- exercise) as within-subject effect and group (elite vs. non-elite soldiers) as a between-subject effect. Level of significance was set to $p < 0.05$. Statistical analyses were conducted using the SPSS (v.20 SPSS Inc.; Chicago, IL).

RESULTS

One subject from the non-elite group was excluded because he got injured and was not able to complete the follow-up echocardiography. Therefore, finally 58 soldiers, 20 in the elite group, and 38 in the non-elite group completed the study.

Subject characteristics are shown in **Table 1**. The subjects in the elite group were older than those in the non-elite group (respectively, 26.6 ± 3.4 vs. 21.7 ± 0.6 years, $p < 0.0001$). There was no difference in body surface area between both groups, even if subjects in the elite group were heavier (78.0 ± 9.0 vs. 73.1

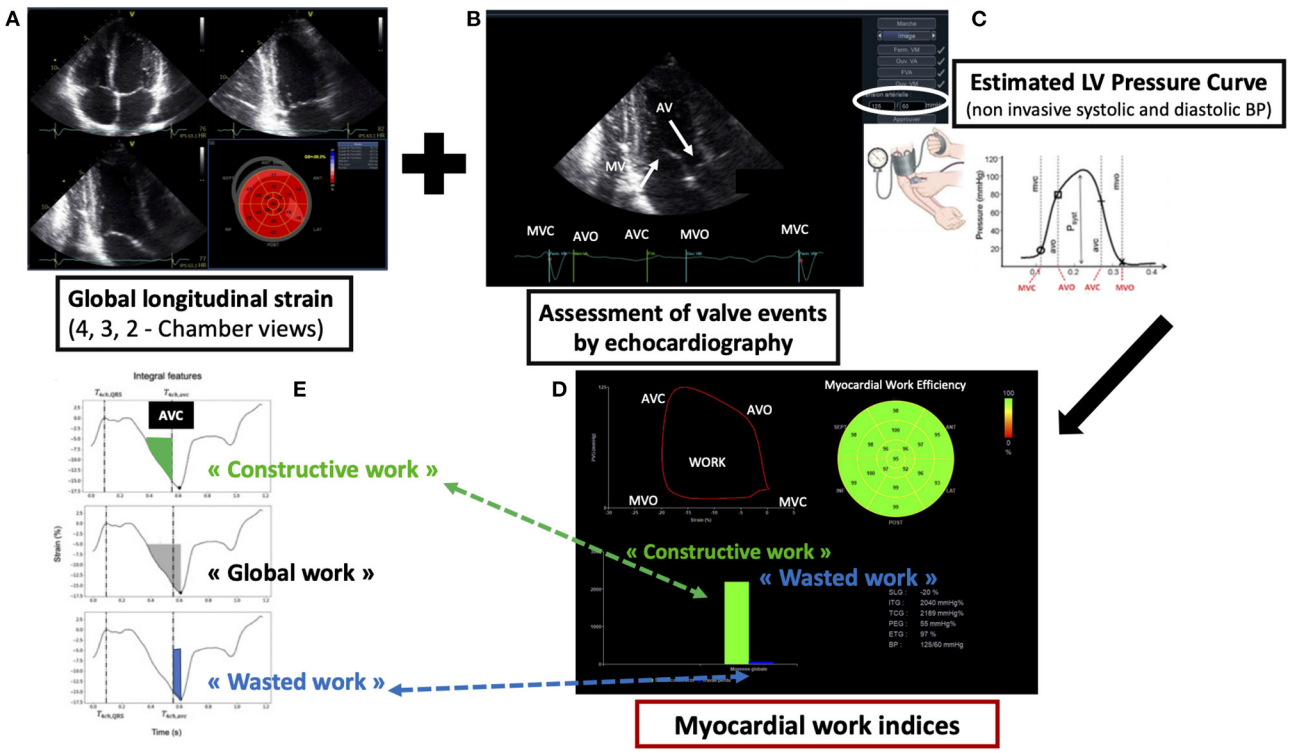

FIGURE 2 | Methodology of myocardial work (MW) assessment. **(A)** Acquisition of apical four-, two-, and three-chamber view and evaluation of global longitudinal strain (GLS) with left ventricular (LV) bull's eye. **(B)** Assessment of valve events by echocardiography (MVC, mitral valve closure; AVO, aortic valve opening; AVC, aortic valve closure; MVO, mitral valve opening). **(C)** Introduction of systolic and diastolic blood pressure; peak systolic LV pressure is assumed equal to the peak arterial pressure recorded from the brachial cuff systolic pressure. A patient-specific LV pressure curve is constructed by the software, adjusting LV pressure curve to the duration of the isovolumic and ejection phases, defined by valvular timing events. Strain and pressure data are synchronized using the R wave on ECG as common time reference. **(D)** Evaluation of global values of all myocardial work (MW) components; bars showing the constructive (green bar) and wasted (blue bar) global work. **(E)** During the isovolumic contraction and LV ejection period, segmental shortening contributes to the final LV ejection, whereas segmental stretch or lengthening does not contribute to LV ejection. As a result, the work performed by the myocardium during segmental shortening represents constructive work (CW), whereas the work performed by the myocardium during stretch or segmental lengthening represents energy loss, defined as wasted work (WW).

$\pm$ 8.5 kg, $p = 0.05$) with a higher body mass index (24.2 $\pm$ 1.5 vs. 22.8 $\pm$ 1.9 kg.m^{-2}, $p = 0.006$). The subjects in the non-elite group lost weight during the boot camp (73.1 $\pm$ 8.5 kg before-exercise vs. 72.4 $\pm$ 7.9 kg post-exercise, $p = 0.001$). No difference in systolic blood pressure (SBP) between groups was observed both before and after exercise. The diastolic blood pressure (DBP) was slightly lower in the non-elite group both before ($p < 0.0001$) and after ($p = 0.005$) exercise. Exercise-induced decrease of SBP was only observed in the non-elite group (121.2 $\pm$ 10.2 vs. 113.5 $\pm$ 10.6 mmHg; $p = 0.001$, respectively, before and after exercise) ($p = 0.032$ for interaction), without any change in DBP. Heart rate demonstrated a significant overall increase following exercise (63.9 $\pm$ 10.5 vs. 81.8 $\pm$ 11.1 bpm, $p < 0.0001$ in the elite group; 58.8 $\pm$ 8.5 vs. 70.3 $\pm$ 12.7 bpm, $p < 0.0001$ in the non-elite group, respectively, before and after exercise), with a higher increase ($p = 0.031$ for interaction) and a higher HR after exercise in the elite group.

Echocardiographic data before and after boot camp are shown in **Tables 2**–**4**. Prior to exercise, no abnormality was detected on the resting echocardiography or ECG performed.

The LVED and LVES volumes were larger in the elite group than in the non-elite group, both before as well as after the boot camp (this was also the case when considering the BSA indexed values; **Table 2**). An exercise-induced increase in LVED volume was only observed in the elite group, nevertheless this exercise increase was not significantly different between both groups ($p = 0.116$ for interaction). LVEF and mean s' mitral wave were not different between both groups, and these parameters were not altered after exercise. No inter-group difference in LV longitudinal strain, mechanical dispersion, LV GCW or LV GWW was observed before and after exercise. However, after exercise, we noted an intra-group reduction of LV longitudinal strain (−21.2 $\pm$ 1.5 vs. −20.0 $\pm$ 1.7%, $p = 0.02$ in the elite group and −21.6 $\pm$ 1.5 vs. −20.2$\pm$1.4%, $p < 0.0001$ in the non-elite group) and of LV GCW (2179.2 $\pm$ 236.6 vs. 1780.6 $\pm$ 527.7 mmHg%, $p = 0.048$ in the elite group and 2231.2 $\pm$ 302.5 vs. 1862.8 $\pm$ 279.3 mmHg%, $p < 0.0001$ in the non-elite group) whereas LV GWW was unchanged. After exercise, the mechanical dispersion increased only in the non-elite group (23.2 $\pm$ 8.0 vs. 27.2 $\pm$ 7.3 ms, $p = 0.094$ in the elite group; 20.9 $\pm$ 6.8 ms vs.

TABLE 1 | Clinical characteristics of the study populations.

	Elite group ($n = 20$)			Non-elite group ($n = 38$)			Comparison between two groups		Interaction
	Pre-exercise	Post-exercise	Pre/post-*p*-value	Pre-exercise	Post-exercise	Pre/Post-*p*-value	Pre-exercise *p*-value	Post-exercise *p*-value	*p*-value
Age (years)	26.6 ± 3.4		–	21.7 ± 0.6		–	<0.0001		
BSA (m^2)	1.97 ± 0.15	–	–	1.90 ± 0.14	1.89 ± 0.12	0.607	0.109	–	
Weight (kg)	78.0 ± 9.0	–	–	73.1 ± 8.5	72.4 ± 7.9	0.001	0.05	–	
BMI ($kg.m^{-2)}$	24.2 ± 1.5	–	–	22.8 ± 1.9	22.5 ± 1.8	0.001	0.006	–	
HR (bpm)	63.9 ± 10.5	81.8 ± 11.1	<0.0001	58.8 ± 8.5	70.3 ± 12.7	<0.0001	0.052	0.001	0.031
SBP (mmHg)	118.1 ± 8.3	117.9 ± 7.7	0.929	121.2 ± 10.2	113.5 ± 10.6	0.001	0.267	0.111	0.032
DBP (mmHg)	73.4 ± 10.5	71.7 ± 7.3	0.523	62.0 ± 6.9	64.3 ± 9.9	0.218	<0.0001	0.005	0.215

BSA, body surface area; BMI, body mass index ($kg.m^{-2}$); HR, heart rate (bpm); SBP, systolic blood pressure (mmHg); DBP, diastolic blood pressure (mmHg).

TABLE 2 | Left ventricular echocardiographic parameters.

	Elite group ($n = 20$)			Non-elite group ($n = 38$)			Comparison between two groups		Interaction
	Pre-exercise	Post-exercise	Pre/post-*p*-value	Pre-exercise	Post-exercise	Pre/Post-*p*-value	Pre-exercise *p*-value	Post-exercise *p*-value	*p*-value
LVED vol. (ml)	117.3 ± 23.6	126.3 ± 21.1	0.031	100.8 ± 17.9	102.9 ± 20.5	0.373	0.004	<0.0001	0.116
LVES vol. (ml)	41.3 ± 9.5	43.6 ± 10.3	0.261	34.3 ± 7.8	34.2 ± 7.5	0.872	0.004	<0.0001	0.210
LVEF (%)	64.8 ± 4	65.7 ± 4.2	0.511	66.0 ± 4.0	66.7 ± 3.6	0.327	0.256	0.309	0.878
Mean S' ($cm.s^{-1}$)	10.7 ± 1.3	11.1 ± 1.5	0.379	10.9 ± 1.1	11.0 ± 1.4	0.654	0.591	0.697	0.549
LV GLS (%)	−21.2 ± 1.5	−20.0 ± 1.7	0.02	−21.6 ± 1.5	−20.2 ± 1.4	<0.0001	0.348	0.652	0.575
Mechanical dispersion (ms)	23.2 ± 8.0	27.2 ± 7.3	0.094	20.9 ± 6.8	29.1 ± 6.1	<0.0001	0.243	0.306	0.093
LV GCW (mmHg%)	2179.2 ± 236.6	1780.6 ± 527.7	0.048	2231.2 ± 302.5	1862.8 ± 279.3	<0.0001	0.219	0.860	0.850
LV GWW (mmHg%)	70.5 ± 21.2	79.1 ± 31.1	0.354	70 ± 27.6	60.2 ± 28.8	0.182	0.551	0.114	0.131
E ($m.s^{-1}$)	0.78 ± 0.16	0.77 ± 0.14	0.758	0.79 ± 0.13	0.81 ± 0.14	0.207	0.906	0.230	0.340
A ($m.s^{-1}$)	0.39 ± 0.09	0.38 ± 0.08	0.803	0.35 ± 0.08	0.43 ± 0.11	<0.0001	0.090	0.129	0.022
DTI (ms)	217.0 ± 35.0	197.4 ± 43.0	0.160	221.6 ± 1.7	193.6 ± 43.1	0.003	0.547	0.766	0.610
E/A	2.05 ± 0.46	2.07 ± 0.42	0.890	2.33 ± 0.58	1.96 ± 0.46	0.004	0.062	0.567	0.072
E/e'	4.45 ± 1.39	4.76 ± 0.61	0.391	4.51 ± 0.94	4.99 ± 0.95	0.01	0.764	0.297	0.568
e' ($cm.s^{-1}$)	16.8 ± 0.21	16.1 ± 0.29	0.309	17.8 ± 0.23	16.5 ± 0.21	0.01	0.135	0.527	0.514

LV, left ventricle; LVED vol,: LV end-diastolic volume (ml); LVES vol., LV end-systolic volume (ml); LVEF, Left ventricular ejection fraction (%); GLS, global longitudinal strain (%); GCW, global constructive work (mmHg%); GWW, global wasted work (mmHg%); E, Peak E mitral velocity (m.s−1); A, Peak A mitral velocity (m.s−1); DTI, E-wave deceleration time (ms); e', early diastolic velocity ($cm.s^{-1}$).

29.07 ± 6.09 ms, $p < 0.0001$ in the non-elite group), nevertheless this exercise increase was not significantly different between both groups ($p = 0.093$ for interaction).

As regards to the right ventricle, prior to exercise RVED basal and mid cavity diameter, and RV systolic area were larger in the elite group than in non-elite one (**Table 3**). No intra-group exercise-induced change in RV dimensions was noted. There was no difference between groups, and no exercise-induced change for conventional right ventricle systolic parameters (RVFAC, TAPSE, and s' tricuspid wave) (**Table 3**). Whereas, due to a lower strain value in the apical segment the longitudinal RV strain of the free wall was lower in the elite than in the non-elite both at baseline and post-exercise; an exercise-induced reduction was observed in both population (−28.0 ± 4.0 vs. −25.3 ± 3.9%, $p = 0.003$ in the elite group and −0.5 ± 2.8 vs. −27.8 ± 3.5%, $p < 0.0001$ in the non-elite group). These exercise-induced alterations were only present in the mid and apical segments, with a preservation of the basal segment.

No inter-group difference was observed for conventional parameters of LV diastolic function before and after exercise (**Table 2**). Nevertheless, diastolic function was significantly affected by exercise only in the non-elite group with a decrease in E wave deceleration time (221.6 ± 1.7 vs. 193.6 ± 43.1 ms, $p = 0.003$), E/A ratio (2.33 ± 0.58 vs. 1.96 ± 0.46, $p = 0.004$), and

TABLE 3 | Right ventricular echocardiographic parameters.

	Elite group ($n = 20$)			Non-elite group ($n = 38$)			Comparison between two groups		Interaction
	Pre-exercise	Post-exercise	Pre/post-*p*-value	Pre-exercise	Post-exercise	Pre/Post-*p*-value	Pre-exercise *p*-value	Post-exercise *p*-value	*p*-value
RVED basal diameter (cm)	3.9 ± 0.5	3.7 ± 0.6	0.337	3.6 ± 0.4	3.7 ± 0.4	0.2	0.050	0.835	0.103
RVED mid cavity diameter (cm)	3.2 ± 0.5	3.1 ± 0.6	0.257	2.8 ± 0.4	2.8 ± 0.3	0.79	0.001	0.068	0.193
RVED area (cm^2)	16.8 ± 2.3	16.1 ± 3.6	0.301	15.4 ± 2.8	15.0 ± 2.5	0.364	0.059	0.184	0.628
RVES area (cm^2)	8.5 ± 1.8	8.3 ± 1.8	0.554	7.6 ± 1.2	7.2 ± 1.6	0.072	0.039	0.031	0.641
RVFAC (%)	49.5 ± 7.6	48.3 ± 6.8	0.625	49.6 ± 6.7	51.9 ± 7.5	0.099	0.943	0.081	0.174
TAPSE (mm)	23.7 ± 4.5	24.9 ± 3.7	0.296	24.6 ± 2.8	25.3 ± 2.8	0.228	0.423	0.646	0.691
S'tric ($cm.s^{-1}$)	14.4 ± 2.1	14.8 ± 2.6	0.560	14.8 ± 0.2	14.9 ± 0.2	0.710	0.476	0.770	0.793
Free wall longitudinal strain (%)	−28.0 ± 4.0	−25.3 ± 3.9	0.003	−30.5 ± 2.8	−27.8 ± 3.5	<0.0001	0.006	0.017	0.917
LB (%)	−25.1 ± 5.8	−25.1 ± 9.2	0.978	−26.0 ± 3.9	−24.5 ± 4.9	0.155	0.388	0.782	0.455
LM (%)	−30.2 ± 5.2	−26.7 ± 6.7	0.007	−31.6 ± 3.7	−29.4 ± 4.2	0.006	0.176	0.122	0.367
LA (%)	−28.8 ± 5.6	−24.5 ± 6.4	0.037	−32.9 ± 4.9	−30.2 ± 5.6	0.016	0.007	0.001	0.455

RV, right ventricle; ED, end diastolic; ES, end systolic; RVFAC, RV fractional area change (%); TAPSE, tricuspid annular plane systolic excursion (mm); S'tric, s tricuspid wave velocity ($cm.s^{-1}$); LB, latero-basal segment; LM, latero-mid segment; LA, latero-apical segment.

TABLE 4 | Atrial parameters.

	Elite group ($n = 20$)			Non-elite group ($n = 38$)			Comparison between two groups		Interaction
	Pre-exercise	Post-exercise	Pre/post-*p*-value	Pre-exercise	Post-exercise	Pre/Post-*p*-value	Pre-exercise *p*-value	Post-exercise *p*-value	*p*-value
LA volume (ml)	40.8 ± 11.3	45.9 ± 13.3	0.103	34.0 ± 11.6	36.7 ± 12.9	0.137	0.072	0.025	0.459
LA Peak atrial longitudinal strain (%)	56.3 ± 4.4	51.9 ± 6.1	0.003	59.6 ± 10.1	51.0 ± 10.1	<0.0001	0.088	0.689	0.091
RA volume (ml)	46.4 ± 15.4	42.1 ± 11.9	0.189	42.8 ± 11.3	45.6 ± 10.4	0.088	0.316	0.246	0.029
RA Peak atrial longitudinal strain (%)	55.5 ± 8.2	49.4 ± 8.8	<0.0001	59.8 ± 9.5	52.0 ± 9.8	<0.0001	0.337	0.374	0.089

LA, left atrium; RA, right atrium.

e' value (17.8 ± 0.23 vs. 16.5 ± 0.21 $cm.s^{-1}$, $p = 0.01$) and an increase in peak A velocity (0.35 ± 0.08 vs. 0.43 ± 0.11 $m.s^{-1}$, $p < 0.0001$) and E/e' ratio (4.51 ± 0.94 vs. 4.99 ± 0.95, $p = 0.01$). Only the exercise-induced increase in peak A velocity was significantly different in both groups ($p = 0.022$ for interaction).

With regards to the atria, no inter-group difference in volumes and functions was observed before exercise (**Table 4**). The volumes of both atria were not significatively affected by exercise, but the exercise-induced changes in RA volume were opposite ($p = 0.029$ for interaction) with a non-significant decrease in RA volume in elite soldiers and a non-significant increase in non-elite soldiers. An exercise-induced decrease in atrial reservoir strain was observed in both groups (LA longitudinal strain: 56.3 ± 4.4 vs. 51.9 ± 6.1%, $p = 0.003$ in the elite group and 59.6 ± 10.1 vs. 51.0 ± 10.1%, $p < 0.0001$ in the non-elite group; RA longitudinal strain: 55.5 ± 8.2 vs. 49.4 ± 8.8%, $p < 0.0001$ in the elite group and 59.8 ± 9.5 vs. 52.0 ± 9.8%, $p < 0.0001$ in the non-elite group).

DISCUSSION

Our study aimed to assess the effect of a boot camp with several days of uninterrupted strenuous endurance and resistance exercise associated with sleep deprivation and mental stress, in two populations of soldiers with different training level. After the boot camp we observed an alteration in ventricular systolic and diastolic functions in both studied populations. 2D-Strain seems more sensitive to detect EICF than conventional echocardiographic parameters. The alterations occurred in both groups, nevertheless some alterations occurred solely in non-elite

group, which raises the question of a potential protective effect of training.

Chronic endurance training induces a physiological cardiac remodeling characterized by a harmonious dilation of the cardiac chambers, and a slight reduction in resting ventricular function (21). This increase in cardiac volumes and mass enables a greater oxygen consumption during exercise (22). Therefore, as expected, the more trained elite group demonstrate a more important cardiac remodeling than the non-elite one. Indeed, the elite group had larger LV ED and ES volumes, RVED basal and mid cavity diameter as compared to the non-elite. Furthermore, as previously described in endurance athletes (23), the peak global longitudinal RV strain was lower in the elite group than in non-elite one (-28.0 ± 4.0 vs. $-30.5 \pm 2.8\%$; $p = 0.006$).

Exercise-Induced Cardiac Fatigue

Our results are in accordance with previous studies which demonstrated frequent alterations in systolic and diastolic functions in response to strenuous acute endurance exercise (6, 7). Even if these alterations did not concern all subjects (24), and was not reported in all studies (25), the post-exercise values reduction seemed to be related to the duration of exercise (2). Therefore, due to the intense and prolonged nature of our exercise protocols, these results were expected.

In both groups we didn't demonstrate any alteration of conventional markers of LV and RV systolic function after boot camp. Indeed, there was no change in LVEF or mean mitral s' wave, TAPSE, RV FAC, and s' tricuspid wave. But we noted a decrease of more subtle markers of LV and RV systolic function as global LV longitudinal strain and global CW analyzed by pressure-strain loops. The global RV free wall longitudinal strain was also decreased, due to an alteration in the mid and apical segments. This discrepancy between the basal segment and the mid/apical segments of the RV free wall, was already demonstrated in a previous study (26), although the mechanisms involved remain to be elucidated.

Both left and right atrial function were also altered with a decrease of their peak longitudinal strain, which might be considered as a subtle alteration of left and right diastolic function (27). The clinical relevance of these changes is still unknown. While it is known, that reduction of atrial strain in master athletes is associated with lone paroxysmal atrial fibrillation (PAF) (28, 29), the fact that this transient reduction in atrial reservoir function is related to an increased risk of occurrence of PAF later remains to be determined. We were unable to provide data on the recovery of this diastolic alteration. However, all elite subjects who were regularly exposed to the same type of endurance exercise had normal baseline echocardiographic parameters. Furthermore, none of the post-exercise values was considered as pathological. Lastly previous studies which have performed follow up echocardiography reported a diastolic function recovery after a period of 28 h (1).

Impact of Training Level

The comparison between both groups of soldiers is challenging, as they did not undergo the same exercise protocol. Nevertheless, both underwent programs adapted to their abilities and training level; the goal was to push them to their very limit. The boot camp used in the elite group was more intense and more prolonged than the one used in the non-elite group (96 vs. 36 h). Therefore, we might have expected a more important alteration of systolic and diastolic parameters in the elite group. Indeed, in previous studies the greatest reduction in post-exercise values was reported in athletes who completed the longest events (2, 24). Our results showed the opposite, mechanical dispersion and usual parameters of diastolic function were only altered in the non-elite group.

After the boot camp we observed an alteration in both studied populations. Indeed, there was a significant decrease in the strain values of the LV, RV, LA, and RA. Furthermore, the comparison between the exercise-induced changes in the different parameters between elite and non-elite groups were not significantly different. Nevertheless, there were some slight differences in the exercise induced changes that might suggest a more important alteration in the non-elite group.

As regards to systolic function, while 2D-strain and myocardial work parameters decreased after exercise in both groups, we observed that mechanical dispersion of LV strain only increased in the non-elite group. An increase in electro-mechanical delay post-exercise has been previously reported, suggesting some degree of LV mechanical discoordination after intense exercise (30). Mechanical dispersion assessed by two-dimensional strain reflects heterogeneous myocardial contraction. We have previously demonstrated that mechanical dispersion is a good marker to differentiate a remodeling from pathological and physiologic origin (17). Furthermore, mechanical dispersion was related to ventricular arrhythmia in post-myocardial infarction patients (31). Nevertheless, further studies are needed to determine if this exercise induced alteration of mechanical dispersion may represent a long-term arrhythmogenic substrate.

As regards to diastolic function, while LA and RA peak longitudinal strain decreased after exercise in both groups, the usual parameters of diastolic function were only altered after exercise in the non-elite group, with a decrease in E/A (as a result of an increase in A wave), E wave deceleration time and e' and an increase in E/e'. These alterations may represent a more marked stage of diastolic dysfunction, the early one being only represented by the alteration of atrial strain. Exercise-induced diastolic dysfunction might be partially explained by a reduction in preload. Indeed, the same findings were demonstrated previously after a marathon, and preload augmentation through passive leg elevation (PLE) corrected some of these alterations (32). But although e' increased with post-exercise PLE, it did not reach pre-exercise supine levels, and did not correct the increase of A wave post exercise, suggesting that some intrinsic impairment in myocardial relaxation and compliance may persist despite normalization of preload (32). The impact of a potential reduction of preload due to the dehydration associated with exercise might also be raised by our results. But, in disfavor of this hypothesis, we noted no decrease in LVED volume in both groups, but an increase in the elite group and a trend of increase in non-elite. Moreover, all subjects could hydrate without restriction during exercise.

A Protective Effect of Training?

As regards to the results of our study, we can speculate that appropriate training prior to strenuous exercise may attenuate EICF. Indeed, the elite underwent a longer duration and harder boot camp; all of these factors which are related with an increase in EICF (2). Nevertheless, the elite group demonstrated less post-acute prolonged endurance exercise-induced modifications. As age does not seem to play a significant role in EICF (2), the difference observed between the two groups studied can be related to the different training level of the soldiers. Indeed, the elite subjects were older and more used to these kind of selection programs, they were also more physically trained, as shown by larger left and right ventricular dimensions. This new finding might be in contradiction with two previous studies, which demonstrated that acute atrial and ventricular response to exercise were independent of training load (24) and cardiorespiratory fitness (i.e., peak $\dot{V}O_2$ and training mileage) (33). An alternative hypothesis might be that the elite were already selected on their resistance to EICF, as they had already undergone several physical selection tests to join the elite.

The Cascade of EICF

Another interesting finding is that deformation imaging seems more sensitive than conventional echocardiographic parameters for assessing EICF. Thus, the echocardiographic cascade of alterations indicative of EICF seems to begin with an alteration of speckle tracking derived parameters of diastolic function (i.e., atrial reservoir function) observed in both studied groups, then by an alteration of speckle tracking derived parameters of systolic function (i.e., RV and LV deformation, LV GCW, and lately mechanical dispersion), then by an alteration of the conventional markers of the diastolic function (i.e., E/A, E-wave deceleration time, e', and E/e') only observed in the non-elite group, and finally by an alteration of the conventional markers of systolic function (LVEF, RV FAC, TAPSE, mitral, and tricuspid waves) which was not observed in this study but reported in previous ones (4–6).

Limits of the Study

We acknowledge several limits in this study. First of all, as already stated, the boot camp protocols were different. The boot camps were part of the usual military preparation, we were therefore not able to change them. But these programs were adapted to the abilities and training level of both populations studied.

For technical reason we were not able to weigh the elite subjects. The weight could be useful to estimate the LV preload but we recall that the systolic BP was not different before and after acute endurance exercise in this group and that the hydration was free for these high-experienced soldiers.

Lastly, the lack of follow-up represents a limit to describe evolutions of the observed alterations but pre-exercise echocardiograms were normal, and several previous studies have shown that the echocardiographic alterations that we reported were transient (1).

CONCLUSIONS

Our study confirms that intense exercise lasting several days without interruption during boot camps induces cardiac fatigue, which is best detected with the 2D strain parameters of systolic and diastolic functions. Alteration occurred in both groups, even in the more experienced one. Nevertheless, there might by a relative protective effect of training level, as diastolic function and LV mechanical dispersion were only altered in the less trained group.

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 Rennes University Hospital and Regional Ethics Committee (Number 35RC13_8801). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

FS, FC, and DM: experiment conception and design. FS, GK, DM, and EG: experiments performed. MC and FS: data analyzed. MC, FS, FC, SL, TL, and ED wrote the paper. All authors read and approved the final manuscript.

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Electrocardiographic and Echocardiographic Insights From a Prospective Registry of Asian Elite Athletes

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Background: Asian representation in sport is increasing, yet there remains a lack of reference values for the Asian athlete's heart. Consequently, current guidelines for cardiovascular screening recommend using Caucasian athletes' norms to evaluate Asian athletes. This study aims to outline electrocardiographic and echocardiographic characteristics of the Asian athlete's heart using a Singaporean prospective registry of Southeast (SE) Asian athletes.

Methods and Results: One hundred and fifty elite athletes, mean age of 26.1 ± 5.7 years (50% males, 88% Chinese), were evaluated using a questionnaire, 12-lead electrocardiogram (ECG) and transthoracic echocardiogram. All ECGs were analyzed using the 2017 International Recommendations. Echocardiographic data were presented by gender and sporting discipline. The prevalence of abnormal ECGs among SE Asian athletes was 6.7%—higher than reported figures for Caucasian athletes. The abnormal ECGs comprised mainly anterior T wave inversions (ATWI) beyond lead V2, predominantly in female athletes from mixed/endurance sport (9.3% prevalence amongst females). None had echocardiographic structural abnormalities. Male athletes had reduced global longitudinal strain compared to females (−18.7 ± 1.6 vs. −20.7 ± 2.1%, $p < 0.001$). Overall, SE Asian athletes had smaller left ventricular cavity sizes and wall thickness compared to non-Asian athletes.

Conclusion: SE Asian athletes have higher abnormal ECG rates compared to Caucasian athletes, and also demonstrate structural differences that should be accounted for when interpreting their echocardiograms compared to athletes of other ethnicities.

Keywords: athlete's heart, sports cardiology, registry, Asian athlete, cardiac remodeling

INTRODUCTION

Asian athletes feature prominently in international competitive sport and continue to show improvement at the pinnacle of physical ability—the Olympic Games (1). Altogether, 48 countries combine to form Asia, the largest and most populous continent in the world with a total population exceeding 4.4 billion (2). Despite this enormous population base, there remains a dearth of data for the Asian athlete's ECG and echocardiogram.

The electrocardiogram (ECG) is instrumental in differentiating pathology from physiology in the athlete's heart (3). ECG screening in athletes over the past decade has seen the development of qualitative and quantitative cutoffs, as well as ethnicity-specific recommendations. For instance, anterior T wave inversions (ATWI) up to lead V2 are deemed physiological in Caucasian athletes, whereas in Black athletes, ATWI up to lead V4 are considered within normal limits when preceded by J-point elevation and convex ST segment elevation. These ECG recommendations have reduced false positive rates substantially while preserving sensitivity in identifying pathology in athletes (4). In parallel to the ECG, echocardiographic imaging of Caucasian and Black athletes has also progressed considerably, leading to the establishment of normal reference values (5).

Physiological ECG and echocardiographic limits for Asian athletes have yet to be defined, with current guidelines recommending using Caucasian athletes' norms to evaluate Asian athletes (6). This study aims to highlight ECG and echocardiographic characteristics for Asian athletes via a prospective registry of athletes from Southeast (SE) Asia. Singapore, an island city-state with a multi-ethnic SE Asian population of Chinese (74.1%), Malay (13.4%), Indian (9.2%), and others (3.3%), forms the base for this study (7).

METHODS

The Singapore Sports Cardiology Registry is a descriptive, cross-sectional, and prospective registry of active elite athletes aged $\geq$18 years representing the country in competitive sport regardless of sporting discipline. The study was carried out between January and October 2018 in the Singapore Sport Institute Sports Medicine Centre, which is the only ambulatory centre in the country that provides medical assessment and clearance for all national athletes prior to sport participation. One hundred and fifty consecutive elite athletes from 32 different sporting disciplines completed a questionnaire where data collected included: age, gender, ethnicity, sporting discipline, training history, medical history, and family history of sudden cardiac death.

Electrocardiography

Standard resting 12-lead ECGs were performed on athletes in a supine position, using an ELI 230 ECG machine (Mortara, Milwaukee, WI) at a paper speed of 25 mm/s. All ECGs were analyzed in the digital unfiltered format for abnormalities based on established ECG interpretation criteria for athletes, namely the European Society of Cardiology recommendations in 2010 (ESC2010), the Seattle Criteria in 2013 (SC2013), the Refined Criteria in 2014 (RC2014) and the International recommendations in 2017 (IR2017) (8–11).

Echocardiography

All recruited athletes underwent resting M-mode, two-dimensional (2D) and Doppler transthoracic echocardiography using a Vivid S6 ultrasound system (GE Healthcare, Milwaukee, WI), in accordance with American and British Society of Echocardiography guidelines (12–14). All echocardiograms were performed immediately after the resting 12-lead ECG. Left ventricular (LV) ejection fraction was measured using the biplane method of disks. Pulsed wave tissue doppler imaging of the septal, lateral LV and tricuspid annuli was performed in the apical 4-chamber view to obtain peak early (e′) and late (a′) myocardial velocities and the ratio of early diastolic transmitral flow velocity to e′ (E/e′).

Radiofrequency data from three cardiac cycles were stored and indices of myocardial deformation obtained by speckle-tracking analysis using EchoPac software (Version 11.1.8, GE Healthcare, Horten, Norway). Automated functional imaging was utilized to track and analyse peak systolic strain using a tri-plane imaging probe. Global longitudinal strain (averaged) was measured for all participants. Measures of right ventricular systolic function, 2D fractional area change and tricuspid annular plane systolic excursion (TAPSE), were also obtained.

LV geometry was classified into four groups based on American and European Society of Echocardiography guidelines: normal geometry, concentric remodeling, eccentric hypertrophy, and concentric hypertrophy (12, 14). This was based on cutoffs for relative wall thickness (abnormal $>$ 0.42) and LV mass index (LV hypertrophy defined as LV mass index $>$95 g/m^2 in females and $>$115 g/m^2 in males).

All echocardiographic images were separately reviewed and analyzed by two independent cardiologists, blinded to the participants' ethnicity, sporting discipline, and training volume. Discrepancies in quantitative parameters were averaged and presented as mean values, whereas mutual discussion was carried out for qualitative differences.

Statistical Analysis

The sample characteristics were presented as mean $\pm$ standard deviation (SD) or frequency (%), depending on their nature. The ECGs and echocardiographic data were presented by gender as well as sport discipline. Sport disciplines, based on the European Association of Preventive Cardiology (EAPC) position statement in 2017, were divided into two groups—skill and power (low to moderate oxygen consumption) vs. mixed and endurance (moderate to high oxygen consumption) (5). Independent *t*-tests were performed to ascertain if there were significant differences in ECGs and echocardiographic parameters between the groups. Regression analyses were carried out to examine the association of demographics (i.e., age, gender, ethnicity), sporting discipline and training hours on ECG abnormalities as well as commonly utilized echocardiographic parameters. Data analysis was performed with STATA version 14 (Statacorp, Texas) and all statistical tests were conducted with 5% level of significance.

Written informed consent was obtained from all participants. All study procedures conformed to the ethical guidelines of the 1975 Declaration of Helsinki.

RESULTS

Baseline Characteristics

Of the 150 SE Asian athletes, there were 75 (50%) males, and the ethnic distribution was Chinese (88%), Malay (5.3%), Indian (3.3%), and others [Sikh, Indian-Chinese and Indonesian] (3.3%). These are reflective of ethnic groups found within SE Asia. Participants had a mean age of 26.1 ± 5.7 years. Their average training duration was 19.3 ± 8.8 h per week, with mean competitive experience of 8.5 ± 4.7 years (**Table 1**).

TABLE 1 | Baseline characteristics and sport classification of athletes.

	Mean ± SD/Frequency (%)
Age (years)	26.1 ± 5.7
Male gender	75 (50)
Ethnic group	
• Chinese	132 (88)
• Malay	8 (5.3)
• Indian	5 (3.3)
• Others	5 (3.3)
Body mass index (kg/m^2)	22.9 ± 3.1
Body surface area (m^2)	1.8 ± 0.2
Training hours/week	19.3 ± 8.8
Number of years competing	8.5 ± 4.7
EAPC sport category	
• Skill	20 (13.3)
• Power	24 (16)
• Mixed	50 (33.3)
• Endurance	56 (37.3)

Baseline demographics between Chinese and non-Chinese athletes were comparable.

Electrocardiographic Data

The most common training-related changes based on IR2017 were: sinus bradycardia (65.3%), early repolarization (46%), and sinus arrhythmia (25.3%). Early repolarization (70.7 vs. 21.3%, $p < 0.0001$) and voltage criteria for LV hypertrophy (17.3 vs. 4%, $p < 0.02$) were more common in males than females. Athletes in mixed and endurance sports demonstrated more sinus bradycardia (73.6 vs. 45.4%, $p = 0.001$), incomplete right bundle branch block (15.1 vs. 2.3%, $p = 0.024$), early repolarization (53.8 vs. 27.3%, $p = 0.004$) and voltage criteria for LV hypertrophy (15.8 vs. 0%, $p = 0.003$) compared to those in skill and power-based sports. Borderline findings based on IR2017 were noted in 3 separate athletes −2 with left atrial enlargement and 1 with complete right bundle branch block.

Using ESC2010, 31 ECGs in our cohort were identified with abnormal findings unrelated to training (20.7% prevalence), and application of SC2013 reduced the number of abnormal ECGs to 13 (8.7% prevalence). Identical results for both RC2014 and IR2017 were obtained (6.7% prevalence). There were no differences in prevalence of abnormal ECGs between Chinese and non-Chinese athletes.

Characteristics of all 10 athletes with abnormal ECGs based on IR2017 are outlined in **Table 2**, and digital ECGs are available as **Supplementary Material**. All were Chinese and engaged in mixed or endurance sports. Of these, 8 athletes (7 females; 9.3% prevalence among female athletes) showed anterior T wave inversions (ATWI) in 2 contiguous leads beyond V1. Echocardiograms did not reveal any structural abnormalities in all 10 athletes apart from LV hypertrophy. Of 4 athletes who consented to undergo cardiac magnetic resonance imaging, no abnormalities were found.

TABLE 2 | Characteristics of athletes with abnormal electrocardiograms based on the 2017 International Recommendations.

No	Age (yrs)	Gender	Ethnicity	BSA (m^2)	Sport	Weekly training hours	ECG abnormality	LVWT (mm)	LVIDD (mm)	LV mass (g)	LVEF (%)	GLS (%)
1	23.4	Male	Chinese	1.87	Kayak	25	QRS 140 msec	12	55	288.9	58	−18
2*	26.4	Male	Chinese	1.80	Marathon	15	2 PVCs	12	60	280.7	56	−19
3	18.0	Female	Chinese	1.58	Tennis	27	ATWI V1-V3	9	44	148.7	58	−19
4*	36.2	Female	Chinese	1.44	Marathon	10	ATWI V1-V4	8	48	132.4	60	−20
5	26.1	Female	Chinese	1.82	Waterpolo	18	ATWI V1-V3	9	50	159.4	61	−22
6*	34.4	Female	Chinese	1.68	Netball	14	ATWI V1-V3	9	47	137.2	67	−23
7	32.2	Female	Chinese	1.72	Netball	10	ATWI V1-V3	7	47	108.8	53	−20
8	33.1	Female	Chinese	1.49	Marathon	10	ATWI V1-V3	7	48	111.3	63	−23
9*	38.8	Male	Chinese	1.47	Marathon	12	ATWI V1-V3	10	52	185.7	59	−20
10	26.7	Female	Chinese	1.52	Dragonboat	22	ATWI V1-V3	7	46	105.9	63	−23

BSA, body surface area; ECG, electrocardiogram; LVWT, Left ventricular wall thickness; LVIDD, Left ventricular internal diameter in diastole; LVEF, Left ventricular ejection fraction; GLS, global longitudinal strain; PVC, premature ventricular contraction; ATWI, Anterior T wave inversion.

**Athletes with cardiac magnetic resonance imaging performed—no pathology detected.*

TABLE 3 | Gender differences in echocardiographic parameters for Singapore athletes.

	Male ($n = 75$)			Female ($n = 75$)			*P*
	Mean	**SD**	**Min, Max**	**Mean**	**SD**	**Min, Max**	
Left heart							
LVWT (mm)	9.4	1.2	7, 13	7.7	1.1	5, 11	<0.001
LVWT/BSA (mm/m^2)	5.1	0.7	3.6, 7.0	4.7	0.8	3.0, 7.2	0.002
LVIDD (mm)	51.6	3.7	43, 63	47.7	3.6	40, 57	<0.001
LVIDD/BSA (mm/m^2)	27.6	2.4	23, 35	29.0	2.7	21, 34	0.001
LVPWD (mm)	9.6	1.3	6, 13	7.9	1.2	5, 11	<0.001
Relative wall thickness	0.37	0.05	0.24, 0.47	0.33	0.05	0.2, 0.5	<0.001
LV mass (g)	181.9	43.7	103, 316.2	122.1	29.3	64.5, 199.6	<0.001
LV mass/BSA (g/m^2)	97.0	22.5	62, 160	74.2	17.7	39.3, 129.6	<0.001
LVEDV (ml)	127.4	22.1	77, 189	94.2	20.1	60, 154	<0.001
LVEDV/BSA (ml/m^2)	68.1	11.7	97.7	56.9	10.9	83.2	<0.001
LV stroke volume (ml)	74.1	14.2	42, 117	56.2	12.4	33, 94	<0.001
LVEF (%)	58.2	4.1	47, 67	60.1	4.0	46, 67	0.004
LA (mm)	36.1	4.6	25, 48	33.0	3.7	25, 43	<0.001
LA/BSA (mm/m^2)	19.3	2.6	14.6, 27.2	20.0	2.2	15.6, 26.5	NS
LA volume (ml)	65.4	19.0	36, 135	53.0	14.1	28, 96	<0.001
LA volume/BSA (ml/m^2)	34.9	9.9	19.6, 70.6	32.1	7.8	17.2, 48.8	NS
E velocity (cm/s)	74.3	14.8	23, 106	84.6	15.1	55, 123	<0.001
DT (ms)	157.3	19.9	118, 208	149.8	19.4	106, 198	0.02
A velocity (cm/s)	39.8	8.0	21, 60	43.0	9.8	25, 69	0.03
E/A	1.9	0.5	0.5, 3.9	2.0	0.5	1.3, 4.2	NS
Septal annular E' (cm/s)	11.8	1.8	7, 16	11.9	1.8	8, 17	NS
Septal annular A' (cm/s)	7.2	1.5	4, 11	6.4	1.1	4, 9	0.001
Septal annular E'/A'	1.7	0.5	0.7, 3.5	1.9	0.4	1.1, 3	0.03
Septal annular E/E'	6.3	1.1	3.3, 8.8	7.3	1.5	4.1, 10.9	<0.001
Septal annular systolic velocity (cm/s)	8.4	1.0	6, 12	8.0	1.0	6, 11	0.01
Lateral annular E' (cm/s)	14.7	2.7	10, 23	15.0	2.5	9, 20	NS
Lateral annular A' (cm/s)	6.8	1.4	4, 11	6.6	1.2	4, 9	NS
Lateral annular E'/A'	2.3	0.7	1.1, 3.8	2.3	0.6	1.3, 4	NS
Lateral annular E/E'	5.1	1.0	2.3, 7.8	5.8	1.2	3.3, 9.8	<0.001
Lateral annular systolic velocity (cm/s)	10.3	2.0	6, 15	10.0	1.6	7, 14	NS
GLS (%)	−18.7	1.6	−16, −22	−20.7	2.1	−15, −24	<0.001
SoV diameter (mm)	32.6	3.5	26, 40	27.5	2.5	22, 35	<0.001
SoV diameter/BSA (mm/m^2)	17.4	1.9	13.7, 21.4	16.7	1.8	12.6, 21.6	0.02
Right heart							
RA volume (ml)	64.6	23.4	25, 155	44.1	13.9	25, 95	<0.001
RA volume/BSA (ml/m^2)	34.4	12.3	14.1, 84	26.6	7.8	15.2, 52.4	<0.001
RVOTpl (mm)	29.6	3.7	22, 40	27.2	4.0	16, 36	<0.001
RVOTp (mm)	33.5	4.7	22, 46	30.5	5.2	20, 49	<0.001
RVOTd (mm)	23.8	2.9	15, 30	21.9	2.9	14, 30	<0.001
RVD basal (mm)	39.2	5.4	14, 54	35.1	3.8	26, 44	<0.001
RVD mid (mm)	34.4	4.2	26, 50	30.6	4.2	20, 42	<0.001
RVD longitudinal (mm)	80.6	7.2	64, 97	71.6	8.0	51, 91	<0.001
TAPSE (mm)	25.1	3.4	19, 37	24.4	3.0	18, 32	NS
RV E' (cm/s)	12.6	2.3	7, 18	12.9	2.0	9, 19	NS
RV A' (cm/s)	8.8	2.3	3, 16	8.6	2.4	5, 15	NS
RV E'/A'	1.5	0.5	0.8, 3.7	1.6	0.5	0.7, 3.2	NS
RV sys vel (cm/s)	12.2	1.8	8, 19	11.6	1.4	9, 15	0.02

(Continued)

TABLE 3 | Continued

LV geometry	No. of athletes	%		No. of athletes	%	
Normal	54	(72)		62	(82.7)	NS
Concentric remodeling	10	(13.3)		3	(4)	
Eccentric hypertrophy	8	(10.7)		8	(10.7)	
Concentric hypertrophy	3	(4)		2	(2.7)	

LVWT, left ventricular wall thickness; LVIDD, left ventricular internal diameter in diastole; BSA, body surface area; PWD, posterior wall thickness in diastole; EDV, end diastolic volume; EF, ejection fraction; CO, cardiac output; CI, cardiac index; LA, left atrium; RA, right atrium; RVOT, right ventricular outflow tract; pl, parasternal long axis; p, proximal; d, distal; RVD, right ventricular diameter; DT, deceleration time; TAPSE, tricuspid annular plane systolic excursion; GLS, global longitudinal strain; SoV, Sinus of Valsalva.

Echocardiographic Data

Comprehensive structural and functional echocardiographic parameters for the cohort by gender and sport discipline are presented in **Tables 3**, **4**, respectively. Normal geometry was encountered in the majority of athletes (77.3%, $n = 116$), followed by eccentric hypertrophy ($n = 16$, 10.7%), concentric remodeling ($n = 13$, 8.7%), and concentric hypertrophy ($n = 5$, 3.3%).

Of the entire cohort, 3 athletes (2% prevalence) were found to have minor structural heart disease that did not impact sporting participation: secundum atrial septal defect (male kayaker), dilated aortic root (male cyclist), and anterior mitral valve leaflet prolapse with mild mitral regurgitation (female triathlete).

Differences Between Genders

Absolute LV wall thickness (LVWT), LVIDD, volumes and mass were significantly larger in male compared to female athletes (**Table 3** and **Figure 1**). In male athletes, diastolic indices, and global longitudinal strain were of smaller magnitudes compared to female athletes. There were no differences between male and female athletes in terms of LV geometry.

Differences Between Sport Disciplines

Athletes from mixed or endurance sports demonstrated significantly increased left and right heart dimensions (i.e., LVWT, LVIDD, LV mass, LV end diastolic volume, LV stroke volume, left and right atrial volumes) compared to those from skill or power-based sports. Diastolic function and global longitudinal strain did not differ significantly between the two groups (**Table 4**).

Differences Between Ethnic Groups

Echocardiographic parameters in Chinese and non-Chinese athletes were comparable for almost all variables.

Regression Analyses

Logistic regression analysis showed that increasing age was an independent predictor for ATWI beyond V2 (odds ratio 1.13, $p = 0.03$) after adjusting for baseline demographics (age, gender, ethnicity, type of sport, training hours). Linear regression analysis showed that male gender and mixed and endurance sport disciplines were independently associated with a statistically significantly higher LVIDD, LVWT, and LV end diastolic volume after adjusting for baseline demographics.

DISCUSSION

This prospective electrocardiographic and echocardiographic registry is the first to evaluate a well-defined cohort of SE Asian elite athletes. It utilizes the contemporary IR2017 and describes a comprehensive range of ECG and echocardiographic characteristics, including values indexed to body surface area. Notably, the prevalence of ATWI beyond lead V2 on ECG was noted to be high at 9.3% for female athletes.

Electrocardiographic Parameters

Comparison With Other Athletic Cohorts

In non-Asian athletes, evolution of ECG interpretation criteria has led to considerable reduction in prevalence of abnormal ECGs while preserving sensitivity for detection of pathology. Prior to the current gold standard IR2017, its predecessor the RC2014 was used to compare athletes from different ethnicities. Reported prevalence rates of abnormal ECGs in Black, Caucasian and Arabic athletes using RC2014 (11.5, 5.3, and 3.6%, respectively) were substantially lower than those with ESC2010 and SC2013 (10, 15). Likewise, our cohort mirrors this trend of reduction in abnormal ECG with application of each newer criterion (**Figure 2**).

Application of IR2017 in a cohort of more than 11,000 adolescent soccer players revealed prevalence rates of abnormal ECGs at 3.6 and 1.6% for black and white athletes, respectively (16). Comparatively, the prevalence of abnormal ECGs in our cohort did not reduce further from RC2014 to IR2017 largely because our population was older in age and unaffected by the inclusion of the juvenile ECG pattern in IR2017 (17).

At 6.7%, the prevalence of abnormal ECGs in our SE Asian athletes is higher than reported figures for most non-Asian athletic populations. This is accounted for predominantly by ATWI beyond lead V2. Specifically, ATWI beyond V2 amongst SE Asian female athletes has a prevalence of 9.3%, more than 4 times the corresponding prevalence of 2.1% in a large cohort of Caucasian female athletes from UK (18).

TABLE 4 | Differences in echocardiographic parameters of Singapore athletes based on sporting discipline.

	Skill and power ($n = 44$)		Mixed and endurance ($n = 106$)		*P value*
	Mean	***SD***	**Mean**	***SD***	
Left heart					
LVWT (mm)	7.8	1.3	8.9	1.4	<0.001
LVWT/BSA (mm/m^2)	4.5	0.6	5.0	0.8	<0.001
LVIDD (mm)	48.1	4.1	50.3	4.0	0.004
LVIDD/BSA (mm/m^2)	27.6	2.4	28.6	2.7	0.025
LVPWD (mm)	8.0	1.3	9.1	1.4	<0.001
Relative wall thickness	0.33	0.05	0.36	0.05	0.002
LV mass (g)	127.3	39.8	162.3	47.1	<0.001
LV mass/BSA (g/m^2)	71.9	17.3	91.3	23.0	<0.001
LVEDV (ml)	98.2	24.3	116.0	26.2	<0.001
LVEDV/BSA (ml/m^2)	55.2	8.8	65.5	12.7	<0.001
LV stroke volume (ml)	58.0	13.7	68.2	16.1	<0.001
LVEF (%)	59.5	4.0	59.0	4.2	NS
LA (mm)	32.3	4.3	35.5	4.2	<0.001
LA/BSA (mm/m^2)	18.5	1.7	20.2	2.4	<0.001
LA volume (ml)	48.3	14.3	63.7	17.2	<0.001
LA volume/BSA (ml/m^2)	27.3	6.3	36.0	8.7	<0.001
E velocity (cm/s)	81.3	18.3	78.7	14.6	NS
DT (ms)	153.9	19.5	153.4	20.2	NS
A velocity (cm/s)	42.7	9.2	40.9	8.9	NS
E/A	2.0	0.6	2.0	0.5	NS
Septal annular E' (cm/s)	12.1	2.0	11.7	1.7	NS
Septal annular A' (cm/s)	7.1	1.5	6.7	1.4	NS
Septal annular E'/A'	1.8	0.5	1.8	0.5	NS
Septal annular E/E'	6.7	1.5	6.8	1.4	NS
Septal annular systolic velocity (cm/s)	8.2	1.0	8.3	1.0	NS
Lateral annular E' (cm/s)	15.1	2.5	14.7	2.6	NS
Lateral annular A' (cm/s)	6.6	1.4	6.7	1.3	NS
Lateral annular E'/A'	2.4	0.6	2.3	0.6	NS
Lateral annular E/E'	5.4	1.4	5.4	1.1	NS
Lateral annular systolic velocity (cm/s)	10.6	1.7	9.9	1.8	0.038
GLS (%)	−20.0	2.2	−19.6	2.0	NS
SoV diameter (mm)	29	3.8	30.5	3.9	NS
SoV diameter/BSA (mm/m^2)	16.6	1.6	17.3	1.9	NS
Right heart					
RA volume (ml)	42.9	15.7	59.1	22.3	<0.001
RA volume/BSA (ml/m^2)	24.0	6.5	33.2	11.3	<0.001
RVOTpl (mm)	26.5	4.4	29.2	3.6	0.001
RVOTp (mm)	30.3	6.2	32.7	4.6	0.024
RVOTd (mm)	21.7	3.0	23.3	3.0	0.006
RVD basal (mm)	35.1	4.2	37.9	5.2	0.001
RVD mid (mm)	31.1	4.0	33.1	4.7	0.01
RVD longitudinal (mm)	74.3	9.4	76.9	8.5	NS
TAPSE (mm)	23.9	2.9	25.1	3.3	0.033
RV E' (cm/s)	13.0	2.1	12.6	2.2	NS
RV A' (cm/s)	8.3	2.1	8.9	2.4	NS
RV E'/A'	1.6	0.5	1.5	0.5	NS
RV sys vel (cm/s)	11.7	1.6	12.0	1.7	NS

LVWT, left ventricular wall thickness; LVIDD, left ventricular internal diameter in diastole; BSA, body surface area; PWD, posterior wall thickness in diastole; EDV, end diastolic volume; EF, ejection fraction; CO, cardiac output; CI, cardiac index; LA, left atrium; RA, right atrium; RVOT, right ventricular outflow tract; pl, parasternal long axis; p, proximal; d, distal; RVD, right ventricular diameter; DT, deceleration time; TAPSE, tricuspid annular plane systolic excursion; GLS, global longitudinal strain; SoV, Sinus of Valsalva.

Whereas, ATWI in non-Asian athletes may prompt further evaluation for possible cardiomyopathy (e.g., hypertrophic cardiomyopathy or arrhythmogenic cardiomyopathy), the incidence of pathological conditions manifesting with ATWI is very low in Singapore (19). For instance, the prevalence of hypertrophic cardiomyopathy in a large unselected young Singapore male population was 0.005% (20). In addition, incidence of sports-related sudden death was <1 in 2 million (21). These data may suggest a physiological rather than pathological explanation for the high prevalence of ATWI. A possible hypothesis is the displacement of the cardiac apex following longstanding endurance activity, which may be further influenced by unique contributions from gender and ethnicity (22).

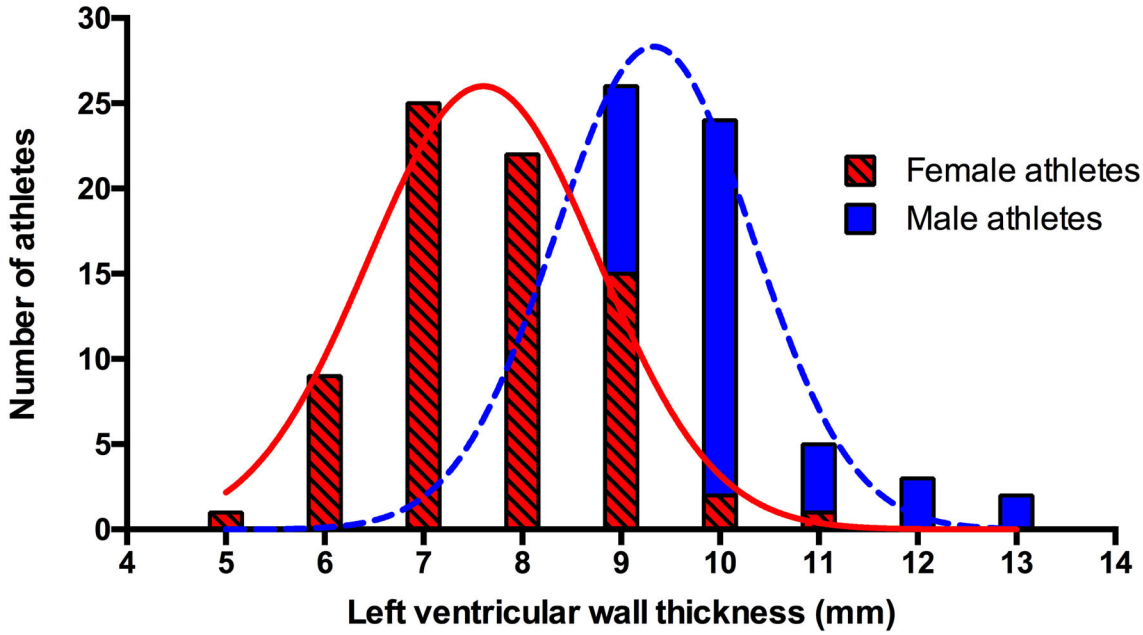
The combined impact of ethnicity, gender, and sport discipline on ATWI deserves validation in a larger cohort. Confirmation of the high prevalence of ATWI up to lead V3 in Asian female endurance athletes combined with normal cardiac function and structure may lead to further refinement of ECG interpretation criteria with additional ethnic-specific cutoffs.

Echocardiographic Parameters

Our study identified gender differences between athletes in global longitudinal strain, where male athletes have reduced GLS compared to females (an absolute difference of 2%). These gender differences corroborate findings by Park et al. in their study of an international cohort of university athletes and provide further insights into gender disparities in physiological cardiac remodeling (23).

Comparison With Other Athletic Cohorts

Compared to Caucasian and Black athletes, both male and female SE Asian athletes had smaller absolute LVIDD and LVWT (5, 6, 24–26) (**Figure 3**). A likely explanation for this is the proportionately smaller body sizes of SE Asians in general. However, the opposite was true when indexed values were used. Amongst male athletes, indexing of LVIDD to



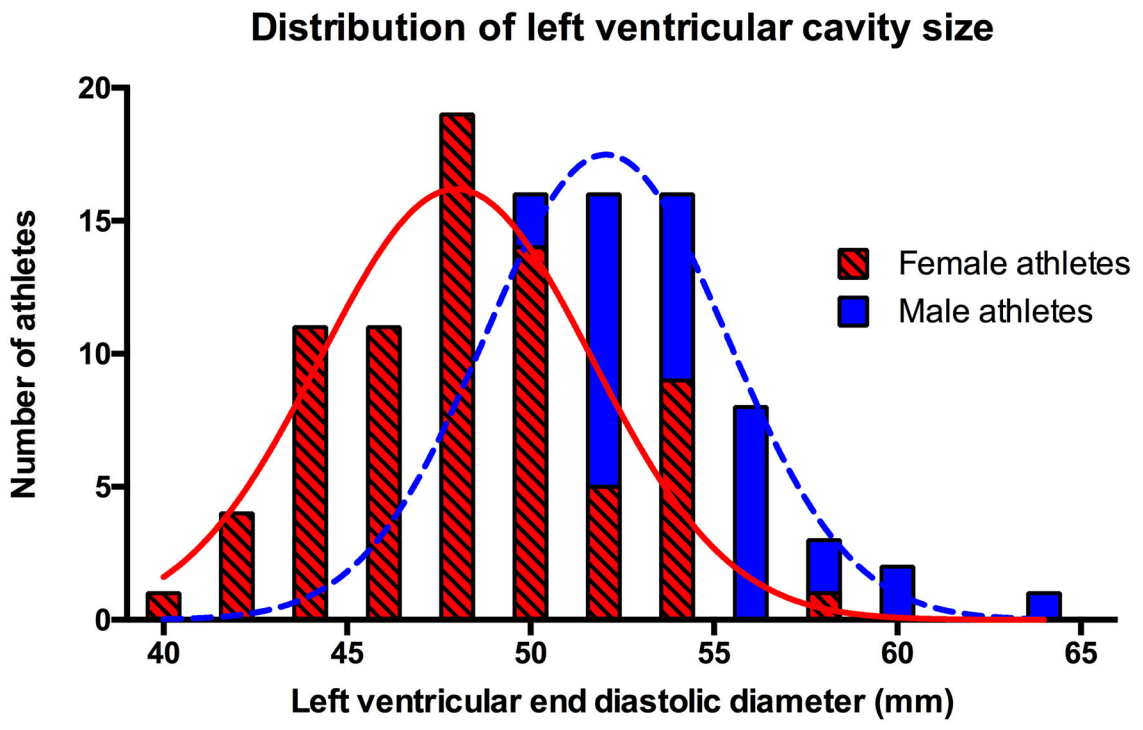


FIGURE 1 | Distribution of left ventricular wall thickness and left ventricular cavity size by gender.

body surface area revealed that a cohort of Caucasian and Black professional basketball players from the United States had smaller dimensions compared to our cohort (25). This may be due to the majority (more than 40%) of our cohort consisting of endurance athletes. Athletes from endurance sports typically develop larger LVIDD compared to strength-trained

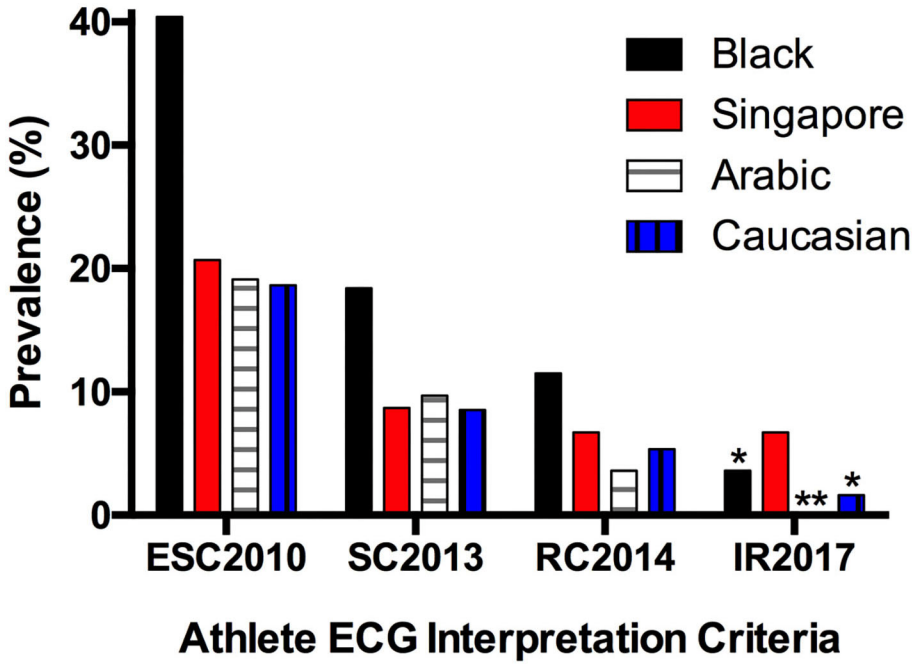


FIGURE 2 | Prevalence of abnormal electrocardiograms in athletes of different ethnicities (10, 15, 16) (*Adolescent athletes; **Data unavailable; ESC, European Society of Cardiology; SC, Seattle Criteria; RC, Refined Criteria; IR, International Recommendations).

athletes or those engaged in mixed sport such as basketball (27, 28).

Our SE Asian athlete cohort LVIDD and LVWT values corroborate with a group of Singapore athletes studied in 2004 and a group of mixed Asian university athletes in 2015 (29, 30). However, when compared to athletes from China and Japan, varying limits were observed with no discernable pattern identified. Male athletes from China and Japan had larger absolute LVIDD than those from our cohort. Nonetheless, this pattern was no longer present after indexing to body surface area (31, 32). China athletes also had higher absolute LVWT compared to our cohort, although the difference between cohorts was reversed after indexing for body surface area.

These differences between varying Asian cohorts underscore the impact of ethnicity on cardiac remodeling in athletes. Riding et al. demonstrated substantial variability in electrical and structural remodeling amongst Black athletes from different parts of the world, highlighting the influence of geographic origin (33). Their findings mirror our comparisons between SE Asian athletes and other East Asian cohorts. This suggests that, despite sharing a common ancestry, Asian athletes from different geographic locations have intrinsic differences in physiological electrical and structural cardiac remodeling. These differences warrant additional study in other Asian cohorts such as Malay, Thai, Filipino and Indonesian athletes, to avoid generalization of findings for all athletes of Asian descent.

Moreover, comparison of echocardiographic parameters indexed to body surface area is challenging as these are uncommonly reported in existing athlete cohorts. We encourage researchers involved in athlete registries to include indexed values to facilitate comparison of echocardiographic parameters.

Limitations

Our registry of Singapore athletes has a sample size of 150 with predominant Chinese ethnicity, limiting applicability to all Asian athletes. Although non-Chinese athletes make up 12% of the cohort, these ethnic groups (Malay, Indian, Sikh, Indonesian) reflect the multi-racial population in Singapore and SE Asia. Importantly, comparison between Chinese and non-Chinese athletes did not reveal any clinically significant differences in demographics, prevalence of abnormal ECG or echocardiographic parameters. Within our cohort, representation from athletes engaging in power-based sports is also limited, with power-trained athletes making up 16% of the cohort.

Not all athletes with abnormal ECGs received comprehensive evaluation beyond echocardiography, for instance cardiac magnetic resonance imaging, exercise testing or 24 h electrocardiographic monitoring, to definitively exclude cardiac pathology. However, none of the athletes with abnormal ECGs were noted to have abnormal symptoms, examination findings or unexplained drop in fitness during their routine 2-yearly pre-competition clinical evaluations to date.

Given the small number of athletes with ATWI, regression analyses should be interpreted with caution.

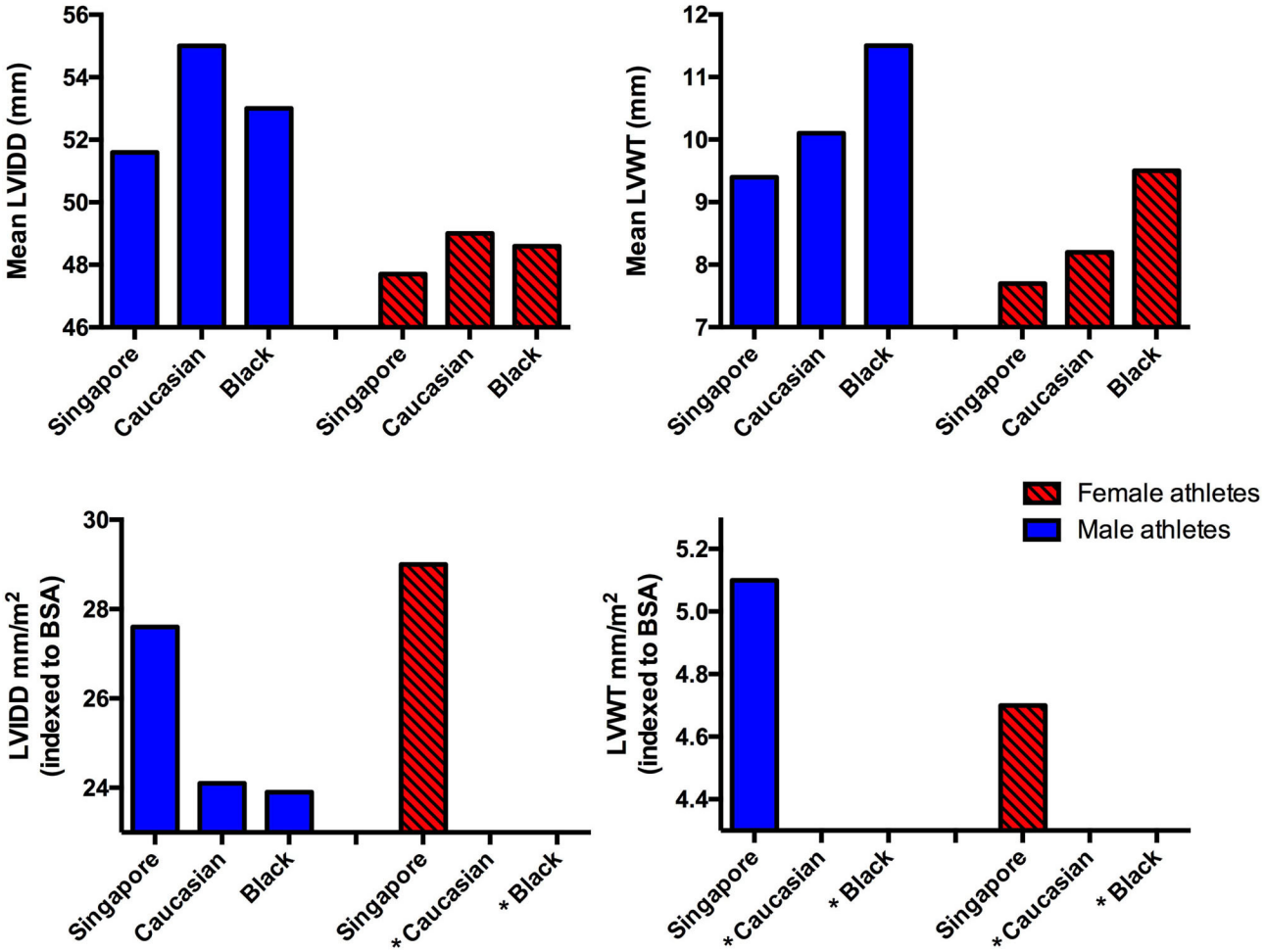


FIGURE 3 | Comparison of mean and indexed left ventricular cavity size and left ventricular wall thickness in athletes from different ethnic groups (5, 6, 24–26) (*Data unavailable).

Finally, we did not perform comparison with matched Caucasian and/or Black athletes to highlight ethnic-specific differences in ECG and echocardiographic characteristics.

CONCLUSION

This prospective sports cardiology registry highlights electrocardiographic and echocardiographic characteristics in a cohort of SE Asian elite athletes as well as differences between other Asian and non-Asian cohorts. Further large-scale prospective registries are necessary to identify aspects of cardiac remodeling unique to athletes of different ethnic backgrounds.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

This study was reviewed and approved by National Healthcare Group Domain Specific Review Board Singapore (2017/00319) and Singapore Sports Institute Institutional Review Board (PH/EXP/018). All participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

LK performed the measurements. MW, RG, FT, and GC were involved in planning and recruitment of participants. TY processed the experimental data, performed the analysis, drafted the manuscript, and designed the figures. NT edited the manuscript. S-PC aided in statistical analysis and interpreting the results. JM, C-HL, DO, AM, SS, and AR provided critical feedback and helped shape the research, analysis, and manuscript. All authors discussed the results and contributed to the final 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.2021.799129/full#supplementary-material

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ORIGINAL RESEARCH
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Age-Related Electrocardiographic Characteristics of Male Junior Soccer Athletes

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Introduction: Very limited data exist on normal age-related ECG variations in adolescents and no data have been published regarding the ECG anomalies induced by intensive training, which are relevant in pre-participation screening for sudden cardiac death prevention in the adolescent athletic population. The purpose of this study was to establish normal age-related electrocardiographic measurements (P wave duration, PR interval, QRS duration, QT, and QTc interval) grouped according to 2-year age intervals.

Methods: A total of 2,151 consecutive healthy adolescent Soccer athletes (trained for a mean of 7.2 ± 1.1 h per week, 100% male Caucasians, mean age 12.4 ± 1.4 years, range 7–18) underwent pre-participation screening, which included ECG and transthoracic echocardiography in a single referral center.

Results: Their heart rate progressively slowed as age increased ($p < 0.001$, ranging from 80.8 ± 13.2 to 59.5 ± 10.2 bpm), as expected. The P wave, PR interval, and QRS duration significantly increased in older age classes ($p = 0.019$, $p = 0.001$, and $p < 0.001$, respectively), and after Bonferroni's correction, the difference remained significant in all age classes for QRS duration. The QTc interval diminished progressively with increasing age ($p = 0.003$) while the QT interval increased progressively ($p < 0.001$).

Conclusions: Significant variations in the normal ECG characteristics of young athletes exist between different age groups related to increasing age and training burden, thus, age-specific reference values could be adopted, as already done for echocardiographic measurements, and may help to further discriminate potentially pathologic conditions.

Keywords: athlete's heart, electrocardiogram, adolescent, reference values, exercise, normal values, nomograms

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INTRODUCTION

The morphological, electrophysiologic, and functional adaptations to regular and intensive physical activity are generally referred to as "the athlete's heart." Race, sex, type of sport, body size, and age at the start of training significantly impact the characteristics of the adult athlete's heart (1–3), but the pediatric athlete's heart has been characterized less and is usually perceived as influenced to a minor extent by exercise-induced remodeling (4). Nonetheless, during adolescence, there is already a growing level of competitiveness, professionalism, and intensive training that affect this maturation period, such that the International Olympic Committee (IOC) has advanced recommendations to promote the healthy and balanced development of the young athletes (5). A recent meta-analysis (6) has shown that pediatric athletes have a greater prevalence of training-related and training-unrelated ECG changes than non-athletes, and the magnitude, prevalence, and distribution of such changes are dependent on the chronological age of the pediatric athlete. Limited data (7) exist on normal age-related ECG changes in adolescents between different age groups and no data have been published regarding the athletic population classed into age intervals of 2 years. We have already published echocardiographic reference values related to physiological remodeling of the adolescent athlete's heart in soccer players (8), therefore in this study, we aimed to establish normal, age-related electrocardiographic measurements (P wave duration, PR interval, QRS duration, and QT and QTc interval) in a large cohort of adolescent athletes according to age at 2-year intervals, and to provide nomograms to better define the pediatric athlete's heart.

METHODS

Study Population

This retrospective study included the same healthy population described in detail elsewhere (8). Among the 2,261 subjects initially screened in our center and described in a previous study (9), 2,151 (95%) subjects were included in this study. In total, 110 subjects were excluded from the study because of any abnormal ECG coupled with an abnormal echocardiographic study (11 subjects), an abnormal echocardiographic finding with a normal ECG (91 subjects), or an incomplete study (eight subjects) (10) (**Supplementary Figure 1**). Briefly, consecutive junior soccer players (7–18 years old, trained for at least 9 months, 100% male, all Caucasian) who underwent pre-participation screening (PPS), including a 12-lead electrocardiogram and transthoracic echocardiography at the Sports Medicine Institute of Rome, Villa Stuart Sport Clinic, FIFA Medical Centre of Excellence, between January 2008 and March 2009 were enrolled. Both the 12-lead ECG and the echocardiographic study were classified as either normal or showing physiological cardiac adaptations to regular exercise (9). Athletes with potential pathological ECGs or echocardiograms have been excluded from this study and analysis. The presence of abnormal or training un-related ECG findings or an abnormal echocardiographic finding, including cardiomyopathy, bicuspid aortic valve, and mitral valve prolapse were considered as the exclusion criteria in order to provide normal values of this population. The local institutional review board approved this retrospective study.

The 12-Lead Electrocardiogram

All 12-lead resting ECGs were performed using standard equipment (Mortara Instruments, Milwaukee, USA) and were recorded at a paper speed of 25 mm/s and a standard gain of 1 mV/cm. The ECGs were evaluated as previously detailed (10, 11). The heart rate and QRS axis were determined. The P-, Q-, R-, S- and T-wave voltages, ST segments, QRS duration, and PR- and QT-interval were measured with calipers and classified according to the 2017 International Recommendations for electrocardiographic interpretation (12) in athletes as normal, borderline, or abnormal ECG findings. The presence of anterior (V1–V3) T-wave inversion was considered to be a juvenile T-wave pattern in individuals <16 years old in presence of normal echocardiographic findings. The corrected QT interval (QTc) was calculated using the Bazett formula, as already stated (11). Furthermore, borderline ECG findings and a normal echocardiographic study were considered to be evidence of physiological cardiac adaptation to regular exercise and required no further investigation. Two independent sport medicine physicians evaluated the ECGs during PPS. Off-line they also manually measured with the use of calipers the ECGs interval and waves included in the analysis. Moreover, all ECGs were reviewed by a cardiologist who was blinded to the athletes' medical history; discrepancies were resolved after consensus.

Echocardiography

All athletes underwent a complete transthoracic Doppler echocardiographic study as a part of the PPS, as detailed elsewhere (8).

Statistical Analysis

Continuous variables are reported as mean ± SD and categorical variables as count (%). Age-wise comparisons were performed with ANOVA and *post-hoc* unpaired *t*-tests with Bonferroni adjustment. Nomogram analysis was performed with the generalized additive models for location, scale, and shape (GAMLSS), which are a general class of statistical models for a univariate response variable developed by Rigby and Stasinopoulos (13). In particular, we relied on the lms function of the GAMLSS package for R (R Foundation for Statistical Computing, Vienna, Austria) and calibrated the centiles, which optimizes the maximum (penalized) likelihood of the model built using the Box-Cox Cole and Green, Box-Cox Power exponential, and Box-Cox t distributions. Two independent experts performed the GAMLSS analysis with dedicated and validated custom-made analyses (DMS changed the GAMLSS functions: calibration, centile.pred, and centiles.boot). Accordingly, centile plots were generated, with accompanying centile tables. For internal validation, we performed bootstrapping, yielding bootstrapped centile tables. Linear correlation was appraised with Pearson correlation, displayed with dendrograms and heatmaps. Statistical significance was set at the 2-tailed 0.05 level. Computations were performed with R 3.6.

RESULTS

A total of 2,151 male adolescent athletes were included in the analysis and their demographic, anthropometric, and echocardiographic findings are summarized in **Table 1**. The distribution of HR, P-wave duration, PR interval, QRS duration, and QT and QTc intervals per **2-year** age classes and quartiles are shown in **Supplementary Figure 1**. We divided it into 2-year classes to be consistent with the previously published studies related to normal ECG systematic values in pediatric patients (7).

As expected, heart rate progressively slowed with age and increasing hours of training ($P < 0.001$, ranging from 80.8 ± 13.2 to 59.5 ± 10.2 bpm). P wave duration progressively lengthened with age ($P = 0.019$) but significance was lost among the different age classes after Bonferroni correction. PR interval and QRS duration significantly increased in older age classes ($P = 0.001$ and $P < 0.001$, respectively) and after Bonferroni's correction, the difference remained significant in all age classes for QRS duration and groups 1–2 vs. 5–6 for PR interval. QT interval progressively increased over time ($P < 0.001$, **Table 1**), but this effect was mainly due to heart rate reduction, as proven by the relatively stable QTc interval duration among the different classes. The prevalence of normal or training-related ECG findings was significantly different among age groups (**Table 2**), with the older age classes displaying the highest prevalence of training-related findings, such as sinus bradycardia, increased QRS voltage for left ventricular hypertrophy, incomplete right bundle branch block, and early repolarization/ST-segment elevation. The prevalence of the anterior T wave inversion reduced progressively with the older age groups, with only 3 (1.3%) cases in 383 athletes aged 15–16 years and 0% in 17–18-year-old athletes, demonstrating the physiological regression of the juvenile pattern with increasing age. Borderline findings were quite uncommon (1.2%) in our series because only athletes with both normal ECGs and echocardiograms were included (**Table 3**).

The nomogram analysis generated detailed centile plots and centile tables for all the parameters of interest, including HR, P wave duration, PR, QRS, QT, and QTc (**Figures 1**, **2**). Both the figures and the **Supplementary Tables** may be useful in identifying normal values based on age classes and centiles. The x-axis shows the age in years, while the y-axis indicates the ECG parameter value. The usefulness of using nomograms is depicted in **Figure 3**.

Correlation analysis highlighted the substantial correlation between the different anthropometric characteristics, arterial pressure measurements, and the ECG parameters, whereas correlations with other features were less robust (**Supplementary Table 1**; **Supplementary Figure 3**). In particular, there was a strong correlation between PR, QRS, and QT duration in milliseconds with all the anthropometric characteristics [body mass index [BMI], body surface area (BSA), lean body mass, height, and weight], with age and with hours of training per week. Systolic and diastolic blood pressure values correlated with the anthropometric characteristics and age but not with the ECG parameters. For HR, an inverse correlation was found with age, training hours, and QT, which was not significant when QTc was considered.

DISCUSSION

Over recent years, several nomograms and reference values for echocardiographic parameters in athletes have been published,

TABLE 1 | Demographic, anthropometric and echocardiographic measurements of the study population.

Age (years)	**Overall**	**Group 1: 7–8**	**Group 2: 9–10**	**Group 3: 11–12**	**Group 4: 13–14**	**Group 5: 15–16**	**Group 6: 17–18**
***n* (%)**	**2,151 (100)**	**141 (7)**	**448 (21)**	**524 (24)**	**546 (25)**	**383 (18)**	**109 (5)**
Height (cm)	156.9 ± 15.9	132.8 ± 5.8 [2,3,4,5,6]	140.9 ± 7.0 [3,4,5,6]	151.6 ± 8.4 [4,5,6]	165.2 ± 8.9 [5,6]	173.9 ± 7.5 [6]	177.9 ± 6.1
Weight (kg)	49.8 ± 14.8	31.2 ± 6.6 [2,3,4,5,6]	37.1 ± 8.2 [3,4,5,6]	44.6 ± 9.5 [4,5,6]	55.1 ± 10.5 [5,6]	65.3 ± 9.6 [6]	69.6 ± 8.9
Training (hr/week)	7.3 ± 1.2	6.3 ± 0.8 [3,4,5,6]	6.3 ± 0.7 [3,4,5,6]	7.0 ± 1.2 [4,5,6]	8.1 ± 0.7	8.1 ± 0.8	8.2 ± 0.9
Duration of training (months)	29.7 ± 12.7	12.3 ± 1.6 [2,3,4,5,6]	14.5 ± 8.6 [3,4,5,6]	28.4 ± 12.2 [4,5,6]	32.7 ± 16.1 [5,6]	41.4 ± 6.0 [6]	64.3 ± 5.7
SBP (mmHg)	110.0 ± 10.6	103.7 ± 12.0 [3,4,5,6]	105.2 ± 10.7 [3,4,5,6]	108.1 ± 9.4 [4,5,6]	112.6 ± 9.2 [5,6]	114.9 ± 9.4	117.0 ± 7.9
DBP (mmHg)	69.2 ± 7.3	65.6 ± 8.3 [3,4,5,6]	66.7 ± 7.2 [3,4,5,6]	67.9 ± 6.6 [4,5,6]	70.6 ± 6.8 [6]	71.8 ± 6.9	73.3 ± 5.9
LVEDD (mm)	46.1 ± 4.9 (25.0, 58.0)	40.4 ± 3.3 (25.0, 48.0) [2,3,4,5,6]	42.4 ± 3.3 (32.0, 54.0) [3,4,5,6]	44.6 ± 3.6 (33.0, 55.0) [4,5,6]	48.0 ± 3.9 (36.0, 58.0) [5,6]	50.6 ± 3.4 (37.0, 58.0)	51.2 ± 3.7 (35.0, 58.0)
LV Mass (g)	106.1 ± 32.7 (35.4, 234.3)	69.5 ± 15.3 (37.6, 118.2) [2,3,4,5,6]	80.5 ± 17.4 (35.4, 142.9) [3,4,5,6]	94.1 ± 21.6 (41.1, 199.3) [4,5,6]	119.0 ± 27.8 (55.9, 234.3) [5,6]	137.0 ± 24.7 (44.8, 213.9)	142.7 ± 26.9 (51.3, 205.5)

Data expressed as mean±sd or as absolute count (% of total). SBP, systolic blood pressure; DBP, diastolic blood pressure; LVEDD, left ventricular end-diastolic diameter; LV, left ventricular.

$p < 0.05$ current group vs. the other group, pairwise comparisons with Bonferroni adjustment for multiple comparisons.

TABLE 2 | Electrocardiographic measurements per age groups.

Age (years)	Overall	Group 1: 7–8	Group 2: 9–10	Group 3: 11–12	Group 4: 13–14	Group 5: 15–16	Group 6: 17–18
n (%)	2,151 (100)	141 (7)	448 (21)	524 (24)	546 (25)	383 (18)	109 (5)
HR (bpm)	68.8 ± 12.8 $p < 0.001$	80.8 ± 13.2 [54; 109] [2,3,4,5,6]	74.2 ± 12.5 [52; 101] [3,4,5,6]	70.2 ± 11.4 [50; 96] [4,5,6]	66.3 ± 11.3 [47; 93] [5,6]	62.5 ± 11.2 [44; 88]	59.5 ± 10.2 [43; 82]
P dur (msec)	69.2 ± 18.3 $p = 0.019$	66.2 ± 16.6 [34; 93]	68.0 ± 18.6 [35; 93]	68.5 ± 18.0 [37; 94]	69.7 ± 17.9 [39; 95]	71.4 ± 19.0 [42; 97]	71.1 ± 20.3 [44; 99]
PR (msec)	136.7 ± 26.8 $p = 0.001$	132.5 ± 24.8 [101; 178] [5,6]	134.1 ± 26.5 [105; 179] [5,6]	136.0 ± 24.6 [107; 180]	136.5 ± 28.6 [109; 184]	140.6 ± 25.1 [112; 188]	142.7 ± 33.8 [115; 193]
QRS (msec)	90.9 ± 10.4 $p < 0.001$	87.4 ± 8.5 [71; 106] [4,5,6]	87.0 ± 9.0 [72; 108] [3,4,5,6]	89.1 ± 10.3 [74; 111] [4,5,6]	91.6 ± 9.8 [76; 113] [5,6]	96.2 ± 10.2 [79; 115]	97.8 ± 9.7 [81; 117]
QT (msec)	377.9 ± 30.0 $p < 0.001$	355.9 ± 25.4 [312; 413] [2,3,4,5,6]	367.9 ± 29.8 [319; 424] [3,4,5,6]	375.1 ± 26.2 [325; 434] [4,5,6]	383.1 ± 29.5 [330; 442] [5,6]	389.7 ± 28.6 [332; 448]	393.1 ± 29.5 [333; 452]
QTc (msec)	395.9 ± 23.3 $p = 0.003$	397.2 ± 19.8 [355; 439]	397.5 ± 20.5 [355; 440] [6]	396.9 ± 21.4 [355; 440] [6]	396.4 ± 20.6 [353; 438] [6]	393.6 ± 21.2 [349; 434]	389.9 ± 23.3 [344; 430]

Data expressed as mean ± sd [2nd; 98th percentile].
$p < 0.05$ current group vs. Group J, pairwise comparisons with Bonferroni adjustment for multiple comparisons.
HR, heart rate; P dur, P-wave duration.

TABLE 3 | Prevalence of training-related ECG findings or borderline findings in the study population per age group.

Finding	Overall	Group 1: 7–8	Group 2: 9–10	Group 3: 11–12	Group 4: 13–14	Group 5: 15–16	Group 6: 17–18	*p*
	2,151 (100)	141 (7)	448 (21)	524 (24)	546 (25)	383 (18)	109 (5)	
Sinus bradycardia (<60 bpm)	512 (23.8%)	9 (6.3%)	41 (9.3%)	84 (15.9%)	152 (27.8%)	167 (43.4%)	59 (53.6%)	<0.001
Increased QRS voltage for LVH	311 (14.5%)	13 (9.2%)	41 (9.3%)	65 (12.3%)	107 (19.6%)	63 (16.4%)	22 (20.0%)	<0.001
Incomplete RBBB	689 (32%)	30 (21.1%)	87 (19.9%)	138 (26.1%)	198 (36.3%)	189 (49.1%)	47 (42.7%)	<0.001
Early repolarization/ST segment elevation	407 (18.9%)	18 (12.7%)	63 (14.4%)	93 (17.6%)	139 (25.5%)	75 (19.5%)	19 (17.3%)	<0.001
Anterior (V1–V3) T wave inversion age<16 years old	120 (5.6%)	21 (14.8%)	49 (11.2%)	32 (6.1%)	14 (2.6%)	3 (1.3%)	0 (0%)	<0.001
Ectopic atrial or junctional rhythm	95 (4.4%)	2 (1.4%)	27 (6.0%)	20 (3.8%)	25 (4.6%)	15 (3.9%)	6 (5.5%)	0.326
1st degree AV block	9 (0.4%)	1 (0.7%)	2 (0.5%)	1 (0.2%)	2 (0.4%)	1 (0.3%)	2 (1.8%)	0.269
Left axis deviation	18 (0.8%)	2 (1.4%)	3 (0.7%)	4 (0.8%)	3 (0.6%)	5 (1.3%)	1 (0.9%)	0.812
Left atrial enlargement	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	- -
Right axis deviation	2 (0.1%)	0 (0%)	0 (0%)	0 (0%)	1 (0.2%)	1 (0.3%)	0 (0%)	0.734
Right atrial enlargement	5 (0.2%)	0 (0%)	0 (0%)	1 (0.2%)	2 (0.4%)	2 (0.5%)	0 (0%)	0.633
Complete RBBB	1 (0.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.3%)	0 (0%)	0.853

Data expressed as absolute count (% of total). AV, atrio-ventricular; LVH, left ventricular hypertrophy; RBBB, right bundle branch block.
$p < 0.05$ current group vs. the other group, pairwise comparisons with Bonferroni adjustment for multiple comparisons.

including left (LV) and right ventricular dimensions, mass, volumes, and aortic root measurements, but to the best of our knowledge, no nomograms exist for electrocardiographic parameters in adolescent athletes. Obtaining reference values in adolescents is especially demanding due to factors such as the development stage and age, and their complex interplay between puberty, sex, and response to training. ECG is the most commonly used test to screen the pediatric population in competitive sports and its interpretation is based on the knowledge on how ECG parameters modify through growth and according to sex. Age and sex-related differences are summarized from the observation that from birth through adolescence, principal modifications are related to decreasing heart rate, increasing QRS voltages, and a widening QRS complex. These data have been provided for the non-athlete pediatric population (14).

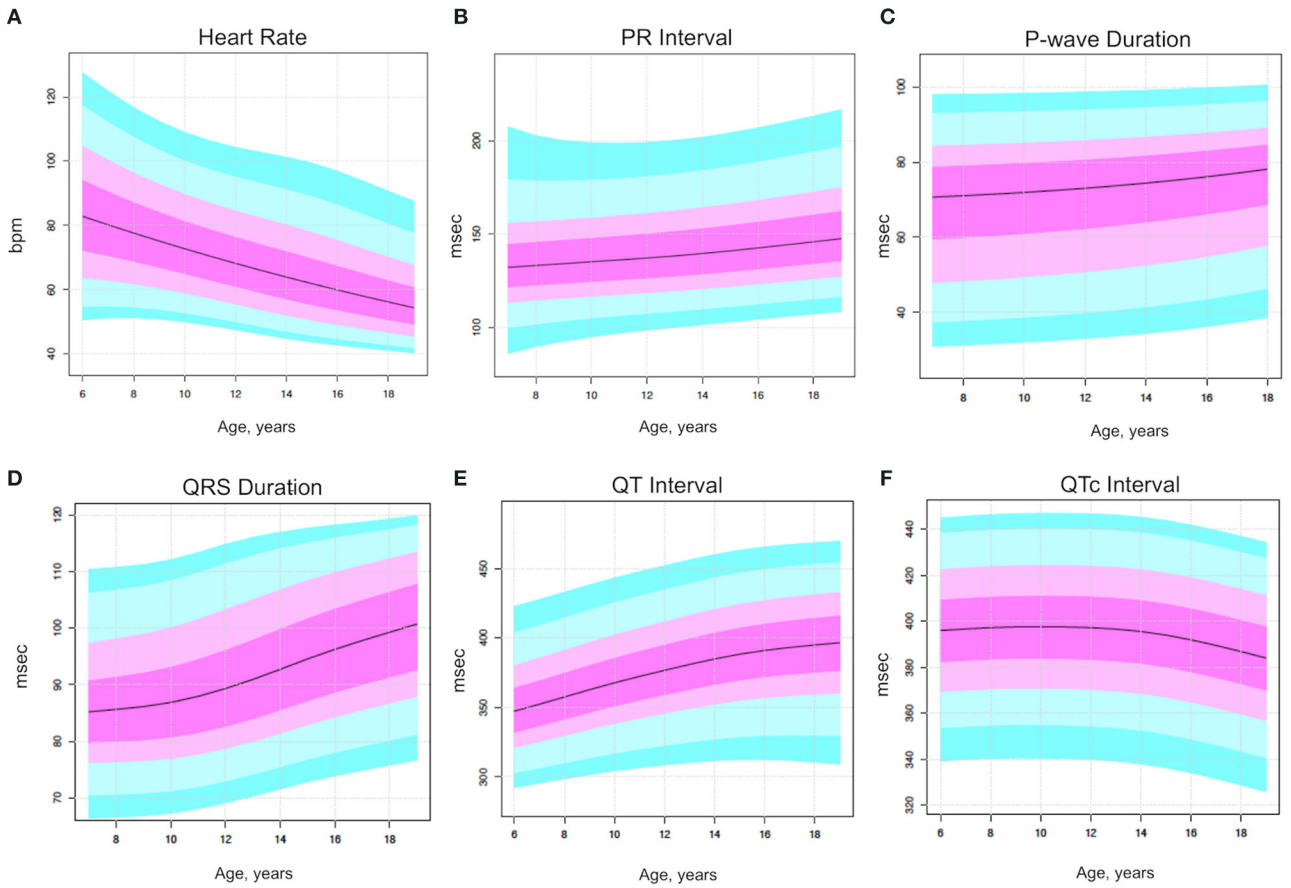

FIGURE 1 | Centile rainbow plots for heart rate (top left panel), P wave duration (right panel), PR (mid-left panel), QRS (mid-right panel), QT (bottom left panel), and QTc (bottom right panel), expressed as median and quartile and age ranges. **(A)** Heart rate. **(B)** *P* wave duration. **(C)** PR duration. **(D)** QRS duration. **(E)** QT duration. **(F)** QTc duration.

In this study, we have sought to provide reference values for normal ECG parameters in a population of more than 2,000 junior athletes evaluated with ECG and echocardiography, which constitute a unique study population of healthy athletes. Our study has shed light for the first time on the temporal evolution of cardiovascular adaptations and describes common training-related ECG modifications in healthy athletes during adolescence, namely: (1) progressive HR reduction culminating in sinus bradycardia; (2) progressive PR elongation which can lead to 1st degree atrioventricular block; (3) increasing QRS duration and development of an incomplete right bundle branch block, while (4) the QTc remains unchanged over time. As pointed out by Cantinotti et al. (15) in their critical review, the current echocardiographic nomograms are limited by numerical and methodological issues, therefore, to generate our electrocardiographic nomograms we used an appropriate sample size and a rigorous statistical approach.

The increasingly early age at which young talents embark on a professional career path, together with growing competitiveness, means that the practice of sports cardiology needs to adapt to guarantee age-appropriate, comprehensive pediatric cardiac evaluations (16). Intensive training already begins to elicit physiological adaptations in athletes as young as 12 years, this change being more pronounced in endurance athletes (6, 17, 18). However, although the structural and functional cardiovascular adaptations to intense exercise are less pronounced when compared with adult athletes, current guidelines do not reflect this distinction, treating adolescent and adult athletes equally. When evaluating an athlete during childhood or adolescence, it is important not only to rule out high-risk features for sudden cardiac death and distinguish physiological adaptations from pathological remodeling but also to take into consideration somatic growth and pubertal development (19–21).

ECG Findings in Athletes vs. High-School Students

The current literature has mainly focused on the prevalence and evolution of uncommon and training-unrelated ECG findings, such as T-wave inversion, which are a common feature of the juvenile pattern when present in the anterior leads (9, 22); however, less is known about age-related physiological ECG characteristics in adolescents. Santini et al. (7) evaluated a substantial population of 24,062 high-school students, describing the anthropometric characteristics, baseline ECG findings, and

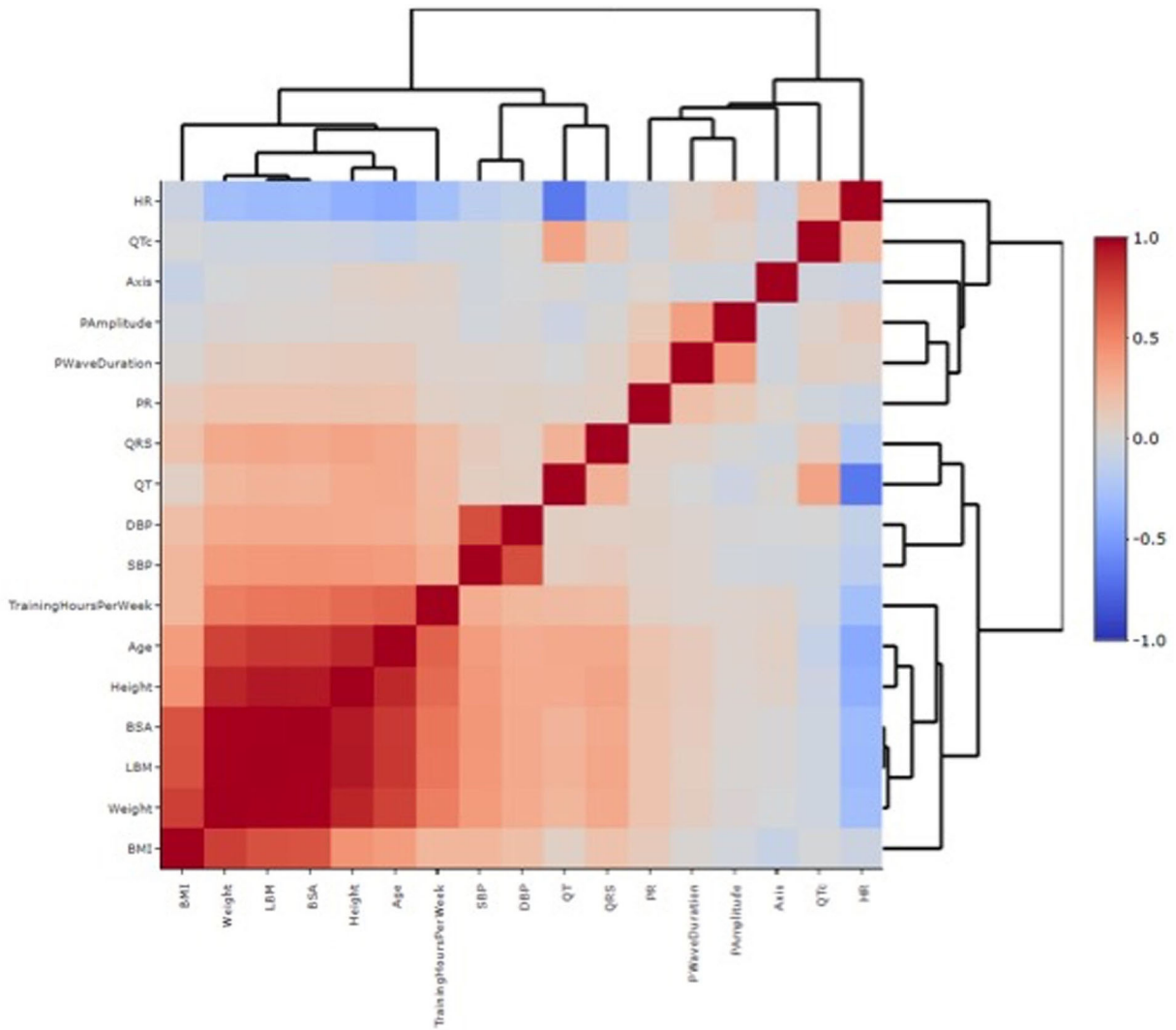

FIGURE 2 | Heatmap correlation between individual features and ECG variables. Each square of the heatmap represents the correlation between the x-axis and the y-axis variables, which ranges between −1 and +1. The closer to +1 the stronger the correlation is (red in the legend, high correlation). The closer to −1 there is an inverse correlation (blue in the legend). White color represents no correlation. The diagonals are all dark red because the heatmap plot is symmetrical about the diagonal and those squares represent the same variable paired together on both axes. The dendrogram highlights the different clusters in which the study population has been divided based on the different variables analyzed.

main clinical findings according to age groups at 2-year intervals. The mean HR slowed with increasing age, as in our population, however, HR ranged from 83.6 bpm for 12–13 years to 74.3 bpm for 18–19 years, while in our population of trained athletes, the same age classes manifested a significantly lower HR value (68 bpm for 12–13 years and 59 bpm for 17–18 years), suggesting the significant impact of intense training. Similarly, the PR interval was also increased (133 ms for 12–13-year-old high-school adolescents vs. 136 ms in 12–13-year-old athletes, reaching 143 ms at 18 years of age) as was the QRS duration (85 ms for 12- to 13-year adolescents vs. 90 ms for athletes, reaching 98 ms at 18 years of age), while the QT was inversely related, probably due to HR reduction (7). Only 67% of the study population of high-school students reported exercising regularly and this percentage declined at higher classes of age, dropping to 57% at 18 years, so almost a third of the student population was composed of sedentary adolescents. However, no data specific to competitive athletes were reported, which conversely constitutes our entire study population and may, therefore, explain the significant differences found when compared to our data.

A similar evolution of the QTc interval in athletes over time has been previously described in the literature (23).

The Usefulness of ECG Nomograms

To the best of our knowledge, the electrocardiographic reference values we have provided represent a precise topography of the physiological evolution of the athlete's heart over time during adolescence and bring to light the growing prevalence

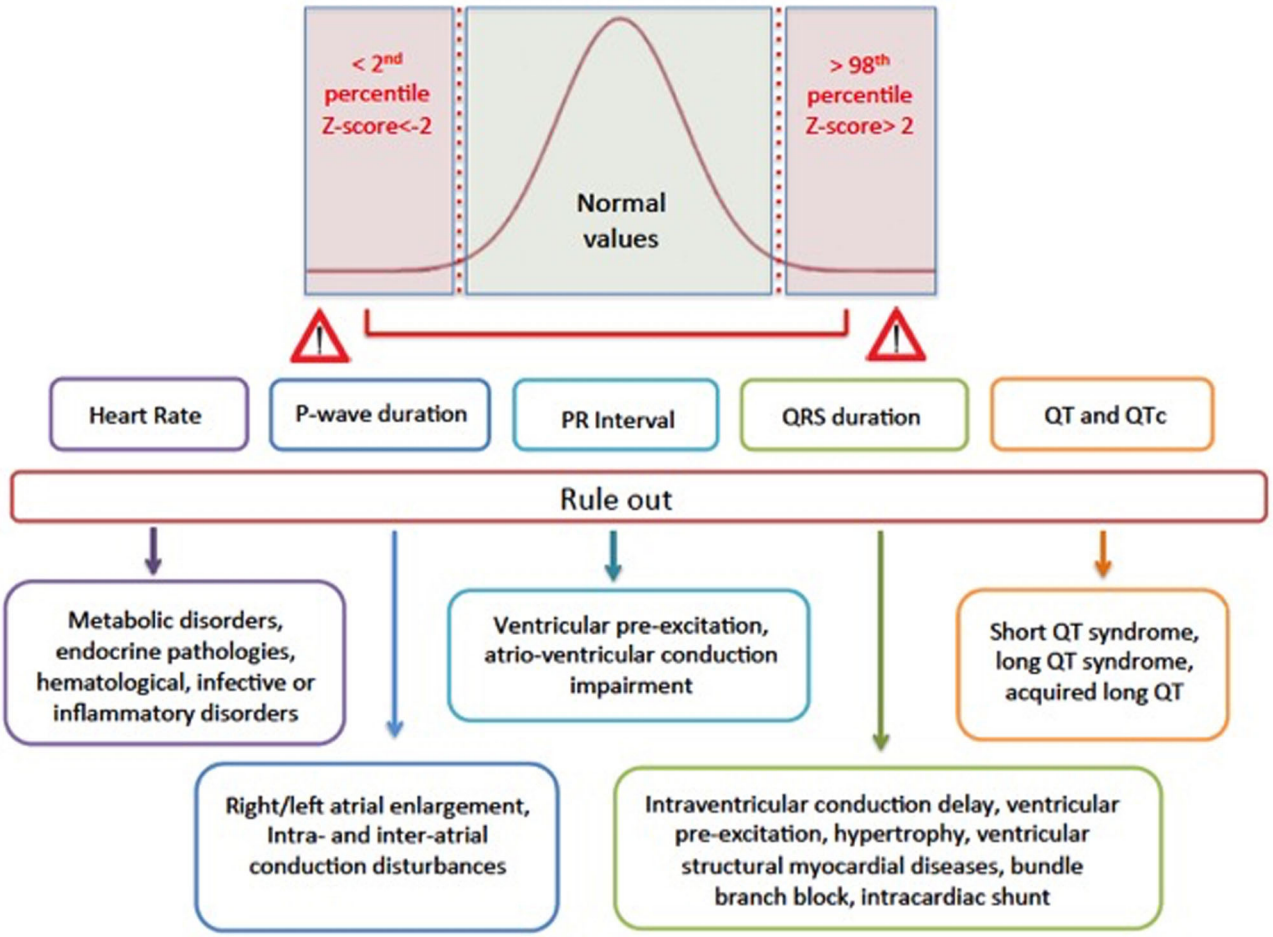

FIGURE 3 | Graphical representation of why reference values are important in clinical practice. Values < 2nd or >98th percentiles correspond to *Z*−scores of <-2 or > 2, respectively, and they may imply the presence of a specific pathology or disease that should be ruled out because that value is outside the normal values, present in the 96% of the study population.

of cardiovascular adaptations to intense and regular training in mixed sports athletes, in which hemodynamic responses and long-term impact on cardiac output and remodeling are balanced between dynamic and static components (24). Recently, several articles have been published on the electrocardiographic characteristics of adolescent athletes (25–27), but none have evaluated the evolving difference between 2-year age classes or provided specific reference values in adolescent athletes with a normal ECG and a normal echocardiographic evaluation. We believe that our electrocardiographic nomograms could be extremely useful in defining normal reference limits and z-scores among different groups of age to aid in differentiating training adaptations from normal growth and maturation, which may be of particular importance when an inherited disease is suspected (**Figure 3**). Sudden cardiac death usually debuts in the young, especially in adolescents affected by inherited arrhythmic diseases and cardiomyopathy. Consequently, improved screening techniques for detecting are strongly required in the clinical arena (28). Recently a large, multicenter study in childhood hypertrophic cardiomyopathy demonstrated that ECG abnormalities were common and varied, but none of them, either in isolation or in the ECG risk score, were associated with the 5-year sudden cardiac death risk (29). Potentially, other individual ECG parameters may improve the current risk prediction models. Bratincsák et al. (14) developed normative standards for 102 ECG variables in the young utilizing z-scores and proposed that expressing ECG variables by *z*-scores will lend to an objective and reproducible evaluation and more confident establishment of ECG-disease correlations. Establishing normative standards and corresponding *z*-scores will be the first step forward a standardized and unbiased approach of assessing ECG variables regardless of age, heading to their use also in sports cardiology. We may speculate that using these reference values and *z*-scores may help to better define the degree of physiological adaptations found in an athlete to support the diagnosis of training-related changes. Referring to both electrocardiographic and echocardiographic nomograms may further enhance the accuracy of PPS in identifying those individuals who fall into a gray zone between the physiological remodeling of the athlete's heart vs. the pathological onset of

inherited cardiomyopathy or channelopathy. Appropriate use of second-level investigation such as MRI as discrepancies relative to the reference electrocardiographic and echocardiographic values arise may successfully rule out or identify an underlying pathology.

Limitations

We must address some study limitations for all retrospective studies. Because of the homogenous study population with respect to sex, ethnicity, and sport practiced (soccer), our results should not be generalized to female adolescent athletes, non-Caucasian athletes, or athletes practicing other sports. Soccer is a mix of high dynamic and moderate static demand; therefore, our results cannot be reliably applied to athletes from power, endurance, or skill disciplines, in particular, our findings may be even more pronounced in endurance athletes. Nevertheless, we are convinced that the novelty of our data can provide an overall idea of the evolution of ECG characteristics among age groups in athletes in general. The effects of training could not be evaluated in a group of matched controls but only with the data available in the literature. The stage of puberty was not accurately assessed using standardized tools, such as the Tanner scale, and we cover a heterogeneous age range from 7 to 18 years. This research should be seen as a preliminary study and the hypothetical additional value of using z-scores in ECG reports needs to be tested in a larger series of adolescents with normal and pathological findings. Such an investigation is currently underway at our centers and the results will be the object of future publications.

CONCLUSION

This study has shed light on the physiological adaptations to exercise among different classes of age in a large cohort of healthy junior athletes. Referring to the specific age-related normal values may provide a more specific reading of the adolescent athlete's ECG. We are confident that this data may be helpful in providing a standardized and unbiased analysis of the ECG to better help discriminate between growth- and training-induced changes and pathological remodeling.

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 Sapienza University of Rome. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

EC, GB-Z, FM, and LS contributed to the conception or design of the study. AN, FS, EG, FQ, CF, AP, and EC contributed to data acquisition, analysis, and interpretation. EC, GB-Z, RR, and DS performed statistical analyses. EC drafted the manuscript. LS, AN, FM, EG, FQ, CF, RA, AS, GF, LC, FP, MP, AP, RR, DS, GB-Z, and EC critically revised the manuscript for key intellectual content. All the authors gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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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.2021.784170/full#supplementary-material

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REVIEW
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Cardiopulmonary Resuscitation and Defibrillator Use in Sports

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Sudden cardiac arrest (SCA) in young athletes is rare, with an estimated incidence ranging from 0.1 to 2 per 100,000 per athlete year. The creation of SCA registries can help provide accurate data regarding incidence, treatment, and outcomes and help implement primary or secondary prevention strategies that could change the course of these events. Early cardiopulmonary resuscitation (CPR) and defibrillation are the most important determinants of survival and neurological prognosis in individuals who suffer from SCA. Compared with the general population, individuals with clinically silent cardiac disease who practice regular physical exercise are at increased risk of SCA events. While the implementation of national preparticipation screening has been largely debated, with no current consensus, the number of athletes who will be diagnosed with cardiac disease and have an indication for implantable defibrillator cardioverter defibrillator (ICD) is unknown. Many victims of SCA do not have a previous cardiac diagnosis. Therefore, the appropriate use and availability of automated external defibrillators (AEDs) in public spaces is the crucial part of the integrated response to prevent these fatalities both for participating athletes and for spectators. Governments and sports institutions should invest and educate members of the public, security, and healthcare professionals in immediate initiation of CPR and early AED use. Smartphone apps could play an integral part to allow bystanders to alert the emergency services and CPR trained responders and locate and utilize the nearest AED to positively influence the outcomes by strengthening the chain of survival. This review aims to summarize the available evidence on sudden cardiac death prevention among young athletes and to provide some guidance on strategies that can be implemented by governments and on the novel tools that can help save these lives.

Keywords: cardiopulmonary resuscitation, automated electrical defibrillator, implantable cardioverter defibrillator, sudden cardiac death, cardiac arrest, out of hospital cardiac arrest, athlete, sports cardiology

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INTRODUCTION

The annual incidence of out-of-hospital cardiac arrest (OHCA) in the general population is estimated between 67 and 170 per 100,000 inhabitants in Europe (1) and 57 per 100,000 inhabitants in the United States (US) (2), widely varying between and within countries. In addition, the causes of sudden cardiac death (SCD) might also differ among different countries, possibly because of differences in population genetics and myocardial substrate and the systematic preparticipation evaluation of athletes (3). Cardiopulmonary resuscitation (CPR) initiated by bystanders is reported to be performed in about half of cases, with significant differences between countries (4).

Sudden cardiac arrest (SCA) or SCD in young athletes is even rarer, although it is often an event of great public attention. In 2014, *Harmon* and colleagues reviewed the incidence of SCD in athletes and concluded that studies with higher methodological quality consistently yielded incidence rates in the range of 1:40,000–1:80,000, and assumed an overall incidence of 1:50,000 in young athletes is a reasonable estimate (5). In **Table 1** and **Figure 1**, we summarize data from studies published from 2006 to 2021, with incidences of SCA ranging from 0.1 to 2 per 100,000 athlete-year (6–24). Most of these studies have shown that the majority of SCA events occur during exercise, despite possible selection bias because of the study sources including databases of more commonly sports organization and media report reviews.

The wide variation in incidences reported might reflect the underreporting of SCA events and the lack of appropriate national sports registries (25) that might allow a more precise epidemiological description of the problem.

This document aims at summarizing the available evidence on SCD prevention among young athletes, and to provide some guidance on strategies that can be implemented by governments and on the novel tools that can help save these lives.

INCREASING TRAINING AND DELIVERY OF BYSTANDER CPR

Governments and sports institutions could invest in educating members of the public, security personnel, and healthcare professionals in the identification of SCA, calling for appropriate help, early initiation of effective CPR, and automated external defibrillator (AED) use, which can be highly lifesaving (26, 27). People are generally unaware of how to deal with SCA events, although teaching CPR maneuvers is valuable and easy, as evidenced that even training as short as 2 h can lead to a major increase in the willingness to start CPR and AED use (28). In addition, after the Australian government provided basic life support (BLS) and AED use training, a 6-month follow-up survey demonstrated highly accurate answers to clinical scenarios involving AED use, although only half of the respondents reported having access to an AED (29).

Training and raising awareness among the population to CPR and eventually AED use should be provided as part of the school civic education, as it is an important issue of public health. This has already been recognized by governments of many countries across Europe and in the US that have legal requirements for CPR education in schools (30, 31). However, it is not known whether legislation has translated into implementation, as demonstrated by a Danish group that performed a nationwide study and demonstrated that school CPR training has not been successfully implemented following 8 years of mandating legislation (32). Over 10 years, temporal trends in volunteer CPR delivery and long-term survival were studied in Denmark, after several national initiatives were implemented to strengthen bystander resuscitation attempts (33). These initiatives included mandatory CPR training in elementary schools, as well as when acquiring a driving license, combined with an increase in voluntary first-aid training (33). An increase in bystander CPR was verified, and it was significantly associated with a concomitant increase in survival following OHCA (33). In 2015, the WHO endorsed the European Resuscitation Council initiative "Kids save lives." This initiative is meant to deal with the gap in the education of CPR, starting with training children from the age of 12 years, for 2-h every year, as a part of educational project of the schools (30). However, in 2018, *Semeraro* et al. found that although education of children in resuscitation is mandatory by law in schools in six countries in Europe and it is a recommendation in another 24 countries, full implementation has not yet been achieved in the majority of them (34). In the US, the effectiveness of school-based AED programs was also studied and it was high, with an AED application in 85% of SCA victims and 85% survival to hospital discharge among students after an event (35).

EFFECTIVENESS OF BYSTANDER DEFIBRILLATION

Efficacy of CPR and AED Use

Sudden cardiac arrest may be caused by asystole, complete heart block with ventricular standstill, electromechanical dissociation/pulseless electrical activity (PEA), pulseless ventricular tachycardia (VT), or ventricular fibrillation (VF). While patients who present with asystole or pulseless electrical activity have a poor prognosis despite CPR delivery, those in whom the first documented rhythm is VT or VF can be effectively treated by defibrillation. In a prospective national survey of the national French ambulance service, involving subjects with 10 to 75 years who suffered sports-related SCD, the first reported rhythm was VF or pulseless VT in 47%, asystole in 42%, and PEA in 11% (9). Therefore, a relevant proportion of underlying arrhythmias for sports-related SCA can potentially be reverted by an AED shock (36).

Although primary prevention by screening professional athletes for cardiovascular diseases at risk for SCA is undertaken, combining this with increased CPR training and the availability of AED, will increase the likelihood of survival of individuals with unpredictable SCA (37). The important role of bystander-provided defibrillation in individuals who suffer OHCA is corroborated by several studies. After the implementation of a nationwide CPR and AED use training in school students in Japan, a retrospective study in elementary and middle school students demonstrated that children were more likely to be

TABLE 1 | Incidence of sports-related sudden cardiac arrests.

Reference	N° of cases	Country/ Population	Years	Incidence (athlete-years)	Methods	Context of events	Age range (mean)
Corrado et al. (6)	55	Venetto, Italy	1979–2004	1.9/100,000	Prospective study, period, including clinical pathological review, regional newspaper screening and postmortem examination to ascertain the causes of SD of screened athletic population.	80% during sports activity, 11% immediately afterward	12–35
Maron et al. (7)	1,049	USA	1980–2006	0.6/100,000	Prospective US National Registry of Sudden Death in Athletes	80% during of immediately after physical exertion, 20% unassociated with physical activity	8–39
Holst et al. (8)	15	Danish young population (5.4 million)	2000–2006	1.2/100,000	Nationwide retrospective study, all death certificates reviewed by 2 independent physicians for possible sports-related SCD	33% while running and 33% while playing soccer. 73% occurred in sports arena.	12–35
Marijon et al. (9)	820	France	2005–2010	0.5/100,000	Prospective surveillance of: (1). National ambulance service reporting, (2). Web-based screening of media releases	6% in young (10–35 years-old) competitive athletes	10–75 (40)
Maron et al. (10)	13	Minnesota State High Schools, USA	1986-2011	0.7/100,000	Prospective US National Registry of Sudden Death in Athletes	54% during competition and 46% during practice or training	12-18
Risgaard et al. (11)	44	Danish young population	2007–2009	0.5/100,000	Nationwide retrospective study, all death certificates reviewed by 2 independent physicians for possible sports-related SCD	75% occurred during non-competitive sports activities. 39% while running and 30% while cycling. 68% occurred in public arena.	12–49
Maron et al. (12)	64	College Athletes, USA	2002–2011	1.2/100,000	Prospective US National Registry of Sudden Death in Athletes and the National Collegiate Athletic Association database	9% during competition, 36% during practice, 22% during recreational activity, 33% unassociated to physical activity	17–26
Toresdahl et al. (13)	18	High school students, USA	2009-2011	1.1/100,000	Prospective observational study of 2149 US high schools participating in the National Registry for AED Use in Sports	100% associated with physical activity	High-school years

(Continued)

TABLE 1 | Continued

Reference	N° of cases	Country/ Population	Years	Incidence (athlete-years)	Methods	Context of events	Age range (mean)
Harmon et al. (14)	79	USA	2003–2013	1.9/100,000	Prospective surveillance of: (1). NCAA Resolutions List, (2). Parent Heart Watch databas, (3). NCAA insurance claims	56% during exertion, 22% at rest, 14% during sleep	17–24
Maron et al. (15)	842	USA	1980–2011	0.8/100,000 in males 0.1/100,000 in females	Prospective US National Registry of Sudden Death in Athletes participating in competitive athletics who had an autopsy-confirmed cardiovascular diagnoses	26% during competition, 39% during practice, 17% during recreational activity, 17% unassociated to physical activity	15–24
Harmon et al. (16)	104	Seven states of the USA	2007–2013	1.5/100,000	Parent Heart Watch database, based on prospective systematic searches of media reports and queries	80% during exertion	14–18
Gräni et al. (17)	69	German and French-speaking regions of Switzerland (7.0 million)	1999–2010	0.5/100,000 in recreational sports 0.9/100,000 in competitive sports	Retrospective review all forensic reports	Incidences refer to whether each type of sports were performed within the 24-h preceding the SCD	10–39
Bohm et al. (18)	144	Germany	2012–2014	0.1–0.2/100,000	Prospective surveillance of: (1). Web-based platform to record sports-related SCD and SCA cases in competitive and recreational athletes, (2). Media-monitoring, (3). Cooperation with 15 institutes of forensic medicine	26% survived. 85% during sports activity, 15% up to 1 hour after sports cessation.75% in public sports facilities	10–79 (47)
Landry et al. (19)	74	Specific area of Ontario, Canada (6.6 million)	2009–2014	0.8/100,000	Retrospective study, review of the Rescu Epistry cardiac arrest database to identify all out-of-hospital cardiac arrests that occurred during participation in a sport	74% during non-competitive sports	12–45
Asatryan et al. (20)	52	German-speaking regions of Switzerland (5.6 million)	1999–2010	0.4/100,000 in recreational sports 1.2/100,000 in competitive sports	Retrospective review all forensic reports	Incidences refer to whether each type of sports were performed within the 24-h preceding the SCD	10–39
Dennis et al. (21)	216	New South Wales, Australia	2006–2015	0.8-1.5/100,000	Retrospective study, review of the database of the department of forensic medicine to identify all sudden deaths related to sports	48% during organized sports, 19% during regular sports and 31% leisure sports activity	7–65

(Continued)

TABLE 1 | Continued

Reference	N° of cases	Country/ Population	Years	Incidence (athlete-years)	Methods	Context of events	Age range (mean)
Bohm et al. (22)	349	Germany	May 2012 –April 2018	0.2/100,000	Prospective surveillance of: (1). Web-based platform to record sports-related SCD and SCA cases in competitive and recreational athletes, (2). Media-monitoring, (3). Cooperation with the German Resuscitation Registry, (4). Cooperation with 15 institutes of forensic medicine.	31% survived. 82% during sports activity, 11% within 30 min and 5% between 30 min-1hafter sports cessation.	10–79 (48)
Peterson et al. (23)	331	USA	2014–2018	2/100,000	Prospective surveillance of: (1). Traditional and social media sources, (2). Reportings to National Center for Catastrophic Sports Injury Research and University of Washington Medicine Center for Sports Cardiology, (3). Regular review of student-athlete deaths on NCAA Resolutions List, National Federation of State High School Associations and Parent Heart Watch database	74% during exercise, 4.2% within 1h after exercise, 12.1% at rest, 6.0% during sleep.	11–29 (17)
Sollazzo et al. (24)	98	Italy	2019	0.5/100,000	One year- long Google search was performed using mandatory and non-mandatory keywords	51% during sports practice, 9% immediately afterwards, 14% during sleep, 25% at rest or during day-to-day activities	12% under 18–years-old, 27% between 18 and 35, 61% over 35

AED, automated external defibrillator; NCAA, National Collegiate Athletic Association; SCD, sudden cardiac death; USA, United States of America.

defibrillated by bystanders and had better neurological outcomes and 1-month survival when the cardiac arrest occurred in schools and other public places (38). Similarly, a systematic review of SCA in schools has shown that outcomes are better than when occurring at other locations, probably because of more frequent witnessed collapses and bystander CPR delivery (39). Aside from schools, other public places such as airports, that serve millions of passengers each year, where the risk of occurrence of SCA events is higher, and where short response times that save lives have been evaluated. As an example, in a prospective study in the three Chicago airports, equipped with seventeen AEDs, eighteen ventricular fibrillations occurred throughout years 2 years (40). In four of these cases, defibrillators were neither nearby nor used within 5 min, and the patients died (40). The overall one-year survival rate with a good neurological outcome was 56% (40). AEDs were also proven to be useful and efficacious when used on commercial airplanes, where early response by the prehospital emergency services is usually not possible (41). In a study performed in this setting, the rate of survival to hospital discharge shock after the shock was 40% and there were no inappropriate shocks (41). Finally, in a prospective observational cohort which included 2,500 shockable OHCA observed by the public, the authors found that survival to hospital discharge [adjusted odds ratio (OR) 2.62, 95% CI 2.07–3.31] and favorable functional outcome (adjusted OR 2.73, 95% CI 2.17–3.44) were significantly higher when a bystander rather than emergency

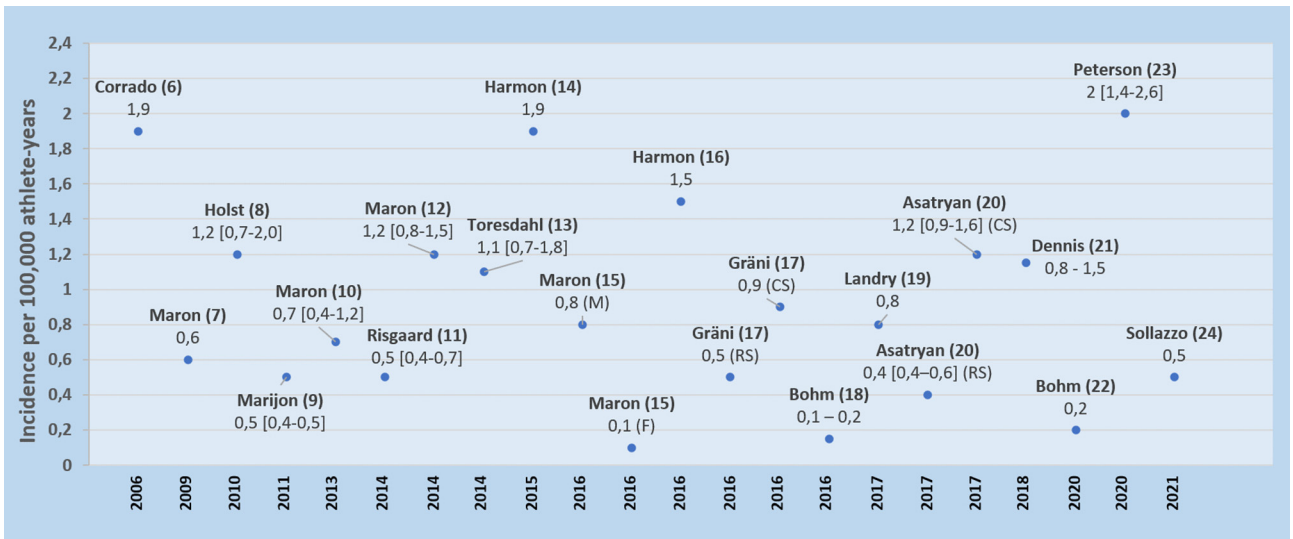

FIGURE 1 | Representation of incidences of sports-related sudden cardiac arrests by ascending date of publication. Mean incidence [95% CI included where available]. CS, competitive sports; F, female; M, male; RS, recreational sports.

medical services (EMSs) professionals provided the initial shock, and the benefit of bystander shock increased progressively as EMS response time became longer (42). Despite the high efficacy of AED use in public places, there is limited AED availability in public spaces in the majority of countries (1) and the scenario is as abysmal in nonprofessional athletic clubs (28, 43, 44). Furthermore, bystander AED use occurs in <2% of OHCAs, and the median arrival time of EMS can extend to 30 min in remote areas, where drone-delivery AED systems might increase the chances of survival (45).

Cost-Effectiveness of AED Use

The cost-effectiveness of training lay volunteers in CPR and AED use and public access to AED has not been well-studied (46), but may be considered a limitation of the strategy. In the Public Access Defibrillation (PAD) trial, 993 community facilities were randomly assigned to a structured emergency response strategy involving lay volunteers trained either in CPR alone or in CPR and the use of AEDs (47). Community facilities included shopping centers, office buildings, recreational/entertainment complexes, hotels, and apartment complexes that were eligible if an equivalent of at least 250 adults of more than 50 years were present for 16 h a day, or if there was a history of one SCA every 2 years (47). The mean number of volunteers trained per facility was 20 (range 1–149). These were laypersons who received training at enrollment and were retrained after 3–6 months and at least once after that (47). The addition of AED use before EMS arrival improved SCA survival to hospital discharge by 2-fold (95% CI 1.07–3.77) (47) and defibrillation by volunteers was associated with an incremental cost of mean $46,700 (95% CI $23,100–$68,600) per quality-adjusted life year, compared with CPR alone, which was stated to be an acceptable difference (48). In the CPR plus AED group, equipment plus training costs $4,453 per cardiac arrest (48). Therefore, in the athlete population, assuming an incidence of 1 per 50,000 athletes-year (5), one should expect to spend 28 times more than in the general population (estimated incidence of SCA in the US: 57 per 100,000 inhabitants—see Introduction part), thus $124,684 per 1 athlete-life saved. Although this may not be cost-effective if only considering the athlete, we should not forget about the risk of SCA in spectators, particularly those older and with cardiovascular risk factors. Furthermore, in a meta-analysis of 1,583 cases (including data from the PAD trial), the number of SCA needed to be treated (NNT) by nonhealthcare professionals trained in CPR plus AED to gain one survival to hospital admission was 17 (49).

Availability of AEDs

Competitive athletes who collapse on exertion can theoretically be rapidly assisted by trained healthcare professionals or club personnel and be defibrillated when an AED is available. SCA was associated with an 8-times higher survival rate compared with nonsports-related SCA, mainly because of better initial management, including bystander CPR and AED use (50). Nevertheless, many studies have demonstrated suboptimal CPR and AED application (28, 43, 44). While professional athletes frequently play in competitions under the supervision of a medical team that is ready to act whenever there is a collapse on the field, amateur athletes are more vulnerable to death after SCA gave the poorer ability of bystanders to assist in this setting. In the Gaelic Athletic Association (GAA), one of the great amateur sporting associations in the world, a survey demonstrated that 60% of the respondents reported that their club owned an AED and only 53% noted to have received formal training to use it (43). Several other studies have demonstrated that the knowledge and willingness to use AED is relatively low among participants in

TABLE 2 | First responder notification and contactless cardiac arrest detection systems using smart devices.

Name of the app/system	Launch year	Country of origin	Countries of implementation	Software	AED registration/ localization
Heartrunner™	2010	Sweden	Sweden, Denmark	Free app available in iOS and Android stores	Yes
GoodSAM™	2013	United Kingdom	United Kingdom, Australia, US, Brazil, Ireland, Finland, Spain	Free app available in iOS, Android and Windows Phones stores	Yes
EHRA First Responder App	2017	Germany	Germany	Free app available in iOS and Android stores	No
HartslagNu CPR call system	2018	Netherlands	Netherlands	Registration site: https://hartslagnu.nl/	Yes

App, application; CPR, cardiopulmonary resuscitation; USA, United States of America.

amateur clubs (28). As an example, among 218 amateur sports clubs in Ireland, 81.3% owned an AED and 12.9% admitted to not maintaining it on a regular basis (44).

Recent Developments in AED Technology

Recently, AED suppliers have worked on devices that are smaller, weight lightweight, and designed to be used by anyone, even children. As an example, HeartHero AED is a miniaturized, portable, and user-friendly AED that guides the user through the CPR process with auditory and visual guides (https://hearthero.com). Although it is not yet FDA approved, it is already available in 33 countries (cost ∼ €595, £495) with the potential to become a useful tool for people at increased risk of SCA that can store the potentially life-saving device at home or carry it with them, ensuring instant access to an AED. In addition, some new AEDs technology allows recording data from the moment it is attached to the patient and makes it transmittable to emergency services and hospitals, thus providing more accurate patient care. Potential limitations for wider use could include the cost for individuals and potential cost-effectiveness given the need for maintenance for appropriate functioning and the fact that those at increased risk of SCA may already have or be eligible for an implantable defibrillator.

SMARTPHONE APP TO LOCATE NEARBY AEDs AND CPR TRAINED LAYPERSONS

In the 2021 European Resuscitation Council guidelines, it is highly encouraged that potential first responders (layperson, police officers, firefighters, and off-duty healthcare professionals) who are near the SCA victim should be notified through an alerting system using a smartphone app or text messaging (**Table 2**) (30). An example of such a system has been reported by Dutch investigators, consisting of a text-message alert system activated by the EMS to dispatch lay rescuers who are close to the victim and locate nearby AEDs (51). This system implementation was associated with a connection of the patient to AED in <6 min in 12.3% and early (≤ 6 min) defibrillation in 7.3% of the cases. In addition, a Swedish group published a blinded randomized controlled trial, where a mobile phone positioning system was used to locate trained responders within 500 meters of patients suffering SCA, at the moment EMS ambulances were dispatched. This system was associated with significantly increased rates of bystander-initiated CPR (62 vs. 48%, $p < 0.001$) (52). In another study from Sweden, when testing a similar system, lay responders arrived at the scene before the EMSs in 26% of the cases, and in 9% it they was able to attach an AED (53). Heartrunner™ (Heartrunner Sweden AB, Sweden) is the Swedish app that connects the EMS with 188,500 citizen responders and 5,000,000 AEDs around Sweden and Denmark (https://heartrunner.com/about-the-system/). When comparing citizen responders arriving before EMS, the early arrival of Heartrunner™-dispatched citizen responders was associated with almost 2-fold increased odds for bystander CPR and more than 3-fold increase in odds for bystander defibrillation (54). Another big player in lay response recruiting and AED localization in the United Kingdom is the GoodSAM™ app (GoodSAM LTD, United Kingdom), which accounts for a database of more than 50,000 AEDs and over 40,000 volunteers registered worldwide (https://www.goodsamapp.org). This app also has a GoodSAM Alerter™ version (GoodSAM LTD, United Kingdom), where laypeople can not only register AEDs, but also press the "Call for Help button" when they witness an emergency or need to get help quickly, and therefore activate both the EMS and the nearest lay volunteer. Finally, many useful apps are yielding multiple exercises, knowledge quizzes, and other information about CPR and cardiac arrest and can be easily downloaded for free by lay people [e.g., Hartstichting™, Netherlands, and the Resuscitation Council UK Lifesavers game app (https://www.resus.org.uk/public-resource/how-we-save-lives/lifesaver-learning/lifesaver)].

ATHLETES WITH POTENTIALLY ARRHYTHMOGENIC DISEASES

Causes of SCA in Athletes

The causes of SCA/D in young athletes vary among different series and countries due in part to the varying methods of referral and ascertainment. While some authors recognized hypertrophic cardiomyopathy (HCM) as the most frequent cause of SCD in athletes from the United States (15, 23) others identified autopsy negative sudden unexplained death (AN-SUD) as the single most

common etiology (14, 55). Arrhythmogenic right ventricular cardiomyopathy has been reported to account for approximately one-fifth of fatal cases in the Veneto Region of Italy (56). Different age groups, ethnicity, and genetics distribution, and also the inclusion of cases of SCA in SCD cohorts may all account for the varying etiologies found in these studies. *Peterson* and collaborators investigated the etiology of SCA/D in US competitive athletes (mean age 16.7 (11–29) years), by reviewing autopsy reports, death certificates, and medical records (23). In this prospective study, the most common cause of SCA/D across all age levels was HCM (21%), followed by idiopathic left ventricular hypertrophy (LVH) (13%), coronary artery anomalies (12%), AN-SUD (10%), arrhythmogenic cardiomyopathy (6%), long QT syndrome (5%) and *commotion cordis* (5%) (23). Similarly, *Maron* and collaborators found that HCM (36%) was the single most common cause of SCD in young athletes (mean age 19 ± 6 years), followed by coronary artery anomalies (19%) and idiopathic LVH (9%) (15). This contrasts with finding from another US study in which AN-SUD was the most frequent etiology of SCD, found in 25% among athletes 17–24 years of age (14). It was followed by coronary artery anomalies (11%), myocarditis (10%), and coronary artery disease (10%), and the incidence of cases of HCM and idiopathic LVH were even lower (8% each) (14). In a United Kingdom registry including athletes aged 29 ± 11 years (range: 7–67 years), AN-SUD (42%) was the most common cause across all age levels, followed by idiopathic LVH or fibrosis (16%) and arrhythmogenic right ventricular cardiomyopathy (13%), HCM and coronary artery anomalies accounting for only 6 and 5%, respectively (55).

Sports Practice and Borderline Indications for an ICD Implantation in Athletes

Implantable cardioverter defibrillator (ICD) indications in athletes should not be different from those in the general population (57, 58). Also, the desire of the athlete to continue sports competition should not represent the primary indication for ICD implantations (58–60), an option that may seem particularly appealing in some patients with cardiomyopathies and channelopathies in whom exertion may increase the risk of arrhythmias. As an example, in patients with asymptomatic long QT syndrome (LQTS) without a prolonged QTc interval (genotype-positive/phenotype-negative), an ICD should only be considered if clinically indicated, namely, if the patient develops symptoms such as palpitations or syncope despite treatment with beta-blockers (57).

In these patients with LQTS, sports participation can be considered, depending on the type and setting of sports, type of genetic mutation, and symptoms (60). Although recent 2020 European guidelines (60) still restrict all the phenotype-positive athletes with LQTS from competitive sports, there is data to support return-to-play approval when patients are optimally treated and have preventive measures and annual follow-up appropriately implemented (61). This study included 494 athletes with LQTS who were given return-to-play approval by a single genetic cardiologist, 16% of whom were symptomatic before diagnosis, and 12% of whom had an ICD. Over a combined follow-up of 2 years, there was no LQTS-sports associated mortality and only 6% had one or more nonlethal LQTS-associated cardiac events.

Recommendations regarding sports participation in patients with channelopathies and arrhythmogenic cardiomyopathies may differ depending on geography. For instance, the 2015 American Heart Association/American College of Cardiology (AHA/ACC) guidelines allowed competitive sports participation in patients with symptomatic or electrocardiographic evident channelopathies (except for swimming in previously symptomatic LQTS1 (*KCNQ1*) mutation carriers), as long as appropriate precautionary measures (e.g., available AED) and disease-specific treatments are in place, and the athlete has been asymptomatic on treatment for at least 3 months (*Class IIb, Level of evidence C*) (62). On the other hand, European groups have been stricter regarding allowance for high-intensity sports practice in patients with the potentially arrhythmogenic disease. This is reflected in a recent EHRA position paper, in which sports participation is only recommended provided lower risk factors are guaranteed (**Table 3**) (63). As an example, patients with arrhythmogenic cardiomyopathy and gene-mutation carriers should avoid competitive sports and high-intensity leisure physical activity as it may worsen ventricular function, trigger life-threatening ventricular arrhythmias and promote disease progression (64, 65). However, in young patients with mild disease, low-to-moderate exercise does not seem to be entirely detrimental and should not be deprived of the health benefits of such activity (65). In addition, in situations where there is an agreement to participate in all competitive sports, these more lenient recommendations are frequently accompanied by an exception including those in whom occurrence of syncope may be associated with serious harm or death (e.g., driving, climbing, and diving) (63).

Efficacy and Safety of ICD in Athletes

Despite safety and efficacy concerns, many patients with ICDs continue regular sports practice, and some participate in competitions. The ICD Sports Safety Registry eased some of these concerns in competitive athletes (66). The investigators enrolled 440 athletes (10–60 years old) who were already engaged in organized competitive sports despite having an ICD. The most frequent diagnoses in this registry were LQTS (20%), HCM (17%), and arrhythmogenic right ventricular cardiomyopathy (13%). A 4-year follow-up study has shown that there were no cases of physical injury or failure to terminate arrhythmia despite participation in vigorous competitive sports (36). *Heidbuchel* et al. published a comparative analysis of these patients to 80 other patients with ICD who were participating in recreational moderate-to-high intensity sports, included in a parallel registry (67). They found similar safety and efficacy outcomes, as well as comparable freedom from 5- and 10-year probable or definite lead malfunction of 97 and 93%, respectively. On the contrary, in addition to the psychological benefits for an athlete, there may also be the potential cardiovascular benefit of continuing sports. A meta-analysis has also shown that in patients with heart failure and an ICD (mean age 54–66 years old, the majority with a

TABLE 3 | Disease-specific recommendation for sports practice in patients with potentially arrhythmogenic conditions.

♥	In patients with frequent **VBPs** or **NSVT**, if no indication of familial or structural underlying disease, all competitive and leisure-time sports activities are allowed (LoE C).
♥	In case of ischaemia with or without **VT**, despite optimal medication and revascularization, only noncompetitive sports are allowed (LoE C).
♥	Athletes with idiopathic, monomorphic **VT**, without haemodynamic compromise during exercise, can resume competitive or leisure-time athletic disciplines* (LoE C).
♥	Athletes with idiopathic, monomorphic **VT** who have undergone successful VT ablation and are without any symptoms or other sign of recurrence during a 3-month follow-up period, can resume full competitive or leisure-time athletic activity (LoE C).
♥	Athletes with idiopathic, monomorphic **VT** who choose to undergo drug treatment for suppression and are without any symptoms during a 3-month follow-up period, including exercise testing or EP study, may resume full competitive or leisure-time athletic activity (LoE C).
♥	It is reasonable to allow all types of sports participation for asymptomatic athletes with an **LQT2** or **LQT3** mutation but QTc < 470/480 ms, and who are on prophylactic beta-blocker therapy (LoE C).
♥	It is reasonable to allow individual sports at low to moderate intensity for asymptomatic athletes with an **LQT1** mutation but QTc <470/480 ms and who are on prophylactic beta-blocker therapy, but team sports and high-intensity sports are discouraged (LoE C).
♥	It is reasonable to allow light to moderate leisure sport activity to asymptomatic **SQTS** patients without family history of SCD (LoE C).
♥	If there is no recurrent event during 3 months in symptomatic **BrS** patients after ICD implantation, leisure or competitive sports may be resumed based on shared decision-making (LoE C).
♥	Asymptomatic **BrS** patients, asymptomatic mutation carriers, and asymptomatic athletes with only an inducible ECG pattern, may participate in all sports that are not associated with an increase in core temperature >39C° (LoE C).
♥	Patients with **CPVT**, under appropriate treatment, if stress-test shows absence of any type of ventricular ectopy/arrhythmia and if the patient is asymptomatic for a minimum of 3 months, low-intensity to moderate leisure-time sports may be considered, including those with an ICD (LoE C).
♥	In individuals diagnosed with possible **AC** based on two minor criteria, sports eligibility should be considered on an individual basis after a comprehensive evaluation of the potential diagnosis (LoE C).
♥	It seems reasonable that athletes with an unequivocal diagnosis of **DCM**, but mildly reduced LV systolic function (EF ≥ 40%) may selectively be allowed to participate in all competitive sports*, provided that specific low risk criteria** are present (LoE C).
♥	It seems reasonable that adult athletes with **HCM** may selectively be allowed to participate in all competitive sports* if: (1) Mild clinical expressions of HCM (2) Low ESC risk score (3) Adult age (LoE C).

EHRA position paper recommendations (63).

♥ *Indicates a "should do this" recommendation, based on at least one randomized trial, or is supported by strong observational evidence that it is beneficial and effective.*

♥ *Indicates general agreement and/or scientific evidence favoring a "may do this" statement, based on randomized trials on a small number of patients or which is not widely applicable.*

AC, arrhythmogenic cardiomyopathy; BrS, Brugada syndrome; CPVT, catecholaminergic polymorphic ventricular tachycardia; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; LoE, level of evidence; LQT, long QT; NSVT, nonsustained ventricular tachycardia; SQTS, short QT syndrome; VBPs, ventricular premature beats; VT, ventricular tachycardia.

**Except those in which syncope may be associated with an enhanced risk for athlete or others (e.g., driving, climbing, diving).*

***(1) Asymptomatic, (2) Without prior history of unexplained syncope, and (3) without frequent/complex ventricular tachyarrhythmias on ambulatory ECG monitoring and exercise testing.*

history of myocardial infarction), exercise training was associated with significant improvement in cardiorespiratory fitness (68).

Although the agreement for sports participation should first be tailored to underlying disease of each patient (**Table 3**) (63), there are also general recommendations for patients who have an ICD. The AHA/ACC stated in 2015 that it is reasonable that patients with an ICD participate in sports with low dynamic and static components (e.g., golf, yoga, bowling) (69), as long as they are free from arrhythmic events requiring device therapy for 3 months (*Class IIa, Level of evidence C*) (58). In addition, participation in sports with higher intensity may be considered, taking into account the likelihood of appropriate or inappropriate shocks and device-related trauma (*Class IIb, Level of evidence C*) (58). In the European guidelines, shared decision-making relating to the continuation of intensive or competitive sports participation is recommended, taking into account the underlying disease, the psychological impact of shocks, the potential risk for third parties, and the fact that intensive sport will trigger more appropriate and inappropriate shocks (*Class IIa, Level of evidence C*) (63, 70). Empowerment of athletes with disorders with potential arrhythmic risk might have advantages such as allowing a more transparent and doctor–patient relationship, avoiding "doctor shopping" and acquiring more knowledge in "gray zone areas" (i.e., exercise in recipients of ICD) (71).

Participation in sports that involve collision (e.g., boxing or rugby) is not recommended because of the risk of damaging the device components, risk of hematoma formation, and subsequent pocket infection (70). For other team sports with some degree of physical contact (e.g., football, basketball, and baseball), a protective shield is recommended, although its effectiveness has never been proven (70). In addition, there are country-specific rules, such as in Italy where competitive sports eligibility for recipients of ICD can be granted in the following situations: (1) asymptomatic subjects; (2) no heart disease in which sport is contraindicated; (3) sports at low-moderate intensity; (4) sports without traumatic risk or with intrinsic risk; (5) sports in which the arm ipsilateral to the device is not repeatedly used; (6) at least 3 months after the last device intervention (72).

Type and Implantation Technique of ICDs in Athletes

The choice of the type of ICD should primarily be based on the underlying disease and potential for arrhythmia. In general, a subcutaneous ICD should be considered in patients who pass screening test (i.e., large enough QRS and small T-waves) and have an indication for ICD when pacing therapy for bradycardia and cardiac resynchronization is not needed, or in whom sustained monomorphic ventricular tachycardia requiring antitachycardia pacing is not anticipated (*Class IIa, Level of Evidence C*) (57). There is no specific evidence supporting either transvenous or subcutaneous ICDs in athletes. In a propensity-matched case-control study of patients aged 35–40 years, the majority (60%) having a diagnosis of HCM and a mean ejection fraction of 58%, subcutaneous ICD was associated with a 70% relative risk reduction of device-related complications

and inappropriate shocks, mainly because of higher rates of lead failures in the transvenous group (73). Despite a lower risk of complications at a mean of 31 months follow-up, subcutaneous ICDs were more expensive, even when accounting for the lower complication-related costs (73). Further comparisons of the safety and efficiency of both systems must be derived from other studies of populations (74, 75), such as the one studied by *Knops* et al. in the only randomized conrolled trial (RCT) published on this subject so far (the PRAETORIAN trial) (76). These were patients with a median age of 63 years, 69% with ischemic cardiomyopathy, and a median left ventricle ejection fraction of 30%, who indicated ICD but no indication for pacing (76). At a median follow-up of 49 months, subcutaneous ICD was noninferior to the transvenous ICD in terms of inappropriate shocks and device-related complications, as fewer lead-related complications were counterbalanced by more frequent pocket hematomas with the subcutaneous ICD (76). A meta-analysis of case–control studies derived similar results, and the reasons for inappropriate shocks differed between both groups: in the subcutaneous ICD, they were primarily due to oversensing (T-wave or noise), whereas in the transvenous ICD they were mostly due to supraventricular tachycardias (77). One can therefore argue that in athletes who do not need an antibradycardic device, a subcutaneous ICD should be preferred. Finally, the *ATLAS S-ICD* trial is an ongoing RCT (NCT02881255, estimated completion date—February 2022) that aims to study the benefit and risks of *Avoiding Transvenous Leads in Appropriate Subjects* who have either inherited arrhythmia syndrome, prior device removal for infection, need for hemodialysis, prior heart valve surgery or chronic obstructive pulmonary disease (78).

Some technical aspects should be considered during the implantation of an ICD in an athlete: namely (1) right-side approach in the case of left arm dominance; (2) submuscular placement of generator; and (3) axillary or cephalic venous access to prevent a subclavian crush (63, 70). In addition, device programming should contemplate adequate rate response pacing, higher detection zones, longer arrhythmia detection intervals, and proactive exclusion of myopotentials interference to prevent inappropriate shocks (63, 70). In a subanalysis of the ICD Sports Registry, detection rates > 200 bpm and detection intervals longer than nominal were associated with decreased risk of total and inappropriate shocks during competition or practice, and higher shock-free survival, respectively (79). To avoid inappropriate shocks during sports activity, a Holter ECG monitoring and exercise testing can be performed to evaluate maximal heart rate during effort and set a threshold for shock delivery at least 20 bpm above the maximal sinus rate observed (72). Finally, treating physicians should have a lower threshold for referring patients/athletes with ICD for ablation of atrial and ventricular arrhythmias that may be the cause of appropriate and inappropriate therapies (63).

CONCLUSION

Sudden cardiac arrest in young athletes is a rare event, although accurate registries are needed to allow more accurate recording of SCA events to facilitate appropriate public health interventions. While some athletes with arrhythmic conditions may be allowed to continue sports practice, particularly in absence of structural heart disease or a channelopathy, some others should be disqualified from sports competition. In those who receive an ICD, special device and implantation choices may apply, and shared decision-making is recommended, taking into account the underlying disease, the psychological impact of shocks, and the type of sports. Nevertheless, athletes with ICDs may be excluded from competitions, depending upon country-specific and competition rules.

Cardiopulmonary resuscitation maneuvers are effective in preventing SCD and are responsible for an 8-times higher survival rates in sports-related SCA, compared with SCA that are not sports related. Initiatives to increase bystander delivery of CPR should be promoted by sports institutions and public health institutions, such as coordinated CPR training starting from school years, as part of the "Kids Save Lives" campaign. Although the distribution of AED in all sports clubs/venues might not be cost effective, further research and modeling into more cost-effective strategies are required but could include a quick and effective app-based mapping and location too to identify the nearest public access AED might help to save lives if an athlete or spectator collapses and requires resuscitation.

AUTHOR CONTRIBUTIONS

MK, FR, RP, CC, and MC conceived the idea for the work. MC and MK drafted the manuscript. RP, FR, CC, FD'A, and AC reviewed the manuscript and provided critical edits. All the authors approved the final manuscript and agreed to be accountable for the content of this study.

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CASE REPORT
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Exertional Dyspnea as the Main Symptom in an Adolescent Athlete With Coronary Artery Anomaly – A Case Report

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Coronary artery anomalies (CAA) are associated with sudden cardiac death (SCD) and the majority of those events occur during exercise. Depending on the anatomic features and severity, CAA usually provoke clinical symptoms of coronary ischemia, mainly syncope and (exertional) chest pain. Here we present a case of a female adolescent athlete with a high-risk CAA variant and an unusual clinical presentation, which delayed diagnosis 2 years after first symptoms were reported. After successful surgical management of the anomalous artery, the patient was determined eligible for competitive sports with unremarkable follow-up examinations.

Keywords: echocardiography, exercise testing, unroofing, arrhythmias, syncope, pre-participation examination, competitive sports

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INTRODUCTION

Coronary artery anomalies (CAA) are congenital disorders defined as an abnormal origin or course of any or the three main epicardial coronary arteries and is estimated to affect 0.2–5.8% of the population, based on criteria and the diagnostic method used (1). CAA are associated with sudden cardiac death (SCD) and the majority of those events occur during exercise (2). In a recent prospective surveillance investigating the etiology and incidence of SCD in US competitive middle school, high school, and college athletes, CAA were responsible for 12.0% of all events. Notably, CAA were the most common cause of SCD in middle school athletes (28%) but represented only 12% of cases in high school athletes and 3% of cases in college and professional athletes (3). Here we present a case of an adolescent athlete with a high-risk CAA variant and an unusual clinical presentation.

CASE DESCRIPTION

A 16-year old female gymnast (height: 150 cm; body mass: 42 kg) was referred to our institute due to progressive exertional dyspnea and exercise intolerance during the previous 2 years without established diagnosis. Medical history revealed an exercise-related syncope 2 weeks prior to referral. Her family history was unremarkable. Resting and exercise ECGs performed 2 years prior to the current examinations were without significant abnormalities. Current resting ECG demonstrated marginal (1 mm) horizontal ST-segment depression in leads II, III,

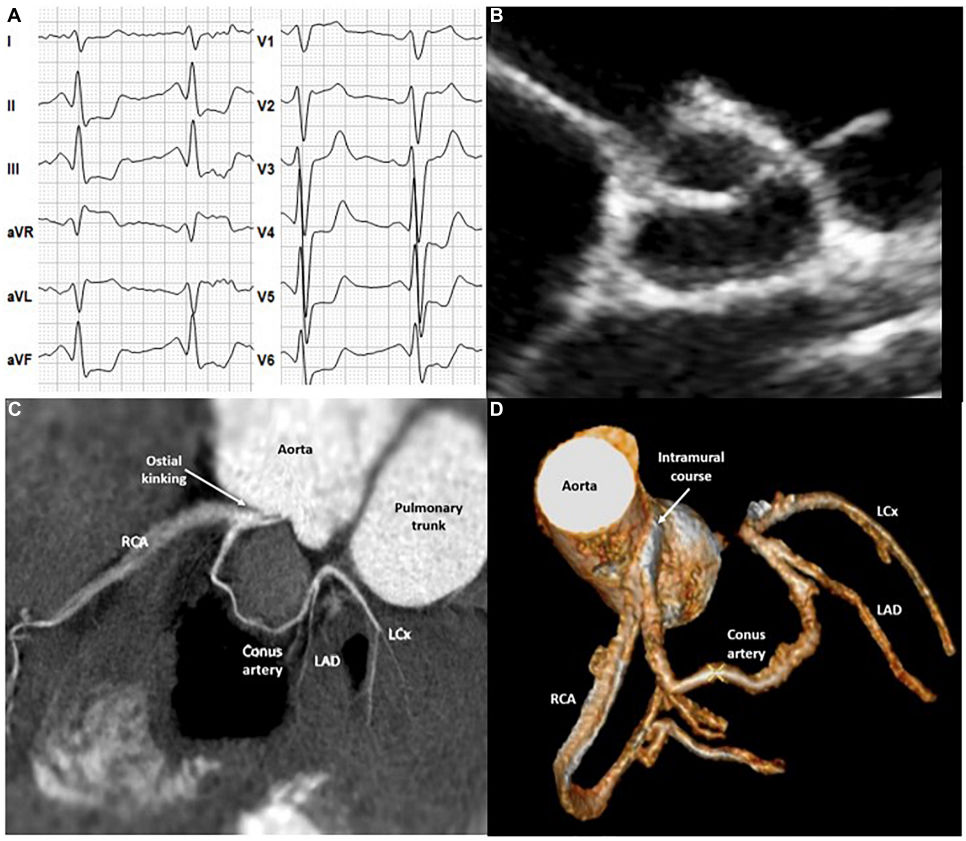

FIGURE 1 | (A) Exercise electrocardiogram. **(B)** Transthoracic echocardiography. **(C,D)** Coronary computed tomography angiography. LCx, Left circumflex artery; LAD, Left anterior descending artery; RCA, Right coronary artery.

and aVF. Exercise testing revealed reduced maximal exercise capacity (105 W; 2.5 W/kg), inadequate chronotropic response and significant (5 mm) horizontal ST-segment depression in leads II, III, aVF, and V4-V6 (**Figure 1A**). Upon transthoracic echocardiography (TTE), no coronary artery ostia could be displayed at the level of the aortic valve (**Figure 1B**). Coronary computed tomographic angiography (CTA) demonstrated an atresia of the left main coronary artery, a single ostium with high takeoff at the ascending aorta above the left sinus of Valsalva with a stenosis due to ostial kinking (**Figure 1C**: CTA) and an intramural course within the aortic wall (**Figure 1D**: 3D CTA reconstruction). A thin conus artery branched off two cm after the common trunk and a left anterior descending and a thin circumflex artery from the conus artery whereas a large right coronary artery could be displayed until the periphery (**Figure 1D**: 3D CTA reconstruction). The patient was managed surgically with unroofing of the intramural segment of the anomalous artery, that is, an incision of the length of the intramural portion and a formation of a neo-orifice (4). Six months after surgery the patient was free of symptoms and exercise testing revealed improved maximal exercise capacity [176 W; 4.1 W/kg)], regular chronotropic response and complete resolution of previous ST-segment depression, so that the patient was determined eligible for competitive sports. Twenty months after surgery exercise capacity further increased to 214 W (4.5 W/kg) without clinical or electrocardiographic signs of myocardial ischemia.

DISCUSSION

Cardiovascular disease is the leading cause of sudden death, also in adolescent athletes (5). Since it is generally assumed that athletes are in great health, as in our case, symptoms commonly do not receive appropriate responses and consequently diagnosis of underlying cardiac disease is often delayed. CAA is the second most common cause of SCD in young adolescent athletes (3) and also present a risk factor for SCD in a non-athletic population (6).

Depending on the anatomic features and severity, CAA usually provoke clinical symptoms of coronary ischemia secondary due to ostial kinking and/or an intramural course of the anomalous vessel and/or compression of the anomalous vessel between the aorta and the pulmonary artery (i.e., interarterial course) (7). In a review of registries of young competitive athletes with autopsy proven CAA as the sole cause of SCD and available clinical data before SCD occurred, syncope and exertional chest pain were the most common symptoms (2). This is in line with another registry where common symptoms included syncope, (exertional) chest pain, and resuscitated SCD. However, most of these patients hat no symptoms and the

diagnosis was established within the diagnostic work-up of an incidental heart murmur (8).

Furthermore, neither routine resting 12-lead- nor exercise electrocardiograms (ECG) yield high diagnostic value, especially in young adolescents (2). This is mirrored in our case, since the patient had unremarkable resting- and exercise ECGs when she first reported symptoms but demonstrated significant abnormalities after 2 years when the final diagnosis was established. Current guidelines on the management of adults with congenital heart disease suggest the use of a stress test either when CAA are an incidental finding or when their clinical significance cannot be completely assessed from anatomic studies (9). Notably, no standardized stress protocols have been proposed so far to stratify CAA-induced ischemia but exercise ECG is often the first test performed considering its cost-effectiveness and wide availability (10). This case also highlights the value of TTE for the prevention of exercise-related SCD, even in case of an asymptomatic athlete with unremarkable resting- and exercise ECG. In Europe, 65% of physicians involved in pre-participation screening of athletes use TTE as part of their standard protocol, even in the setting of a normal clinical evaluation and resting ECG (11). Of note, in a study with short (5 min) TTE protocol tailored for pre-participation screening of athletes, the origin of the left coronary artery was identified in 99% and the origin of the right coronary artery in 96% of the cases (12). Thus, displaying the ostia of the coronaries should be part of the standard TTE protocol not only when screening athletes but is obligatory whenever syncope or exertional symptoms including dyspnea are reported. In the present case, the orifices of the coronary arteries could not be visualized at the sinus of aorta upon TTE due to a high takeoff of the single coronary artery from the ascending aorta. Thus, TTE was non-diagnostic or inconclusive in this case, prompting further imaging. CTA is currently considered the gold standard for establishing the diagnosis and assessing the risk for SCD, especially in case of persisting symptoms but other investigations are inconclusive. CTA provides a more detailed assessment of coronary artery anatomy with cardiac magnetic resonance being an alternative. Both examinations yield very high negative predictive value and thus may rule out CAA, but are also relevant for considering differential diagnosis, such as atherosclerotic obstructive coronary artery disease and myocardial bridging. Of note, myocardial bridging present an intramural tract as seen in this case, but has normal coronary artery origin. Considering the widespread availability of CTAs, coronary catheter-based angiography is rarely used in the diagnostic work-up in adolescents with ischemia-like symptoms due to its invasive nature. Another differential diagnosis to consider are coronary artery spasm, where invasive coronary angiography may be considered to establish the diagnosis by intracoronary acetylcholine-testing. However, in intracoronary spasms thoracic pain usually presents at rest or during ordinary activity and are usually found in patients with underlying atherosclerotic coronary arteries (13).

The prognostic consequences and subsequently management of CAA are extremely variable, and each therapeutic choice should be tailored to the patient's characteristics and the choice of surgical technique depends mostly on the origin of the anomalous vessel and the extent of the intramural tract (4). Anomalous aortic origin of a coronary artery is frequently characterized by a stenosis due to ostial kinking and an intramural course within the aortic wall, which can be safely repaired by unroofing the intramural segment, as performed in this study (4, 9).

Eligibility for sport competition participation needs to take coronary anatomy and the presence of inducible ischemia into account. High risk anatomy as indicated by orifice >1 cm above the sinotubular junction, stenosis due to ostial kinking, and the intramural course as seen in this case are established exercise-related SCD risk factors, since vigorous systolic expansion of the aorta during exercise may lead to further coronary artery kinking and occlusion. Thus, signs of ischemia within exercise stress testing preclude participation in most competitive sports with a moderate and high cardiovascular demand (14). In asymptomatic individuals with an anomalous coronary artery that does not course between the large vessels or does not have a ostial kinking with reduced lumen or intramural course, participation in competitive sports may be considered after adequate counseling on the risks provided that there is an absence of inducible ischemia (14). In case of successful surgical repair of CAA, return to all sports may be considered 3 months after surgery in asymptomatic athletes in the absence of inducible myocardial ischemia or complex cardiac arrhythmias during maximal exercise testing (14). Cardiopulmonary exercise testing enables readmitting a patient to exercise practice following surgical repair based on individual functional capacity.

In the present case, 6 months after surgery the patient was free of symptoms and exercise testing revealed complete resolution of previous ST-segment depression, so that the patient was determined eligible for competitive sports with improvement of exercise capacity from 105 Watt (2.5 W/kg) to 214 W (4.5 W/kg) without clinical or electrocardiographic signs of myocardial ischemia 20 months after surgery.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patient provided written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MS wrote the first draft of the manuscript. KH contributed to the radiologic discussion of the manuscript and provided CT images for the manuscript. PC and JN contributed to the (differential) diagnostic discussion of the manuscript. All authors contributed to the article and approved the submitted version.

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Association of Light-Intensity Physical Activity With Mortality in the Older Population: A Nationwide Cohort Study

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Background: There is a paucity of information about mortality related to light-intensity physical activity (LPA) in the older population. We examine the associations between physical activity and mortality, focusing on the effect of light-intensity physical activity and the dose-response relationship between physical activity and mortality.

Methods: We analyzed a total of 58,537 participants aged ≥ 65 years (mean age, 73.9 ± 5.8 years; male, 36.0%) in the Korean National Health Insurance Service database between 2009 and 2012. The Date of the end of follow-up was December 31, 2013. Individuals were divided into four categories according to physical activity intensity: totally sedentary (43.3%), LPA only (35.8%), LPA and moderate- to vigorous-intensity physical activity (MVPA) (16.3%), MVPA only (4.5%). Physical activity was quantified using standardized self-reported questionnaires which composed of the duration and frequency of physical activity.

Results: During a mean follow-up of 39.6 ± 14.0 months, 5,651 (9.7%) deaths occurred. Compared with totally sedentary individuals, those in the LPA only, LPA and MVPA, and MVPA only groups showed 26% [hazard ratio (HR) 0.74, 95% confidence interval (CI) 0.68–0.82], 27% (HR 0.73, 95% CI 0.63–0.84), and 34% (HR 0.66, 95% CI 0.54–0.79) lower all-cause mortality risk, showing an inverse relationship between physical activity intensity and mortality risk. In contrast, the LPA only, LPA and MVPA, and MVPA only groups represented a stronger inverse association with CV mortality (LPA: HR 0.76, 95% CI 0.62–0.92; LPA with MVPA: HR 0.74, 95% CI 0.55–0.999; MVPA, HR 0.57, 95% CI 0.37–0.87). Among participants performing LPA alone, participants performing less than the recommended dose of physical activity had lower

all-cause mortality than those with sedentary activity (1–249 MET-min/week: HR 0.74, 95% CI 0.67–0.82, 250–499 MET-min/week: HR 0.65, 95% CI 0.59–0.72).

Conclusion: Physical activity, even low doses of LPA, was associated with reduced mortality risk in the elderly population. This study may motivate sedentary individuals to engage in any physical activity for mortality benefits.

Keywords: sport cardiology, exercise, light-intensity physical activity, elderly, all-cause mortality, cardiovascular mortality

INTRODUCTION

Physical activity is associated with a reduced risk of vascular, non-vascular disease, and mortality (1). Recent physical activity guidelines recommend at least 150–300 min per week of moderate-intensity physical activity (MPA) or 75–150 min per week of vigorous-intensity physical activity (VPA), which is equivalent to 500–999 metabolic equivalent task (MET)-min/week, in elderly (aged ≥ 65 years) (2, 3). Achieving >150 min/week moderate-intensity aerobic exercise is associated with a lower risk of morbidity, mortality, disability, and frailty compared with being sedentary (4, 5). However, most guidelines of physical activity are similar in middle-aged adults and older adults (3). It is estimated that >60% of elderly adults could not achieve 150 min per week of moderate- to vigorous-intensity physical activity (MVPA) (6). They have difficulty engaging in exercise due to their health condition. Also, the insufficiency of knowledge of the association between physical activity and health benefits and lack of physician advice to encourage exercise were barriers to exercise (6). Recently, the benefits of physical activity at doses below the current guideline-recommended level were reported. Wen et al. (7) reported health benefits in individuals who engaged in moderate-intensity physical activity at half the recommended amount. Hupin et al. reported a low dose of MVPA below recommended level reduced mortality by 22% in elderly adults. Mortality was further reduced in those who engaged in a higher dose of physical activity in a dose-dependent manner (8). However, whether light-intensity physical activity (LPA) can reduce mortality in the older population has not been revealed. To investigate this association, we analyzed the association between physical activity and mortality in older adults in a nationwide cohort. We focused on the dose-response relationship between LPA and mortality.

MATERIALS AND METHODS

Study Population

Data were collected from the National Health Insurance Service of Korea (NHIS)-Senior database, which included data on 558,147 individuals recruited by the 10% simple random sampling method from a total of 5.5 million subjects aged ≥ 60 years in the National Health Information Database (9, 10). The NHIS-Senior database covered 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 (4-2021-0850).

From the Korean NHIS-Senior database, 278,003 participants aged ≥ 65 years who had available health check-up data between 2009 and 2012 were enrolled in this study. We excluded those with missing information on physical activity (n = 209,503). Also, those who achieved energy expenditure exceeding the guideline target range (>1,000 MET min/week) (n = 9,963) were excluded to evaluate the dose-response of physical activity below the recommended dose. Finally, a total of 58,537 subjects were included in the study and followed up until December 2013 (**Figure 1**).

Physical Activity Level Assessment

The leisure-time physical activity level was quantified using standardized self-reported questionnaires using a 7-day recall method (11). The survey was composed of three questions that addressed the usual frequency (days per week) of (i) VPA for at least 20 min, (ii) MPA for at least 30 min, and (iii) LPA for at least 30 min. VPA was defined as intense exercise that caused severe shortness of breath, such as running and bicycling at high speed. MPA was defined as exercise that caused mild shortness of breath, such as brisk walking and bicycling at the usual speed. LPA was defined as walking at a slow or leisurely pace.

Ratings of 3.0, 4.0, and 8.0 METs were assigned for LPA, MPA, and VPA, respectively (12). Physical activity-related energy expenditure (MET-min/week) was calculated by summing the product of frequency, intensity, and duration. The total energy expenditure level was stratified into 0, <250, 250–499, and 500–1,000 in an explorative manner. Totally sedentary group was defined as individuals without any leisure-time physical activity. The participants were categorized according to physical activity intensity into LPA only, LPA and MVPA, and MVPA only groups.

Covariates

Sociodemographic variables included age, gender, and economic status. The baseline economic status was determined based on the relative economic levels categorized into 11 levels ranging from group 0 (lowest) to group 10 (highest) according

Abbreviations: ACSM/AHA, American College of Sports Medicine and American Heart Association; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; ICD-10, The International Classification of Disease-10th revision; LPA, light-intensity physical activity; MET, metabolic equivalent task; MPA, moderate-intensity physical activity; MVPA, moderate- to vigorous-intensity physical activity; NHIS, The National Health Insurance Service of Korea; VPA, vigorous-intensity physical activity.

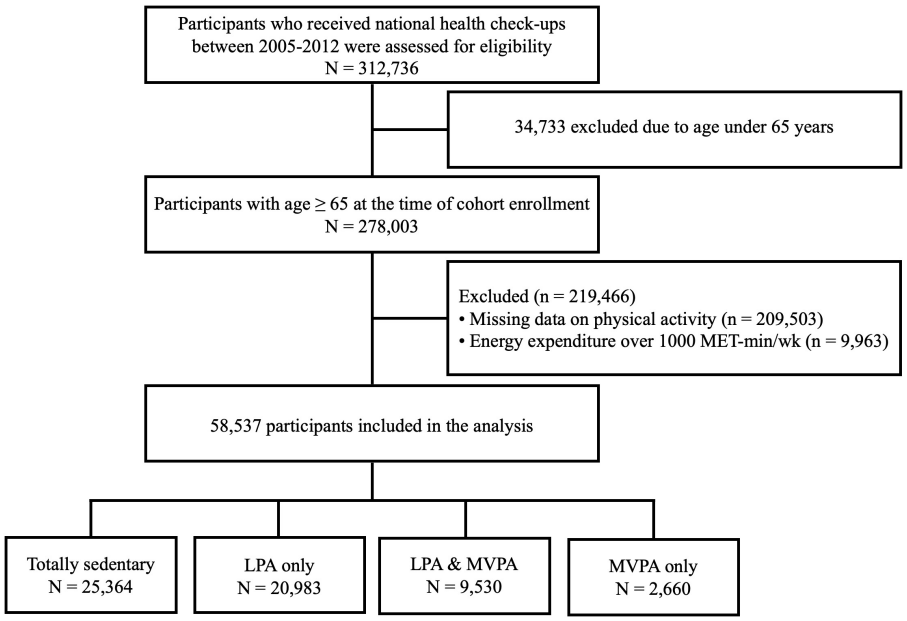

FIGURE 1 | Summary of the statistical analysis design. LPA, light intensity physical activity; MVPA, moderate- to vigorous-intensity physical activity; MET, metabolic equivalent of task.

to their health insurance premiums paid, which directly reflect each individual's income level. Baseline comorbidities were verified using the International Classification of Disease-10 (ICD-10) codes and prescription medication before the index data (**Supplementary Table 1**). To improve diagnostic accuracy, comorbidities were identified when the condition was a discharge diagnosis or was recorded at least twice in an outpatient setting, similar to our previous studies (10, 12–20).

Outcomes

The primary outcome was all-cause mortality. The date of death and ICD-10 codes were verified from the National Population Registry of the Korea National Statistical Office using unique personal identification numbers (10, 12–20). NHIS and the National Statistical Office are national agencies serving all residents in the Republic of Korea, providing a complete event check. We investigated cause-specific mortality based on causes of death because exercise can be associated with cardiovascular (CV)-related and non-CV-related mortality. We defined CV death as death from diseases of the circulatory system (ICD codes I00–I78). The follow-up period was defined as the time from the index date that participants registered in this cohort to death or the end of the study period, whichever came first.

Statistical Analyses

Descriptive statistics were used to analyze baseline characteristics and comorbidities. Categorical variables are expressed as frequencies (percentages). Continuous variables were reported as means ± standard deviations or medians with interquartile ranges. Categorical variables were compared using the Pearson chi-square test, and continuous variables were compared using one-way analysis of variance or the Kruskal-Wallis test, as appropriate.

The incidence rates of outcomes 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 (HRs) and 95% confidence intervals (CIs) for mortality according to physical activity level. Multivariable Cox regression models were constructed with adjustment for age, sex, income level, residential area (urban or non-urban), body mass index, hypertension, diabetes mellitus, dyslipidemia, smoking, alcohol intake, chronic kidney disease, chronic obstructive lung disease, chronic liver disease, malignancy, cardiovascular medications (aspirin, P_2Y_{12} inhibitor, statin, anticoagulant, beta-blocker, angiotensin converting enzyme inhibitor or angiotensin receptor blocker, calcium channel blocker, digoxin, and diuretics) and Charlson comorbidity index. Categorical measures of physical activity intensity and energy expenditure level were treated as an ordered value in Cox regression analysis to evaluate *P* value for linear trend. Restricted cubic spline curves were used to examine the effects of continuous values of physical activity (0 MET-min/week as reference) on death. Restricted cubic splines were fitted with three knots by treating the amount of physical activity as a continuous variable using the "rms" package.

We conducted subgroup analyses for the primary outcome stratified by age, sex, body mass index, and other baseline comorbidities. For sensitivity analysis, we performed separate analyses in those who did not perform any activity exceeding LPA.

TABLE 1 | Baseline characteristics.

	Totally sedentary(*N* = 25,364)	LPA only(*N* = 20,983)	LPA & MVPA(*N* = 9,530)	MVPA only(*N* = 2,660)
Age, mean (SD)	74.9 ± 6.4	73.4 ± 5.3	72.7 ± 5.0	72.1 ± 4.8
Male	8,224 (32.4%)	7,541 (35.9%)	4,012 (42.1%)	1,280 (48.1%)
BMI, mean (SD)	23.5 ± 3.6	23.8 ± 3.4	23.9 ± 3.2	24.1 ± 3.2
Economic status				
Low	8,321 (32.8%)	6,387 (30.4%)	2,814 (29.5%)	746 (28.0%)
Middle	5,721 (22.6%)	4,617 (22.0%)	2,014 (21.1%)	611 (23.0%)
High	11,322 (44.6%)	9,979 (47.6%)	4,702 (49.3%)	1,303 (49.0%)
Systolic blood pressure (mmHg), mean (SD)	131.2 ± 17.5	131.6 ± 17.0	130.9 ± 16.8	131.0 ± 16.4
Diastolic blood pressure (mmHg), mean (SD)	78.3 ± 10.7	78.3 ± 10.4	78.3 ± 10.2	77.9 ± 10.0
Hypertension	15,888 (62.6%)	12,836 (61.2%)	5,716 (60.0%)	1,535 (57.7%)
Diabetes mellitus	5,315 (21.0%)	4,648 (22.2%)	1,969 (20.7%)	580 (21.8%)
Dyslipidemia	12,496 (49.3%)	10,977 (52.3%)	5,020 (52.7%)	1,408 (52.9%)
CKD or ESRD	7,009 (27.7%)	5,036 (24.0%)	2,110 (22.2%)	568 (21.4%)
COPD	3,559 (14.0%)	2,558 (12.2%)	1,120 (11.8%)	285 (10.7%)
Liver disease	7574 (29.9%)	6,455 (30.8%)	2,922 (30.7%)	795 (29.9%)
Any malignancy	4,018 (15.8%)	3,418 (16.3%)	1,550 (16.3%)	454 (17.1%)
Current smoker	2,776 (11.0%)	2,466 (11.8%)	1,170 (12.4%)	325 (12.3%)
Current alcohol drinker	1,877 (7.4%)	1,841 (8.8%)	927 (9.8%)	327 (12.4%)
Charlson comorbidity index, mean (SD)	3.3 ± 2.8	3.2 ± 2.7	3.0 ± 2.6	2.9 ± 2.6
Total physical activity, METs				
0	25,364 (100.0%)	0	0	0
1-500	0	11,980 (57.1%)	3,318 (34.8%)	1,497 (56.3%)
500-1000	0	9,003 (42.9%)	6,212 (65.2%)	1,163 (43.7%)
Depressive mood	1,507 (54.0%)	1,589 (54.0%)	850 (50.9%)	284 (55.3%)
Lower extremity function				
Gait disturbance during TUG†	96 (3.5%)	80 (2.7%)	35 (2.1%)	5 (1.0%)
Time taken in TUG (sec)†, median [Q1, Q3]	9.0 [7.0,10.0]	9.0 [7.0,10.0]	9.0 [7.0,10.0]	8.0 [7.0,10.0]
Cognitive function				
Positive rate in KDSQ‡	649 (23.2%)	669 (22.7%)	367 (21.9%)	116 (22.6%)
KDSQ score‡, median [Q1, Q3]	1.0 [0.0, 3.0]	1.0 [0.0, 3.0]	1.0 [0.0, 3.0]	1.0 [0.0, 3.0]
ADL scale§ , median [Q1, Q3]	6.0 [6.0, 7.0]	6.0 [6.0, 7.0]	6.0 [6.0, 7.0]	6.0 [6.0, 7.0]
Medication				
Aspirin	9,141 (36.0%)	7,572 (36.1%)	3,473 (36.4%)	941 (35.4%)
P_2Y_{12} inhibitor	2,377 (9.4%)	1,833 (8.7%)	754 (7.9%)	221 (8.3%)
Statin	5,956 (23.5%)	5,590 (26.6%)	2,498 (26.2%)	694 (26.1%)
Anticoagulant	380 (1.5%)	345 (1.6%)	118 (1.2%)	40 (1.5%)
ACE inhibitor or ARB	9,184 (36.2%)	7,592 (36.2%)	3,397 (35.6%)	930 (35.0%)
Beta-blocker	7,091 (28.0%)	5,856 (27.9%)	2,603 (27.3%)	669 (25.2%)
Calcium channel blocker				
DHP	10,997 (43.4%)	8,884 (42.3%)	3,877 (40.7%)	1,067 (40.1%)
Non-DHP	1,214 (4.8%)	1,018 (4.9%)	452 (4.7%)	116 (4.4%)
Digoxin	812 (3.2%)	575 (2.7%)	218 (2.3%)	60 (2.3%)
Diuretics	10,299 (40.6%)	8,137 (38.8%)	3,521 (36.9%)	940 (35.3%)

Values are expressed in n (%), mean ± SD (standard deviation), or median [Q1, Q3].

ADL, activities of daily living; BMI, body mass index; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; ESRD, end-stage renal disease; KDSQ, Korean Dementia Screening Questionnaires; LPA, light intensity physical activity; MET, metabolic equivalent of task; MVPA, moderate- to vigorous-intensity physical activity; TUG, timed up and go test.

†*TUG test measures the time that a person takes to rise from a chair, walk 3 m, turn around, walk back to the chair, and sit down. The more time taken indicates the poor physical function and balance.*

‡*KDSQ including five items. Each item on the KDSQ is scored from 0 to 2, with a higher score indicating poorer function and a greater frequency. KDSQ score ≥ 4 indicates positive.*

§ *A measurement of routine activities people do every day without assistance, which include eating, bathing, getting dressed, toileting, mobility, and continence. Higher scores indicate better and independent physical performance.*

TABLE 2 | Incidence and hazard ratio with 95% confidence intervals for all-cause death, cardiovascular (CV) cause death, and non-CV-cause death according to physical activity intensity.

Group	Total Patient, *n*	Event, *n*	Crude incidence per 1,000 Patient-Years	Absolute reduction in event rate (95% CI)	Hazard ratio (95% CI)*	p-Value	p for trend†
All-cause mortality							<0.001
Totally sedentary	25,364	3,316	40.5		1.00 (reference)		
LPA only	20,983	1,572	22.6	17.9 (16.2–19.6)	0.74 (0.68–0.82)	<0.001	
LPA and MVPA	9,530	613	19.0	21.5 (19.4–23.5)	0.73 (0.63–0.84)	<0.001	
MVPA only	2,660	150	16.2	24.2 (21.3–27.1)	0.66 (0.54–0.79)	<0.001	
CV-cause mortality							0.006
Totally sedentary	25,364	880	10.7		1.00 (reference)		
LPA only	20,983	361	5.2	5.6 (4.7–6.4)	0.76 (0.62–0.92)	0.006	
LPA and MVPA	9,530	129	4.0	6.7 (5.8–7.7)	0.74 (0.55–0.999)	0.049	
MVPA only	2,660	27	2.9	7.8 (6.5–9.1)	0.57 (0.37–0.87)	0.009	
Non-CV-cause mortality							<0.001
Totally sedentary	25,364	2,436	29.7		1.00 (reference)		
LPA only	20,983	1,211	17.4	12.3 (10.8–13.9)	0.74 (0.66–0.83)	<0.001	
LPA and MVPA	9,530	484	15.0	14.7 (13.0–16.5)	0.73 (0.62–0.86)	<0.001	
MVPA only	2,660	123	13.3	16.4 (13.8–19.0)	0.68 (0.55–0.84)	<0.001	

CI, confidence interval; LPA, light intensity physical activity; MVPA, moderate- to vigorous-intensity physical activity.
**Adjusted for age, sex, income level, residential area (urban or non-urban), body mass index, hypertension, diabetes mellitus, dyslipidemia, smoking, alcohol intake, chronic kidney disease, chronic obstructive lung disease, liver disease, malignancy, cardiovascular medications (aspirin, P_2Y_{12} inhibitor, statin, anticoagulant, beta-blocker, angiotensin converting enzyme inhibitor or angiotensin receptor blocker, calcium channel blocker, digoxin, diuretics), Charlson comorbidity index and energy expenditure.*
†Categorical measures of physical activity intensity were treated as an ordered value.

All tests were two-tailed, with a p-value of <0.05 considered significant. Statistical analyses were conducted using R programming version 4.1.0 (The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline Characteristics

In total, 58,537 participants (men 36.0%) with a mean age of 73.9 ± 5.8 years were included in the analysis. Baseline characteristics according to physical activity intensity are summarized in **Table 1**. With regard to physical activity intensity, 43.3, 35.8, 16.3, and 4.5% of participants were included in the totally sedentary, LPA only, LPA and MVPA, and MVPA only groups, respectively. Of the total participants, 46,347 (79.2%) did not perform any activity beyond LPA. The distribution of exercise dose according to physical activity intensity is presented in **Supplementary Figure 1**. Participants performing physical activity tended to be younger, male-predominant, less likely to have comorbidities (particularly hypertension, chronic obstructive pulmonary disease (COPD), chronic kidney disease, and osteoporosis), and less affected by gait disturbances during the Timed Up and Go Test than totally sedentary participants. There were no significant differences in Activities of Daily Living scale, which represents the functional status of older adults.

Physical Activity Intensity, All-Cause Mortality, Cardiovascular Mortality, and Non-cardiovascular Mortality

During a mean follow-up of 39.6 ± 14.0 months, 5,651 (9.7%) deaths occurred. The overall incidence of mortality during follow-up was 29.3 per 1,000 person-years. When stratified by physical activity intensity, the incidence was 40.5, 22.6, 19.0, and 16.2 per 1,000 person-years in the totally sedentary, LPA only, LPA and MVPA, and MVPA only groups, respectively (**Table 2**). Compared with the totally sedentary group, the LPA only (HR 0.74, 95% CI 0.68–0.82), LPA and MVPA (HR 0.73, 95% CI 0.63–0.84), and MVPA only groups (HR 0.66, 95% CI 0.54–0.79) were associated with a lower risk of mortality.

The incidence of CV mortality was 10.7, 5.2, 4.0, and 2.9 per 1,000 person-years in the totally sedentary, LPA only, LPA and MVPA, and MVPA only groups, respectively. Compared with the totally sedentary group, the LPA only (HR 0.76, 95% CI 0.62–0.92), LPA and MVPA (HR 0.74, 95% CI 0.55–0.999), and MVPA only groups (HR 0.57, 95% CI 0.37–0.87) were associated with a lower risk of mortality (**Table 2**).

TABLE 3 | Incidence and hazard ratio with 95% confidence intervals for all-cause death, CV cause death, and non-CV-cause death in those who did not perform any activity beyond LPA, according to energy expenditure (MET-min/week).

	Total patient, *n*	Event, *n*	Crude incidence per 1,000 patient-years	Absolute reduction in event rate (95% CI)	Hazard ratio (95% CI)*	p-value	p for trend†
All-cause mortality							<0.001
Totally sedentary	25,364	3,316	40.5		1.00 (reference)		
<250 MET-min/week	4,971	449	26.6	13.9 (11.1–16.7)	0.74 (0.67–0.82)	<0.001	
250–500 MET-min/week	7,009	454	19.6	20.9 (18.6–23.1)	0.65 (0.59–0.72)	<0.001	
500–1,000 MET-min/week	9,003	669	22.6	17.9 (15.7–20.0)	0.70 (0.64–0.76)	<0.001	
CV-cause mortality							<0.001
Totally sedentary	25,364	880	10.7		1.00 (reference)		
<250 MET-min/week	4,971	111	6.6	4.2 (2.8–5.6)	0.71 (0.58–0.86)	0.001	
250–500 MET-min/week	7,009	107	4.6	6.1 (5.0–7.2)	0.61 (0.50–0.75)	<0.001	
500–1,000 MET-min/week	9,003	143	4.8	5.9 (4.8–7.0)	0.60 (0.50–0.72)	<0.001	
Non-CV-cause mortality							<0.001
Totally sedentary	25,364	2,436	29.7		1.00 (reference)		
<250 MET-min/week	4,971	338	20.0	9.7 (7.3–12.2)	0.75 (0.67–0.85)	<0.001	
250–500 MET-min/week	7,009	347	15.0	14.7 (12.8–16.7)	0.67 (0.60–0.75)	<0.001	
500–1,000 MET-min/week	9,003	526	17.8	12.0 (10.1–13.9)	0.73 (0.66–0.80)	<0.001	

CI, confidence interval; LPA, light intensity physical activity; MVPA, moderate- to vigorous-intensity physical activity.
**Adjusted for age, sex, income level, residential area (urban or non-urban), body mass index, hypertension, diabetes mellitus, dyslipidemia, smoking, alcohol intake, chronic kidney disease, chronic obstructive lung disease, liver disease, malignancy, cardiovascular medications (aspirin, P_2Y_{12} inhibitor, statin, anticoagulant, beta-blocker, angiotensin converting enzyme inhibitor or angiotensin receptor blocker, calcium channel blocker, digoxin, diuretics) and Charlson comorbidity index.*
†Categorical measures of total energy expenditure level were treated as an ordered value.

The incidence of non-CV mortality was 29.7, 17.4, 15.0, and 13.3 per 1,000 person-years in the totally sedentary, LPA only, LPA and MVPA, and MVPA only groups, respectively. Compared with the totally sedentary group, the LPA only (HR 0.74, 95% CI 0.66–0.83), LPA and MVPA (HR 0.73, 95% CI 0.62–0.86), and MVPA only groups (HR 0.68, 95% CI 0.55–0.84) were associated with a lower risk of mortality (**Table 2**).

The cumulative incidence of all-cause mortality, CV mortality, and non-CV mortality showed progressively lower trends with increasing physical activity intensity (**Supplementary Figure 2**).

Physical Activity Dose and Mortality

Among the 58,537 participants, 46,347 (79.2%) participants, including 20,983 with LPA, did not perform any activity beyond LPA. In the LPA only group, 4,971 (10.7%), 7,009 (15.1%), and 9,003 (19.4%) participants performed 1–249, 250–499, and 500–1,000 MET-min/week of LPA, respectively. The cumulative incidence of mortality was lower in the group with 250–499 MET-min/week of LPA (**Supplementary Figure 3**). Compared with those in the totally sedentary group, participants with 1–249 MET-min/week of LPA (HR 0.74, 95% CI 0.67–0.82), 250–499 MET-min/week (HR 0.65, 95% CI 0.59–0.72), and 500–1,000 MET-min/week of LPA (HR 0.70, 95% CI 0.64–0.76) showed a lower risk of mortality (**Table 3**). Similar trends were observed in the MVPA group (**Supplementary Figure 4**). Even once a week of LPA was associated with significantly lower risks of all-cause mortality than the totally sedentary group (**Figure 2**).

Non-linear Relationship Between Physical Activity and All-Cause Mortality

Figure 3 shows the relationship between physical activity and all-cause mortality risk according to physical activity intensity using a restricted cubic spline curve. A non-linear relationship between LPA and mortality risk showed a continuous decrease in mortality risk until 360 MET-min/week (120 min/week: HR 0.63, 95% CI 0.57–0.71) and a plateau. The relationship between MVPA and mortality risk showed a continuous decrease in mortality risk until 528 MET-min/week or 132 min/week. For the same exercise duration, MVPA was associated with lower all-cause mortality than LPA.

Subgroup Analysis

The HR for all-cause mortality according to physical activity dose in different subgroups in those who did not perform any activity beyond LPA is presented in **Supplementary Figure 5** and shows a consistent decrease in risk regardless of subgroups except in

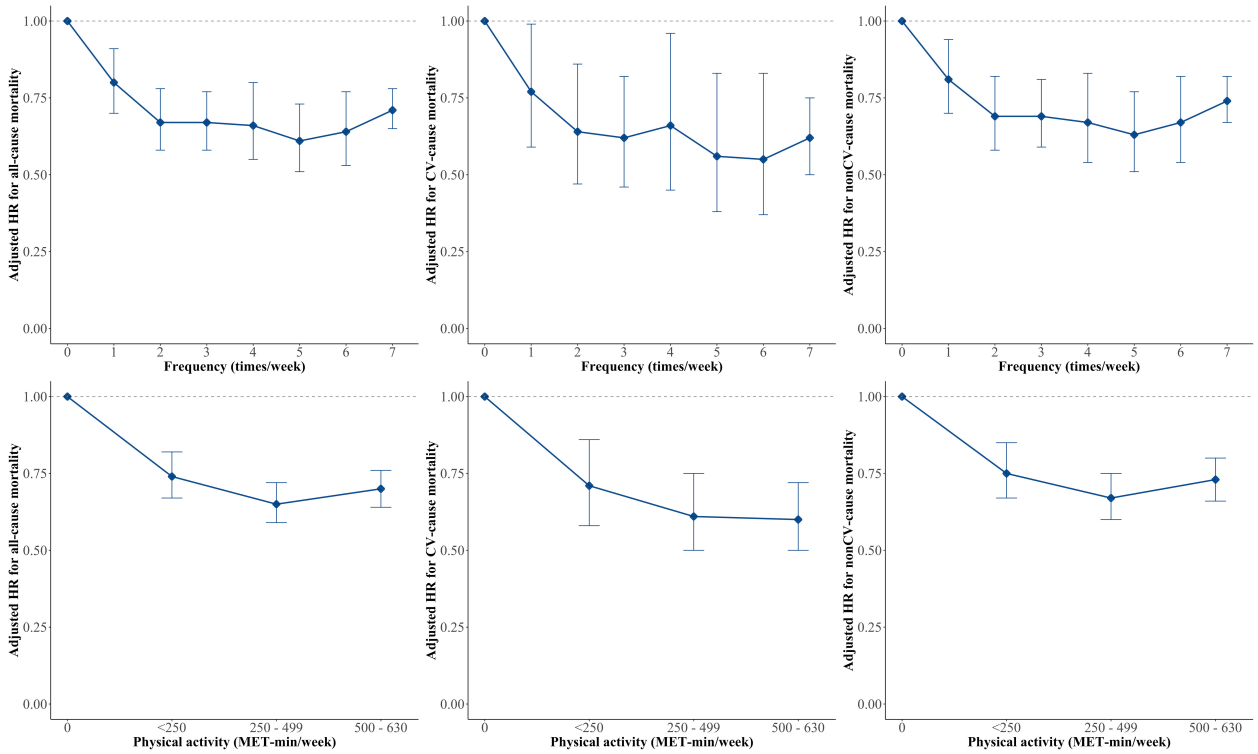

FIGURE 2 | Hazard ratios (HRs) of All-cause, CV, and non-CV-mortality by exercise frequency, and physical activity level in those who did not perform any activity beyond LPA. Multivariable Cox regression models were constructed with adjustment for age, sex, income level, residential area (urban or non-urban), body mass index, hypertension, diabetes mellitus, dyslipidemia, smoking, alcohol intake, chronic kidney disease, chronic obstructive lung disease, liver disease, malignancy, cardiovascular medications (aspirin, P_2Y_{12} inhibitor, statin, anticoagulant, beta-blocker, angiotensin converting enzyme inhibitor or angiotensin receptor blocker, calcium channel blocker, digoxin, diuretics) and Charlson comorbidity index. CV, cardiovascular; MPA, moderate-intensity physical activity; MET, metabolic equivalent of task.

subjects with obesity and COPD. The HR for all-cause mortality according to physical activity intensity in different subgroups in the overall population is presented in **Supplementary Figure 6**.

DISCUSSION

In this study, 46,347 (79.2%) older participants did not perform any activity beyond LPA. Second, compared with those in the totally sedentary group, older adults performing LPA alone had a reduced risk of all-cause mortality, CV mortality, and non-CV mortality. Third, this finding was consistently observed regardless of the comorbidities. Finally, the risk of all-cause mortality was continuously reduced by LPA alone until 360 MET-min/week and reached a plateau. These results suggest that light physical activity alone can be beneficial in reducing mortality in older adults.

Physical Activity and Mortality in Older Adults

It is estimated that >60% of older people could not achieve 150 min per week of MVPA (6). In this study, 82.7% (55,616/68,500) of older adults were not able to achieve guideline-recommended exercise, suggesting that it may have been too demanding for them. Moreover, 79.2% of the older adults did not have physical activity beyond LPA.

Recent studies reported that the effect of LPA might be beneficial in older adults (7, 21, 22). Previous guidelines recommended MPA or VPA alone in elderly adults, although recent studies showed that LPA was also associated with improving cardio-metabolic health and reducing mortality risk (23). Another study showed that sedentary behavior was associated with negative health effects (24). Therefore, recently published WHO 2020 Guidelines on physical activity recommended replacing sedentary time with physical activity of any intensity, including LPA (3). The latest International Exercise Recommendations in Older Adults suggested that aerobic exercises including walking, stair climbing, stationary cycling, dancing, and aquatic exercise may start with a duration of 5–10 min and progress to 15–30 min with appropriate intensity using heart rate and/or perceived exertional scales (25). However, recent studies on LPA and mortality had a small number of participants and did not show consistent results (26, 27).

This study showed that all-cause mortality can be reduced even with LPA alone in older adults. Manson et al. (28) reported that both walking and vigorous exercise are associated with reduced cardiovascular events among 73,743 postmenopausal women aged 50–79 years. According to Saint-Maurice et al.'s

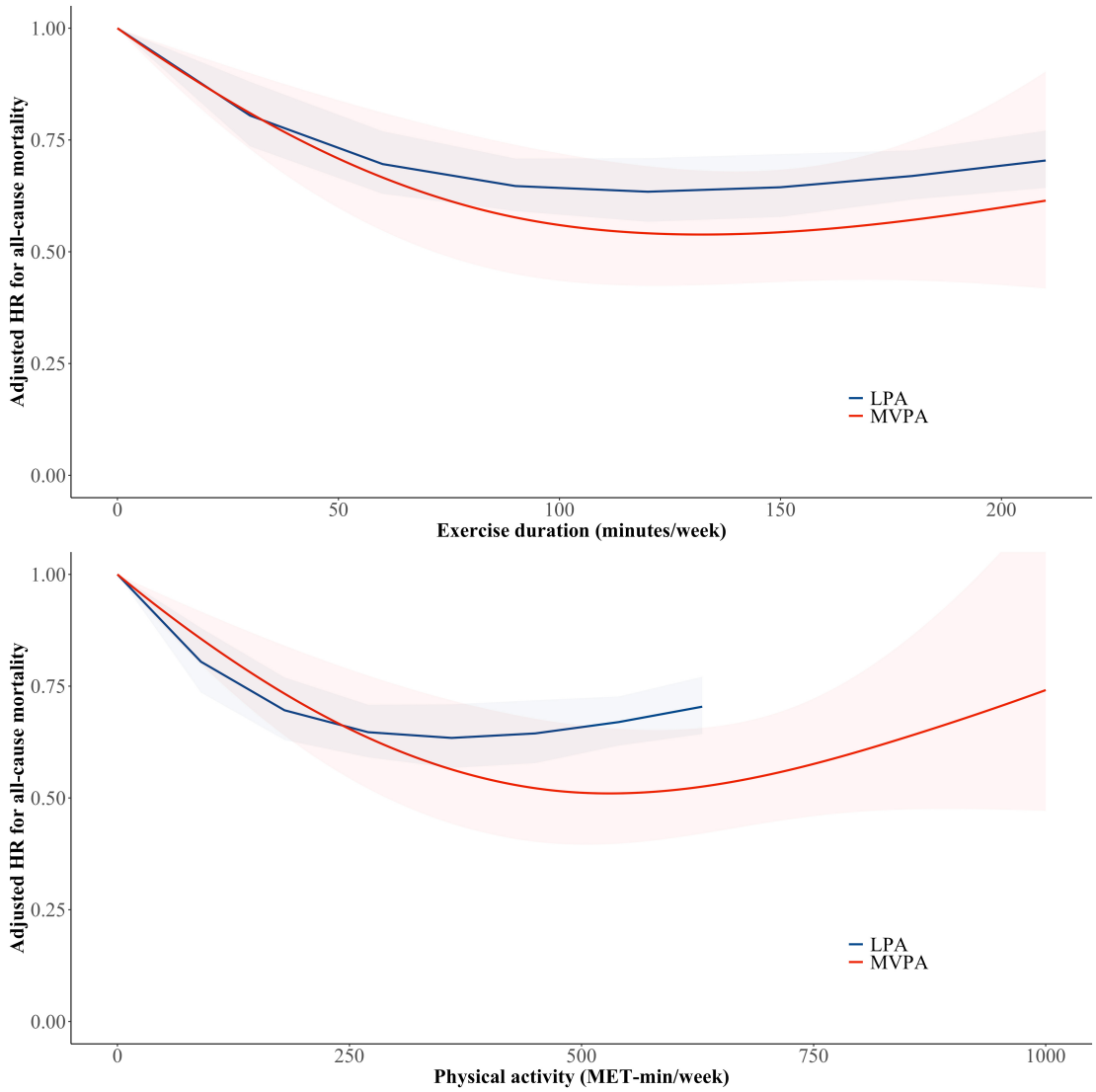

FIGURE 3 | Non-linear relationship between physical activity and all-cause mortality risk according to physical activity intensity. Restricted cubic spline curves were constructed with regard to physical activity treated as a continuous variable. The red and blue lines and shades indicate adjusted hazard ratio and 95% confidence intervals for subjects with light-intensity physical activity and moderate to vigorous physical activity, respectively. LPA, light-intensity physical activity; MET, metabolic equivalent of task; MVPA, moderate- to vigorous-intensity physical activity.

study (29), based on a representative sample of US adults (mean age, 56.8 years), daily step count was significantly associated with all-cause mortality. However, higher step intensity was not associated with lower mortality after adjusting for the total number of steps per day.

The Dose-Response Relationship Between Physical Activity and Mortality

We found the dose-response relationship between physical activity and mortality by calculating the total amount of physical activity as a continuous variable. The positive effect of increased physical activity on mortality started at a low dose of total physical activity. These results imply that even a low dose of physical activity, rather than sedentary behavior, could reduce the mortality risk.

The reduction in the risk of all-cause mortality was decreased in both LPA and MVPA with a further increase in the amount of exercise. The risk of all-cause death was reduced by 37% at 360 MET-min/week and by 49% at 528 MET-min/week in the LPA only and MVPA only groups, respectively. This finding suggests that the reduction in all-cause mortality is greater with more intensive exercise. Wang et al. (30) suggested that participants with a higher proportion of VPA to total physical activity had a lower mortality.

The physical activity for older adults should be individualized according to their biological age, comorbidity, safety, and

functional capacity (31). Nauman et al. (32) suggested that personalized metric for physical activity using individual's sex, age, and heart rates was useful for quantifying the amount of PA needed to produce significant health benefits. Recommendation from the American College of Sports Medicine and American Heart Association (ACSM/AHA) define aerobic intensity for healthy adults in absolute terms, e.g., moderate-intensity comprises 3.0–6.0 MET activities. The older adult recommendation from ACSM/AHA defines exercise intensity as relative to fitness (33). The range of 30–60 min of light-intensity activity a day could be sufficient in older adults with functional limitations.

Limitation

This study had some limitations. First, such studies using administrative databases could be susceptible to errors arising from coding inaccuracies. To minimize this issue, we used the same definitions that we had already validated in previous studies using the Korean NHIS cohort (10, 12–20). Second, it relied on self-reported data on physical activity, as collected at baseline. The answer at the time of questionnaire completion may not represent the actual physical activity status throughout life. Furthermore, behavioral changes that occurred during the follow-up period could not be assessed in this study. Also, it might be inappropriate to assign MET levels for the respective intensity groupings without knowing the cardiorespiratory fitness levels of the participants. This is because a proportion of the older adults likely had low fitness levels which would have made it difficult to perform activity in between 4 and 8 and above 8 METs. Despite these limitations, this study has strength in that it included a large number of older adults who had physical activity data. We assessed the dose-response relationship between physical activity and mortality and focused on the effect of LPA on the incidence of mortality. Various sensitivity analyses showed consistent results, which supports our main result.

CONCLUSION

The analyses of the Korean NHIS-Senior database showed a reduced mortality risk in individuals with LPA than in those with totally sedentary behavior. The mortality risk was reduced in a dose-dependent manner even less than the recommended dose of physical activity. Replacing sedentary time with any activity, even low doses of LPA could play a role in reducing the mortality risk in inactive older adults.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Review Board of the Yonsei University Health System (4-2021-0850). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

JK and BJ designed the study. P-SY, B-EP, TSK, and S-HL assisted with data acquisition and interpretation. SC, S-YL, and YHC performed statistical analyses. DK and M-YL contributed to the discussion. JK, DK, and BJ drafted the manuscript. P-SY and BJ revised the manuscript. All authors read and approved the final 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.2022.859277/full#supplementary-material

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Longitudinal Associations Between Cumulative Physical Activity and Change in Structure and Function of the Left Side of the Heart: The Tromsø Study 2007–2016

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Background: Current knowledge about the relationship between physical activity (PA) and cardiac remodeling is mainly derived from cross-sectional studies of athletes, and there is a knowledge gap of this association in the general adult and elderly population. Therefore, we aimed to explore the longitudinal association between cumulative PA and change in cardiac structure and function in a general adult and elderly population.

Methods: This longitudinal study includes 594 participants from the sixth (Tromsø6, 2007–08) and seventh (Tromsø7, 2015–16) survey of the Tromsø Study. Cardiac structure and function were assessed by echocardiography at two time points, and PA was self-reported by questionnaire at both time points. PA volume was expressed as cumulative PA (Low, Moderate, and Hard) and the association with left atrial (LA) and left ventricular (LV) structure and function was assessed using ANCOVA.

Results: Overall, LA diameter index (LADi) increased significantly more in Hard compared to Moderate PA (+0.08 cm/m^2, 95% CI 0.01–0.15, $p = 0.020$) from Tromsø6 to Tromsø7. When stratified by sex or age, higher levels of cumulative PA were associated with increased LADi in males and in participants <65 years only. Indexed LV mass (LVMi) increased significantly more in Moderate than in Low PA (+3.9 g/m$^{2.7}$, 95% CI 0.23–7.57, $p = 0.037$). When stratified by sex or age, these changes in LVMi and indexed LV diameter (LVDi) were only significant in females. No significant associations were observed between cumulative PA and change in relative wall thickness, E/e' ratio, e' velocity, LV ejection fraction, and LADi/LVDi ratio.

Conclusion: Higher levels of cumulative PA were associated with increased LADi in males and participants <65 years, and with increased LVMi and LVDi in females. Despite cardiac chamber enlargement, the pump function of the heart did not change with higher levels of PA, and the atrioventricular ratio was unchanged. Our results indicate that cardiac chamber enlargement is a physiological response to PA.

Keywords: athlete's heart, cardiac, echocardiography, ejection fraction, exercise, left atrium, left ventricle, public health

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INTRODUCTION

Changes in cardiac structure and function can occur as a result of physiological remodeling from exercise or pathological remodeling (1). Whereas, physiological remodeling is considered benign adaptations, pathological remodeling is associated with increased risk of cardiovascular diseases and mortality. Both left atrial (LA) enlargement and left ventricular (LV) hypertrophy are independent risk factors for cardiovascular morbidity and mortality (2–4) in the general population, and occurs in response to risk factors such as hypertension, diabetes mellitus, and obesity via mechanisms such as increased pressure and volume overload (5).

Exercise-induced cardiac remodeling is generally considered a benign physiological adaption of exercise, and is characterized by enlarged cardiac chambers and increased LV wall thickness (6). Paradoxically, exercise-induced cardiac remodeling may mimic pathological remodeling (7, 8), and elite endurance athletes may have cardiac chamber size that overlap the size seen in cardiac pathology (7, 9, 10). However, it is observed that LA function (11, 12) and LV diastolic function (13, 14) are preserved in dynamic sport-elite athletes with LA enlargement, as well as in athletes with LV enlargement (7, 15).

Current knowledge about the relationship between physical activity (PA) and cardiac remodeling is mainly derived from cross-sectional studies of athletes (16), and there is a knowledge gap of this association in the general adult and elderly population. Hence, as most studies investigating the relationship between exercise and cardiac remodeling are cross-sectional, more longitudinal studies are needed. Therefore, our main objective was to explore the longitudinal association between cumulative PA and change in cardiac structure and function in a general adult and elderly population.

MATERIALS AND METHODS

Study Population

The Tromsø Study is a single-center population-based cohort study with seven repeated health surveys of the population of the Tromsø municipality, Norway (17). This study includes participants from the sixth (Tromsø6, 2007–08) and seventh (Tromsø7, 2015–16) survey of the Tromsø Study.

In total, 623 participants provided valid data on self-reported PA in combination with valid echocardiography data from Tromsø6 and Tromsø7. We excluded participants with valvular heart disease at baseline ($n = 21$). Furthermore, eight participants were excluded due to missing data on the covariate hypertension. Finally, our analytical sample consisted of 594 participants free from valvular heart disease, and with valid data on PA, echocardiography, and covariates at baseline (**Figure 1**). However, the number of participants differed slightly between the different analyses due to missing images and/or due to images with inappropriate quality.

Physical Activity

PA was assessed using the Saltin-Grimby Physical Activity Level Scale (18), where the participants rank their leisure-time PA on a four-level scale. In our study, we summed up the participants' ranked leisure-time PA in Tromsø6 and Tromsø7 and combined them in a total cumulative score (**Figure 2**). Furthermore, we divided the cumulative score into three cumulative PA categories: (1) Low (total score 2–3), (2) Moderate (total score 4), and (3) Hard PA (total score 5-8).

Cardiac Structure and Function

Echocardiographic examinations in Tromsø6 and Tromsø7 were performed by two qualified sonographers, for Tromsø6 collected from October 2007 to December 2008, using an Acuson Sequoia C512 (Acuson, Mountain View, California, USA) ultrasound scanner and for Tromsø 7 collected from August 2015 to October 2016 using a GE Vivid E9 (GE Medical, Horten, Norway) ultrasound scanner. The echocardiographic assessments were performed with the use of standard imaging planes in the left lateral decubitus position according to the joint American and European guidelines (19). In Tromsø6, the echocardiographic measurements were performed online in one heart cycle but remeasured if deviating from eye-balled estimates. In Tromsø7, the echocardiographic measurements were performed off-line on 3–5 consecutive cardiac cycles by a physician experienced in echocardiography (co-author MS), and the average was used in the analysis.

Cardiac dimensions were measured by M-mode echocardiography in the parasternal short axis view at the aortic valve level, after alignment of left ventricle in long axis view, according to the leading edge-to-leading edge convention (19). LV internal dimensions were measured at the end of diastole and systole and indexed to body surface area (LVDi) as cm/m^2 (20). LA anteroposterior diameter was measured at the end of the LV systole and indexed to body surface area (LADi) as cm/m^2. LA volume was measured at the end of the LV systole and calculated using the Simpson's biplane method from the apical four- and two chamber views and indexed to body surface area as mL/m^2. LADi/LVDi ratio was calculated. Relative wall thickness was calculated with the formula (2 x posterior wall thickness) / (LV internal end-diastolic diameter). LV myocardial mass was calculated according to the cube formula (19), and further indexed to height by raising height to the power of 2.7 (LVMi), and are presented as $g/m^{2.7}$ (21). LV ejection fraction (LV EF) was calculated using the Teichholz formula (22).

All Doppler examinations were performed in apical four-chamber view according to current recommendations (23). Mitral valve Doppler measurements were performed with a 2 mm Doppler sample volume placed between the mitral leaflet tips. Tissue Doppler measurements were performed with a 5 mm Doppler sample volume located at the septal and lateral side of the mitral annulus. Measurement of peak flow velocity in early diastole (E-wave) was measured with pulsed Doppler. Mitral annular e' velocity was measured with pulsed-wave tissue Doppler in both lateral and septal basal regions and furthermore averaged. E/e'ratio was calculated. Valvular heart disease was defined by the following criteria: (a) aortic stenosis

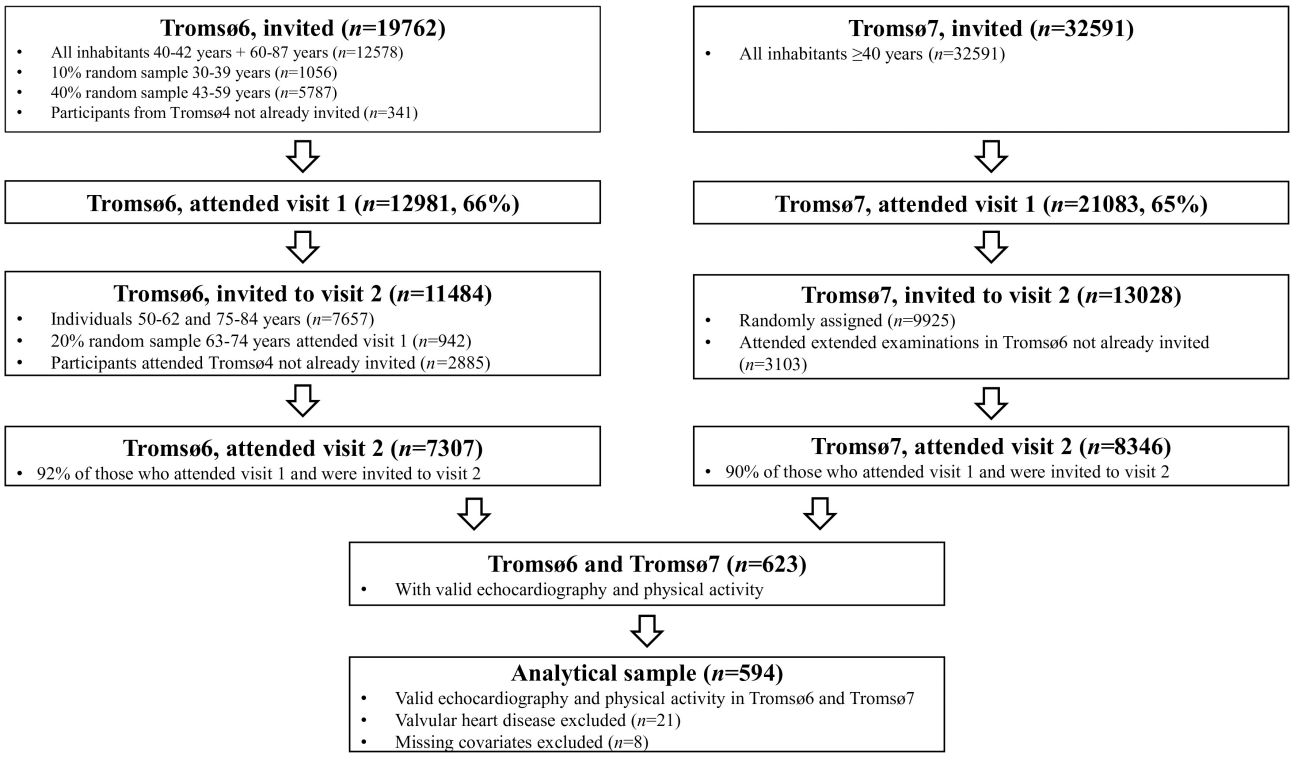

FIGURE 1 | Flowchart over inclusion of participants: The Tromsø Study 2007–2016.

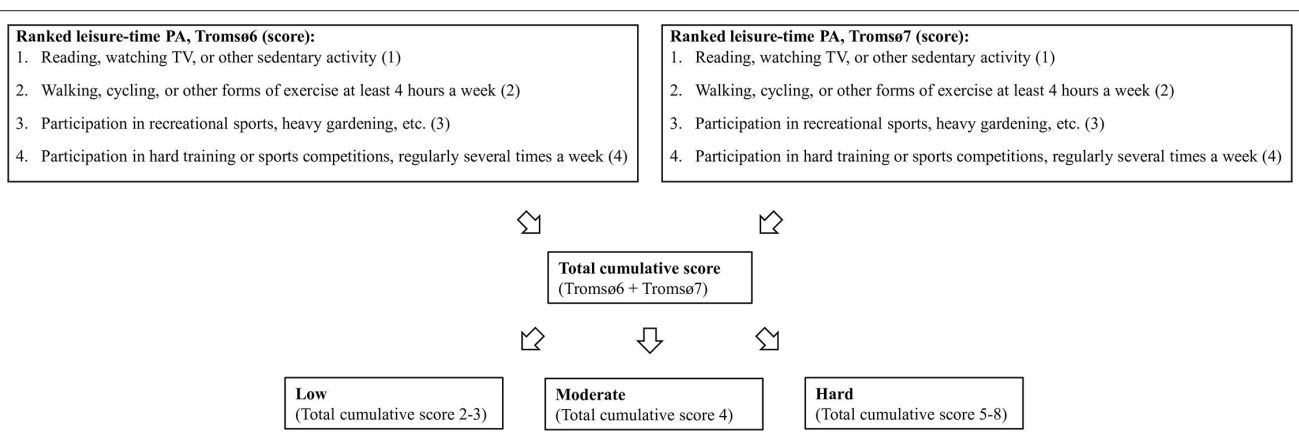

FIGURE 2 | Overview of summation of PA from Tromsø6 and Tromsø7 into cumulative PA categories: The Tromsø Study 2007–2016. PA: physical activity.

(aortic valve mean gradient ≥15 mmHg) by continuous Doppler (24), (b) presence of mitral or (c) aortic regurgitation detected by color Doppler imaging with mitral insufficiency graded according to regurgitant jet area >4 cm^2 (25), and aortic regurgitation graded by vena contracta width by color M-mode divided by of LV outflow tract diameter (>30% graded as moderate or higher) (25), and/or (d) mitral stenosis (E-wave deceleration time >350 msec and mitral E-wave >1 m/s) by pulsed Doppler (26). However, mitral stenosis was not identified in any subjects in our analytical sample.

In Tromsø7, an intra- and inter-observer study was performed on the echocardiography data (27). Intra-class correlation coefficients on Doppler indices and linear measurements were 0.90–0.99 in the intra-observer study and 0.84–0.98 in the inter-observer study. In Tromsø6, intra- and inter-observer variability on Doppler indices was evaluated by Bland-Altman analysis (24). The results showed mean inter-observer differences (95% limits

of agreement) in the mean aortic gradient of −0.06 mmHg (−3.06 to 3.18). Intra-observer analysis gave a mean difference of −0.04 mmHg (−1.86 to 1.78) and 0.30 mm Hg (−3.96 to 4.56), respectively, in the two observers.

Covariates

Details about collection of baseline data are described elsewhere, and all data were collected by specially trained research technicians (28). Baseline data from Tromsø6 include the following covariates extracted from self-reported questionnaires, physical examinations, and blood samples: Daily smoking (yes or previously/never), diabetes (yes/no), use of antihypertensives (currently or previously/never), myocardial infarction (previously/no), stroke (previously/no). Alcohol consumption was the product of two questions, one reporting number of units of alcohol and one reporting frequency of drinking.

Blood pressure was recorded three times with 1 min intervals after 2 min seated rest with an automatic device (Dinamap Pro care 300 Monitor, GE Healthcare, Oslo, Norway), the average from reading two and three was used in our analyses. Blood pressure was classified into hypertension groups (21): (a) Normotensive (systolic blood pressure <140 mmHg, diastolic blood pressure <90 mmHg, and no self-reported use of antihypertensives), (b) hypertensive, controlled (systolic blood pressure <140 mmHg, diastolic blood pressure <90 mmHg, and self-reported use of antihypertensives), (c) hypertensive, uncontrolled (systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg, and self-reported use of antihypertensives), or d) hypertension, untreated (systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg, and no self-reported use of antihypertensives). Height and weight were measured to the nearest decimal with participants wearing light clothing and no footwear. Body mass index was calculated as weight (kg) divided by height squared (m^2).

Data on atrial fibrillation was derived from the diagnosis registry of the University Hospital of North Norway, the only hospital in the region, by linking the hospitals records of atrial fibrillation to the participants' unique Norwegian national 11-digit identification number (29). Blood samples were analyzed for low-density lipoprotein (LDL) cholesterol at the Department of Clinical Chemistry, University Hospital of North Norway.

Statistical Methods

Descriptive characteristics of the study population are presented as means with standard deviations (SD) or percentages with number of observations (*n*). The associations between cumulative PA and cardiac structure and function were evaluated by one-way analysis of covariance with Bonferroni adjusted *post hoc* comparisons. Data are presented as adjusted means with standard error (SE), and effects with 95% confidence intervals (CI) unless otherwise stated. Model 1 is unadjusted, model 2 is adjusted for age, sex, body mass index, and hypertension groups.

Sex*PA was a significant interaction term in the association between PA and change in LA diameter ($p = 0.024$), body mass index*PA was a significant interaction term between PA and change in E/e' ratio ($p = 0.028$), and hypertension (normotensive/hypertensive)*PA was a significant interaction term between PA and change in average e' ($p = 0.040$).

To test the robustness of the fully adjusted model 2, we performed sensitivity analyses excluding participants with known cardiac pathologies (atrial fibrillation, myocardial infarction, stroke, and LV EF <40%) stepwise. Moreover, we performed sensitivity analysis adjusted for additional covariates (smoking, alcohol consumption, diabetes, and LDL cholesterol) stepwise added to the model.

For sensitivity analyses of the PA assessments, we compared the mean PA score in Tromsø6 with the mean PA score in Tromsø7, stratified by level of cumulative PA (**Supplementary Table S1**), to assess whether there were differences in PA score between Tromsø6 and Tromsø7 within each level of cumulative PA. Moreover, the activity level within each level of cumulative PA was quantified with accelerometry-measured PA, assessed by a triaxial accelerometer (wGT3X-BT, ActiGraph LLC, Pensacola, FL, USA), in Tromsø7 (**Supplementary Table S2**).

All statistical analyses were performed using SPSS version 28 (SPSS Inc., IL, USA), with a two-sided alpha ≤0.05 considered statistically significant.

RESULTS

In total, 266 males (61.1 ± 8.9 years) and 328 females (58.9 ± 9.9 years), ranging from 37 to 76 years, were included in our study. Descriptive baseline characteristics of the analytical sample, stratified by PA, is given in **Table 1**.

Overall, there was a significant difference in increase in LADi ($p = 0.018$) and LVMi ($p = 0.037$) between groups of cumulative PA in multivariate adjusted analyses (**Supplementary Table S3**). No significant differences were observed between cumulative PA and change in the other echocardiography variables (LVDi, relative wall thickness, E/e' ratio, e' velocity, LV EF, and LA/LV ratio) (**Supplementary Table S3**).

Cumulative PA and Change in LADi From Tromsø6 to Tromsø7

Overall, from Tromsø6 to Tromsø7, LADi increased significantly more in Hard compared to Moderate PA, with a mean group difference in LADi enlargement of 0.08 cm/m^2 (95% CI 0.01–0.15, $p = 0.020$) (**Table 2**). No significant differences in LADi change were observed between Hard and Low PA ($p = 0.128$) and Moderate and Low PA ($p = 1.000$).

In sex-stratified adjusted analysis (**Table 2**), LADi in males increased significantly more in Hard (0.30 cm/m^2, SE 0.03) than in Moderate (0.14 cm/m^2, SE 0.03) and Low PA (0.18 cm/m^2, SE 0.04), with a mean group difference of 0.12 cm/m^2 (95% CI 0.00–0.24, $p = 0.047$) between Hard and Low, and a mean group difference of 0.16 cm/m^2 (95% CI 0.06–0.26, $p < 0.001$) between Hard and Moderate PA. No statistical difference between Moderate and Low PA was observed ($p = 1.000$). In females, no differences were observed ($p = 0.852$).

TABLE 1 | Descriptive baseline characteristics stratified by level of cumulative physical activity: The Tromsø Study 2007–2008.

	Low PA ($n = 140$)	Moderate PA ($n = 259$)	Hard PA ($n = 195$)	Total ($n = 594$)
Age, years	61.4 (9.0)	59.2 (9.4)	59.9 (10.0)	60.0 (9.6)
Sex, % (*n*) female	60.7 (85)	62.9 (163)	41.0 (80)	55.2 (328)
Body mass index kg/m^2	28.1 (4.6)	26.3 (3.7)	26.3 (3.6)	26.7 (4.0)
Systolic blood pressure, mmHg	141.1 (21.0)	136.6 (20.9)	136.6 (22.7)	137.7 (21.6)
Diastolic blood pressure, mmHg	78.1 (10.7)	78.0 (9.7)	78.4 (10.5)	78.2 (10.2)
LDL cholesterol, mmol/L	3.7 (1.0)	3.6 (1.1)	3.6 (0.9)	3.6 (1.0)
Hypertension, controlled, % (*n*)	11.4 (16)	6.2 (16)	6.2 (12)	7.4 (44)
Hypertension, uncontrolled, % (*n*)	17.9 (25)	11.6 (30)	15.4 (30)	14.3 (85)
Hypertension, untreated, % (*n*)	32.1 (45)	34.7 (90)	29.7 (58)	32.5 (193)
Myocardial infarction, %	5.8 (8)	5.0 (13)	3.7 (7)	4.8 (28)
Stroke, %	2.9 (4)	1.2 (3)	2.1 (4)	1.9 (11)
Atrial fibrillation, %	2.9 (4)	1.2 (3)	2.6 (5)	2.0 (12)
Diabetes, %	8.7 (12)	2.7 (7)	3.7 (7)	4.4 (26)
Smoking daily, % (*n*)	23.9 (33)	18.1 (47)	8.8 (17)	16.4 (97)
Alcohol, units/month	9.8 (13.6)	9.6 (11.1)	10.8 (11.6)	10.1 (11.9)
Echocardiography				
LV mass, g	176.5 (54.9)	155.1 (44.9)	175.2 (55.4)	166.7 (51.9)
LV mass, g female	156.3 (40.5)	132.2 (28.7)	138.8 (33.7)	139.9 (34.6)
LV mass, g male	207.3 (59.9)	194.0 (40.4)	200.8 (53.5)	199.7 (50.7)
LV mass index, g/h$^{2.7}$	42.8 (12.2)	37.5 (8.7)	40.9 (11.5)	39.8 (10.8)
LV mass index, g/h$^{2.7}$ female	41.6 (12.0)	35.2 (7.7)	36.7 (9.9)	37.2 (9.8)
LV mass index, g/h$^{2.7}$ male	44.5 (12.4)	41.3 (9.0)	43.8 (11.7)	43.1 (11.0)
LA diameter, cm	3.8 (0.5)	3.6 (0.5)	3.8 (0.5)	3.7 (0.5)
LA diameter, cm female	3.6 (0.5)	3.4 (0.4)	3.6 (0.4)	3.5 (0.4)
LA diameter, cm male	4.0 (0.4)	4.0 (0.5)	4.0 (0.6)	4.0 (0.5)
LA diameter index, cm/m^2	2.0 (0.2)	2.0 (0.2)	2.0 (0.3)	2.0 (0.2)
LA diameter index, cm/m^2 female	2.0 (0.3)	2.0 (0.2)	2.0 (0.2)	2.0 (0.2)
LA diameter index, cm/m^2 male	2.0 (0.2)	2.0 (0.2)	2.0 (0.3)	2.0 (0.3)
LV diameter, cm	5.1 (0.5)	5.0 (0.5)	5.2 (0.5)	5.1 (0.5)
LV diameter, cm female	5.0 (0.5)	4.9 (0.4)	4.9 (0.4)	4.9 (0.4)
LV diameter, cm male	5.3 (0.5)	5.3 (0.5)	5.4 (0.5)	5.3 (0.5)
LV diameter index, cm/m^2	2.7 (0.3)	2.7 (0.3)	2.8 (0.2)	2.7 (0.3)
LV diameter index, cm/m^2 female	2.8 (0.3)	2.8 (0.3)	2.8 (0.2)	2.8 (0.3)
LV diameter index, cm/m^2 male	2.6 (0.2)	2.6 (0.3)	2.7 (0.3)	2.6 (0.3)
LA/LV ratio	0.7 (1.0)	0.7 (0.1)	0.7 (0.1)	0.7 (0.1)
E/e' ratio	6.6 (1.7)	6.3 (1.4)	6.3 (1.7)	6.3 (1.6)
LV ejection fraction, %	70.8 (7.2)	70.8 (7.2)	71.2 (7.2)	70.9 (7.2)
LV ejection fraction <40%, % (*n*)	0.0 (0)	0.0 (0)	0.6 (1)	0.2 (1)

Numbers are mean ±standard deviation or percentage and n. PA, physical activity, LDL, low-density lipoprotein, LV, left ventricular, LA, left atrial.

In age-stratified adjusted analysis (**Table 2**), LADi in participants <65 years increased significantly more in Hard (0.21 cm/m2, SE 0.03) than in Moderate (0.11 cm/m^2, SE 0.03) PA, with a mean group difference of 0.10 cm/m^2 (95% CI 0.01–0.18, $p = 0.025$). No statistical difference between Hard and Low PA ($p = 0.474$), or between Moderate and Low PA ($p = 1.000$) was observed. No statistical differences in LADi between groups were observed for participants ≥65 years ($p = 0.262$).

Associations between cumulative PA and cross-sectional LADi in Tromsø7 are presented in **Figure 3**. Significant associations between cumulative PA and LADi were observed in males, in participants <65 years, and in the overall analysis. Moreover, similar trends in the association between cumulative PA and LADi were observed in unadjusted, baseline adjusted, and in fully adjusted analysis. Associations between cumulative PA and cross-sectional LA volume index in Tromsø7 are presented in **Figure 4**. Significant associations between cumulative PA and LA volume index were observed in females, in participants <65 years, and in the overall analysis. Moreover, similar trends in the association between cumulative PA and LA volume index were observed in unadjusted, baseline adjusted, and in fully adjusted analysis.

TABLE 2 | Longitudinal associations between cumulative physical activity and change in left atrial diameter index: The Tromsø Study 2007–2016.

	(*n*)	Model 1, baseline (mean ± SE)	Model 1, change (Delta ± 95% CI)	Model 1 (*p*-value)	Model 2, baseline (Adjusted mean ± SE)	Model 2, change (Delta ± 95% CI)	Model 2 (*p*-value)
Total	572			0.011*			0.018*
Low PA	133	1.98 (0.02)	0.19 (0.14, 0.24)	Ref.	2.00 (0.02)	0.18 (0.13, 0.24)	Ref.
Moderate PA	249	1.98 (0.02)	0.17 (0.13, 0.21)	1.000	2.01 (0.02)	0.17 (0.13, 0.22)	1.000
Hard PA	190	2.02 (0.02)	0.26 (0.21, 0.30)	0.139	2.06 (0.02)	0.26 (0.21, 0.30)	0.128
Hard vs. Moderate				0.010			0.020
Males	258			<0.001*			<0.001*
Low PA	54	1.94 (0.04)	0.20 (0.12, 0.28)	Ref.	1.96 (0.04)	0.18 (0.10, 0.27)	Ref.
Moderate PA	91	1.97 (0.03)	0.13 (0.07, 0.19)	0.529	2.00 (0.03)	0.14 (0.08, 0.21)	1.000
Hard PA	113	2.00 (0.02)	0.30 (0.25, 0.35)	0.117	2.02 (0.03)	0.30 (0.24, 0.36)	0.047
Hard vs. Moderate				<0.001			<0.001
Females	314			0.950*			0.852*
Low PA	79	2.01 (0.03)	0.18 (0.11, 0.25)	Ref.	2.03 (0.03)	0.18 (0.10, 0.25)	Ref.
Moderate PA	158	1.99 (0.02)	0.19 (0.14, 0.24)	1.000	2.03 (0.02)	0.20 (0.14, 0.26)	1.000
Hard PA	77	2.05 (0.03)	0.19 (0.12, 0.26)	1.000	2.10 (0.03)	0.21 (0.13, 0.28)	1.000
Hard vs. Moderate				1.000			1.000
<65 years	363			0.015*			0.031*
Low PA	80	1.93 (0.03)	0.17 (0.11, 0.24)	Ref.	1.95 (0.03)	0.15 (0.08, 0.22)	Ref.
Moderate PA	169	1.98 (0.02)	0.13 (0.09, 0.18)	1.000	2.00 (0.02)	0.11 (0.06, 0.17)	1.000
Hard PA	114	1.98 (0.02)	0.24 (0.18, 0.29)	0.388	2.02 (0.03)	0.21 (0.15, 0.27)	0.474
Hard vs. Moderate				0.012			0.025
≥65 years	209			0.420*			0.262*
Low PA	53	2.06 (0.04)	0.21 (0.13, 0.30)	Ref.	2.06 (0.04)	0.23 (0.14, 0.32)	Ref.
Moderate PA	80	2.00 (0.03)	0.25 (0.18, 0.32)	1.000	2.00 (0.03)	0.28 (0.20, 0.26)	1.000
Hard PA	76	2.09 (0.03)	0.29 (0.21, 0.36)	0.585	2.10 (0.03)	0.33 (0.24, 0.41)	0.312
Hard vs. Moderate				1.000			1.000

**p-value for main effect. Left atrial diameter index (LADi) and delta are presented as cm/m^2. Model 1, unadjusted; Model 2, age, sex, body mass index, hypertension groups; PA; physical activity; LA, left atrial; SE, standard error; CI, confidence interval.*

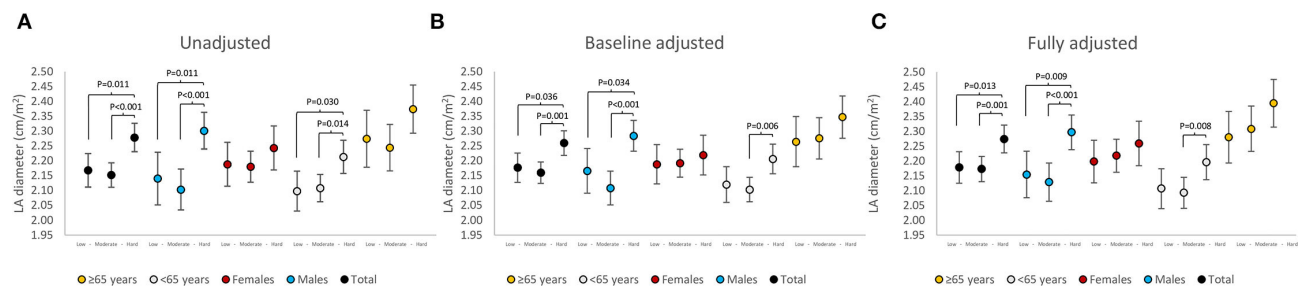

FIGURE 3 | Associations between cumulative PA and cross-sectional LA diameter index (LADi) in Tromsø7. **(A)** is unadjusted, **(B)** is adjusted for baseline LADi in Tromsø6, **(C)** is adjusted for baseline LADi in addition to age, sex, body mass index, and hypertension groups. Differences between groups of cumulative PA are indicated with *p*-values. Error bars indicate 95% CI. PA, physical activity; LA, left atrial; CI, confidence interval.

Cumulative PA and Change in LVMi From Tromsø6 to Tromsø7

Overall, from Tromsø6 to Tromsø7, LVMi increased significantly more in Moderate compared to Low PA, with a mean group difference in LVMi enlargement of 3.9 g/m$^{2.7}$ (95% CI 0.23–7.57, $p = 0.037$) (**Table 3**). No significant differences in LVMi change were observed between Hard and Low PA ($p = 0.172$) and Hard and Moderate PA ($p = 1.000$).

In sex-stratified adjusted analysis (**Table 3**), LVMi in females increased significantly more in Moderate than in Low PA, with a mean difference in change of 5.6 g/m$^{2.7}$ (95% CI 1.61–9.53, $p = 0.002$), and in Moderate than Hard PA, with a mean difference in LVMi enlargement of 4.1 g/m$^{2.7}$ (95% CI 0.35–7.92, $p = 0.027$). No significant difference between Hard and Low PA (p=1.000) was observed. In males, no significant differences were observed ($p = 0.224$). In age-stratified adjusted analysis (**Table 3**), no significant differences were observed ($p \geq 0.182$).

TABLE 3 | Longitudinal associations between cumulative physical activity and change in left ventricular mass index from baseline: The Tromsø Study 2007–2016.

	(*n*)	Model 1, baseline (Mean ± SE)	Model 1, change (Delta ± 95% CI)	Model 1 (*p*-value)	Model 2, baseline (Adjusted mean ± SE)	Model 2, change (Delta ± 95% CI)	Model 2 (*p*-value)
Total	494			0.077*			0.037*
Low PA	109	42.0 (1.0)	2.91 (0.53, 5.30)	Ref.	40.8 (0.9)	2.02 (−0.67, 4.70)	Ref.
Moderate PA	218	37.1 (0.7)	6.29 (4.60, 7.97)	0.071	38.8 (0.7)	5.92 (3.84, 8.00)	0.033
Hard PA	167	40.3 (0.8)	5.28 (3.35, 7.21)	0.391	41.1 (0.8)	5.10 (2.88, 7.33)	0.172
Hard vs. Moderate				1.000			1.000
Males	215			0.335*			0.224*
Low PA	43	45.1 (1.6)	3.46 (−0.93, 7.84)	Ref.	42.4 (1.6)	3.31 (−1.53, 8.15)	Ref.
Moderate PA	78	40.9 (1.2)	3.97 (0.71, 7.23)	1.000	41.7 (1.2)	3.86 (0.04, 7.68)	1.000
Hard PA	94	43.2 (1.1)	6.74 (3.77, 9.70)	0.670	44.3 (1.1)	7.25 (3.79, 10.72)	0.516
Hard vs. Moderate				0.651			0.412
Females	279			0.002*			0.001*§
Low PA	66	40.0 (1.1)	2.56 (−0.08, 5.19)	Ref.	38.9 (1.1)	0.86 (−2.17, 3.89)	Ref.
Moderate PA	140	35.0 (0.8)	7.58 (5.77, 9.39)	0.007	36.4 (0.9)	6.43 (4.09, 8.77)	0.002
Hard PA	73	36.6 (1.1)	3.40 (0.89, 5.91)	1.000	38.3 (1.0)	2.30 (−0.56, 5.15)	1.000
Hard vs. Moderate				0.025			0.027
<65 years	339			0.431*			0.182*§
Low PA	71	40.3 (1.1)	4.91 (2.44, 7.38)	Ref.	40.4 (1.1)	3.56 (0.67, 6.46)	Ref.
Moderate PA	158	36.2 (0.7)	6.84 (5.19, 8.50)	0.604	38.5 (0.8)	6.39 (4.23, 8.56)	0.196
Hard PA	110	37.3 (0.9)	5.97 (3.99, 7.96)	1.000	39.0 (0.9)	5.67 (3.34, 8.00)	0.616
Hard vs. Moderate				1.000			1.000
≥65 years	155			0.223*			0.204*
Low PA	38	45.1 (1.8)	−0.81 (−6.02, 4.40)	Ref.	42.9 (1.7)	−0.66 (−6.31, 4.99)	Ref.
Moderate PA	60	39.5 (1.5)	4.83 (0.68, 8.98)	0.289	40.0 (1.5)	5.20 (0.60, 10.44)	0.255
Hard PA	57	46.2 (1.5)	3.94 (−0.31, 8.20)	0.494	45.9 (1.6)	4.71 (−0.51, 9.93)	0.459
Hard vs. Moderate				1.000			1.000

**p-value for main effect.*

§Assumption of equality of error variances is violated.

Left ventricular mass index (LVMi) and delta are presented as g/m$^{2.7}$.

Model 1, unadjusted; Model 2, age, sex, body mass index, hypertension groups; PA, physical activity; LV, left ventricular; SE, standard error; CI, confidence interval.

In analysis of the association between cumulative PA and change in LVDi, significant associations were observed in females only (**Supplementary Table S4**). LVDi increased significant more in Moderate (0.07 cm/m^2 ± SE 0.03) than in Low PA (−0.06 cm/m^2, SE 0.04), with a mean group difference of 0.13 cm/m^2 (95% CI 0.03 to 0.24, $p = 0.010$). However, no significant differences in LVDi change were observed between Hard and Low PA ($p = 0.087$) and Hard and Moderate PA ($p = 1.000$).

Associations between cumulative PA and cross-sectional LVMi in Tromsø7 are presented in **Figure 5**. Significant associations between cumulative PA and LVDi were observed in females only. Moreover, similar trends in the association between cumulative PA and LVMi were observed in unadjusted, baseline adjusted, and in fully adjusted analysis.

Cumulative PA and Change in Cardiac Function From Tromsø6 to Tromsø7

The observed association observed between cumulative PA and change in LA/LV ratio overall ($p = 0.075$), stratified by sex ($p \geq 0.065$), or stratified by age ($p \geq 0.083$) was non-significant (**Supplementary Table S5**). No significant association was observed between cumulative PA and change in Mitral annular e' velocity overall ($p = 0.903$), stratified by sex ($p \geq 0.529$), stratified by age ($p \geq 0.749$), or stratified by hypertension ($p \geq 0.196$) (**Supplementary Table S6**). No significant association was observed between cumulative PA and change in change in E/e' ratio overall ($p = 0.253$), stratified by sex ($p \geq 0.286$), stratified by age ($p \geq 0.213$), or stratified by body mass index ($p \geq 0.180$) (**Supplementary Table S7**). No significant association was observed between cumulative PA and change in LV EF overall ($p = 0.970$), stratified by sex ($p \geq 0.652$), or stratified by age ($p \geq 0.556$) (**Supplementary Table S8**).

Sensitivity Analysis

When we stepwise, or jointly, excluded participants with known cardiac pathologies, we observed rather similar associations between cumulative PA and change in echocardiography measurements as in the fully adjusted

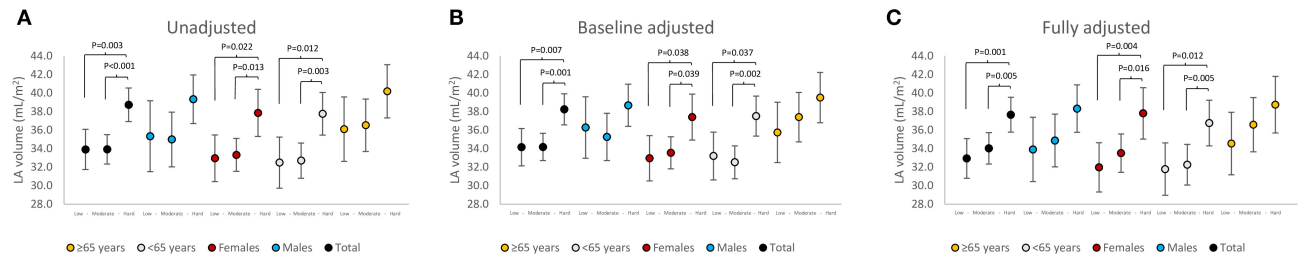

FIGURE 4 | Associations between cumulative PA and cross-sectional LA volume index (LAVi) in Tromsø7. **(A)** is unadjusted, **(B)** is adjusted for baseline LADi in Tromsø6, **(C)** is adjusted for baseline LADi in addition to age, sex, body mass index, and hypertension groups. Differences between groups of cumulative PA is indicated with *p*-values. Error bars indicate 95% CI. PA, physical activity; LA, left atrial; CI, confidence interval; LADi, LA diameter index.

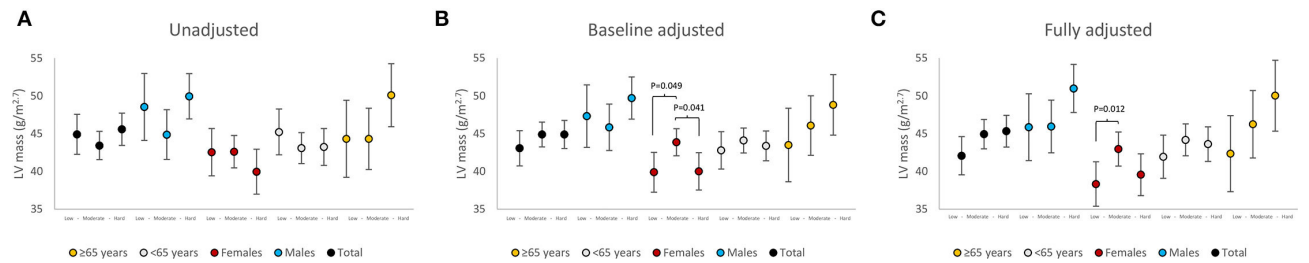

FIGURE 5 | Associations between cumulative PA and cross-sectional LV mass index (LVMi) in Tromsø7. **(A)** is unadjusted, **(B)** is adjusted for baseline LVMi in Tromsø6, **(C)** is adjusted for baseline LVMi in addition to age, sex, body mass index, and hypertension groups. Differences between groups of cumulative PA are indicated with *p*-values. Error bars indicate 95% CI. PA, physical activity; LV, left ventricle; CI, confidence interval.

model 2 (**Supplementary Table S9**). Furthermore, when smoking, alcohol consumption, diabetes, and LDL cholesterol were stepwise added to model 2, the associations between cumulative PA and change in LADi and between cumulative PA and change in LVMi did not change, except when diabetes was added to the model, the association between cumulative PA and LVMi was no longer significant ($p = 0.068$).

DISCUSSION

Exercise-induced cardiac remodeling is well documented in athletes. Our longitudinal study adds to this knowledge by showing that more moderate levels of habitual PA over time is associated with cardiac remodeling also in a general adult and elderly population. The main finding from our study is that higher levels of cumulative PA was associated with increased LA size in males and in participants <65 years, and that moderate level of cumulative PA was associated with increased LV size in females.

Despite the association between cumulative PA and increased LA and LV sizes, indices of cardiac pump function and atrioventricular remodeling did not differ significantly between groups of cumulative PA. This may indicate that cardiac chamber enlargement is a physiological response to PA.

Cumulative PA and Increased LA and LV Sizes

In our study of the general population, we observed that Hard cumulative PA was associated with a larger increase in LADi than lower PA levels; although when stratified by sex or age, increased LADi was only observed in males and in participants <65 years. Furthermore, Moderate cumulative PA was associated with increased LVMi and LVDi, but only in females when stratified by sex or age.

Our observations are at large consistent with previous studies of athletes. Several meta-analyses have reported that LA and LV sizes are larger in endurance trained athletes compared to non-athletes or sedentary controls (9, 30–32). Moreover, the relationship between endurance training and increased LV volume and mass has been demonstrated in a recent meta-analysis of both males and females (33). Additionally, the relationship between endurance training and increased LA volume, LV volume and LV mass has been confirmed in endurance trained young male and female athletes after 90 days of training (34). Similarly, increased LV volume and mass has been demonstrated in young sedentary males and females after 1 year of intensive endurance training (35).

Furthermore, the relationship between endurance training and enlarged LA volume and LV volume has been confirmed in middle-aged sedentary males and females after 10 months high-intensity endurance training (36); both LA and LV volumes increased significantly, but were considerably smaller when compared with a control group of age matched endurance athletes with a long history of endurance training (36). Additionally, a relationship between high levels of cumulative lifetime training hours and larger LA volume has been observed in males (37, 38), but no association between cumulative lifetime training hours and change in LV diameter or mass (38). Similarly,

Mahjoub and colleagues demonstrated that LA volume increased after only 6 weeks of high-intensity endurance training in endurance trained men, whereas no change in LV mass, volume, or diameter was seen (39).

The findings from the previously discussed studies demonstrate that extensive LA and LV remodeling requires high amounts of endurance training stimuli over a long time. Similarly, our results indicate that the left atrium adapts faster to exercise than the left ventricle, and that sufficient and potentially higher stimulus from exercise intensity and volume is required for the left ventricle to remodel. The faster LA remodeling may be explained by the fact that the LA walls are thinner than the LV walls (11), and therefore are more affected by the hemodynamic overload during exercise according to the Laplace's law. In our study, the stimulus from moderate levels of habitual PA over time may have been insufficient to induce LV remodeling, which may explain the lack of association between cumulative PA and increased LV sizes in our study, except for females with Moderate PA. Furthermore, the lack of association between cumulative PA and change in LV size is supported by our sensitivity analysis, as the association between cumulative PA and change in LVMi became weaker and non-significant when we adjusted for diabetes.

Age and Sex Modifications

It is well documented that the prevalence of cardiovascular risk factors such as hypertension increase progressively with age, with a prevalence of 60% in participants ≥60 years (21). Untreated hypertension causes LV hypertrophy, which impairs LV relaxation and induces LV diastolic dysfunction and LA enlargement (21). Thus, the lack of increase in LADi in participants ≥65 years may be due to age related changes in the heart.

The observed sex differences in the association between cumulative PA and LA size may be explained by physiological and morphological differences between males and females (40). Females are on average smaller, have lower lean mass and a different sex hormone profile than males, which significantly impacts cardiac size (41). As females generally have smaller cardiac chambers than males (19), males exhibit more pronounced cardiac changes despite similar relative increase in chamber sizes (41). Finally, there may be quantitative and qualitative differences in exercise patterns between males and females (40). This is supported by accelerometry-measured data from the general adult and elderly population, where females accumulated more minutes of light PA and males accumulated more minutes of moderate and vigorous PA (42, 43).

Cumulative PA and Change in Cardiac Function

Despite the association between cumulative PA and increased LA and LV sizes, no significant differences in mitral annular e' velocity, E/e' ratio, LV EF, or LADi/LVDi ratio were observed between groups of cumulative PA. Thus, our results demonstrate that changes in indices of LV diastolic and systolic function, and atrioventricular chamber ratio, do not differ between groups of cumulative PA. The observed cardiac chamber enlargement with higher levels of cumulative PA in our study seems to be a physiological adaptation to exercise.

Our observations are consistent with previous reports of preserved cardiac function in athletes with exercise-induced cardiac remodeling. Studies of endurance athletes and elite soccer players have observed that LV diastolic function, as measured by Mitral valve and/or Tissue Doppler imaging, is preserved or even supranormal in athletes with cardiac chamber enlargement (13, 14, 38, 44). Also, studies have observed that LV systolic function, as measured by LV EF and/or LV fractional shortening, is normal in athletes with cardiac chamber enlargement (13, 15). Furthermore, preserved LV systolic function in athletes, as measured by LV EF and LV fractional shortening, has been confirmed in a meta-analysis of males and females at rest and during exercise (31). The authors observed no differences in LV systolic function between athletes and matched control subjects (31). Additionally, the effects of endurance training has been evaluated in a recent meta-analysis, where it was demonstrated that LV systolic function, as measured by LV EF and LV stroke volume, was slightly increased in males, but unaltered in females (33). In cross-sectional studies from the general population, no significant associations between increased LA volume and LV diastolic dysfunction, as measured by E/e' ratio, e', and/or tricuspid regurgitation velocity, was observed in physically active participants (45, 46).

In contrast, Lakatos and colleagues observed normal, but lower LV systolic function, as measured by LV EF and/or LV global longitudinal strain, in elite endurance athletes compared to non-athletes (47). Similarly, despite no difference in LV EF, it has been observed that LV global longitudinal strain was lower in elite endurance athletes than in non-athletes (13). With exercise-induced LV remodeling, it is possible that less myocardial deformation is required to obtain the same stroke volume. Therefore, reduced LV global longitudinal strain may be an adaptive change in elite endurance athletes (13).

Our observations of a balanced LADi/LVDi ratio, despite increased LA and LV sizes, is consistent with studies observing symmetrical enlargement of all four chambers (34), and that LA volume/LV volume ratio is similar despite LA enlargement in endurance athletes (13). An increased LA/LV ratio may be due to increased LV pressure and/or LV diastolic impairment, whereas an increased LA chamber with normal LA/LV ratio likely reflects a physiological adaptation to exercise (13).

In contrast to preserved pump function and balanced remodeling in the athlete's heart, increased risk of atrial fibrillation is seen in both adult and elderly endurance athletes (48, 49). It is suggested that LA enlargement itself may be a substrate for atrial fibrillation in athletes (50, 51), and therefore that the athlete's heart may potentially be proarrhythmic independent of other abnormalities. However, convincing data linking the combination of exercise and LA size to AF are lacking and are largely speculative (50, 52). Moreover, in a recent study investigating the acute effects of strenuous endurance exercise on atrial size and function in master athletes (53), the authors reported no exercise-induced atrial dysfunction or change in atrial size after an ultramarathon compared with

baseline. Moreover, acute exercise-induced atrial fibrillation was uncommon during the race (53).

Strengths and Limitations

The main strength of our study is the longitudinal design with repeated measurements of PA and echocardiographic structural and functional data, which enables evaluation of the direction of the associations as well as change from baseline. Moreover, the broad diversity of covariates allowed us to adjust for multiple potential confounders.

Our study has several limitations that should be addressed. First, due to the observational nature of this study, causation cannot be established. Second, LADi, LVDi, and LV EF were assessed by linear measurements, which are less accurate and have more geometrically assumptions than the recommended biplane volume calculated parameters (19). However, in Tromsø7, we found moderate correlation between biplane-calculated EF and Teichholz-calculated EF ($r = 0.42$), and between LADi and LA volume index ($r = 0.45$). Furthermore, LVDi correlated strongly with LV volume index ($r = 0.87$). Third, our study lacks assessment of LA function which may distinguish between pathological and physiological remodeling (8). Fourth, self-reported PA is prone to both recall- and social desirability bias (54), and misclassifications would probably underestimate the true effects of PA. However, in a sub-study of Tromsø6, self-reported PA using the Saltin-Grimby Physical Activity Level Scale was significantly correlated with maximal oxygen uptake (females $r_s = 0.40$, males $r_s = 0.44$, both $p < 0.001$) (55). Moreover, there was a significant positive linear trend between maximal oxygen uptake and levels of self-reported PA (55). This is consistent with the sensitivity analysis of cumulative PA performed on our analytical sample (**Supplementary Table S2**). Fifth, we cannot exclude residual confounding by measured or unmeasured variables (e.g. masked hypertension or sex hormones). Finally, the relatively low sample size in our study represents a potential limitation. However, baseline characteristics did not differ between our analytical sample and the total cohort attending the first visit in Tromsø6 ($n = 12{,}981$), which strengthens our external validity to other Northern-European Caucasian adult populations.

In conclusion, higher levels of cumulative PA were associated with increased LADi in males and participants <65 years, and with increased LVMi and LVDi in females. Despite the association between cumulative PA and cardiac chamber enlargement, the function of the heart did not change with higher levels of PA, and the atrioventricular ratio was unchanged. This indicate that cardiac chamber enlargement is a physiological response to PA.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because the legal restriction on data availability is set by the Tromsø Study Data and Publication Committee to control for data sharing, including publication of datasets with the potential of reverse identification of deidentified sensitive participant information. The data can however be made available from the Tromsø Study upon application to the Tromsø Study Data and Publication Committee. Requests to access the datasets should be directed to the Tromsø Study, Department of Community Medicine, Faculty of Health Sciences, UiT The Arctic University of Norway; e-mail: tromsous@uit.no.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Regional Committee for Medical and Health Research Ethics, Tromsø, Norway (20828/REK Nord). The participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

KH, BW, and BM contributed to conception or design of the work. KH drafted the manuscript. All authors contributed to acquisition or analysis of the data. All authors contributed to interpretation of the data, critically revised the manuscript, gave final approval, and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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SUPPLEMENTARY MATERIAL

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Physical Exercise in Resistant Hypertension: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Physical exercise reduces blood pressure (BP) in patients with hypertension in general but more evidence is needed specifically for a high-risk phenotype associated with intensive medication, resistant hypertension (RH). In this systematic review and meta-analysis, we aimed to summarize current evidence of the exercise effects on BP in patients with RH. A systematic search was conducted in PubMed, Web of Science and Cochrane Library (from inception to 3rd November, 2021). A random effects meta-analysis was performed when at least two trials assessed the effect of either acute or regular exercise (vs. a control condition) on the same outcome. Ten studies ($N = 380$ participants; 51% female; mean age 52 to 67 years) were included in the review, of which four ($N = 58$) and six ($N = 322$) assessed the effects of acute and regular exercise, respectively. Evidence overall suggests that a single bout of acute exercise results in a short-term ($\leq$24 h) reduction of BP, although no meta-analysis could be performed. As for regular exercise, three randomized controlled trials ($N = 144$, 50% female) could be meta-analyzed, which showed that exercise training intervention (8–12 weeks, 3 sessions/week) significantly reduces 24-h (−9.9 mmHg, 95% confidence interval −15.4−4.4 for systolic BP; and −5 mmHg, −7.0−3.0 for diastolic BP) and daytime ambulatory BP (−11.7 mmHg, −17.8−5.7; and −7.4 mmHg, −11.9−2.9). In summary, physical exercise appears as an effective option to reduce BP in patients with RH, although more research is needed to confirm these findings as well as to determine the most effective exercise characteristics.

Keywords: office blood pressure, ambulatory blood pressure, nighttime, daytime, hypertensives

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INTRODUCTION

Approximately 12–15% of hypertensive patients have resistant hypertension (RH) (1), traditionally defined as above-goal clinic ("office") blood pressure (BP) (i.e., systolic BP (SBP)/diastolic BP (DBP) >130/80 mmHg (2) or >140/90 mmHg (3) according to the American College of Cardiology/American Heart Association or European Society of Cardiology/European Society of Hypertension guidelines, respectively) despite the concurrent use of three or more antihypertensive drugs — commonly including a diuretic, a long-acting calcium channel blocker, and a blocker of the renin-angiotensin system — at maximum or maximally tolerated oral doses (1). RH also includes patients whose BP achieves target values on ≥4 antihypertensive medications (i.e., 'controlled' RH) (1). Because the management

of this condition based solely on medications has proven only partially successful (1), non-pharmacological strategies should also be considered.

Lifestyle, particularly physical exercise, can play an important role in BP management in individuals with hypertension (4). Meta-analytical evidence shows that exercise training intervention reduces not only office (5) but also ambulatory BP (ABP) in these individuals (6), with the latter measure being a stronger predictor of cardiovascular diseases (CVD) and mortality (7). Notably, there is recent meta-analytical evidence that a single bout of acute exercise (8) and regular exercise training (6) induce significant short (≤24 h) and mid-term (up to ∼6 months) reductions in ABP, respectively, among patients with hypertension in general. Furthermore, exercise has minimal side effects compared with drugs (9) and is considered as effective as most antihypertensive agents to reduce office BP (10). However, although the benefits of both acute and regular exercise on BP are well-established in patients with hypertension in general (5, 6, 8), scarcer evidence is available in the context of RH specifically.

Available evidence on the effects of exercise intervention in individuals with RH shows promising results, as confirmed by some non-systematic reviews (11–14). Different trials have reported a beneficial effect of acute (15, 16) or regular exercise (17–20) on office BP or ABP in patients with RH. However, to the best of our knowledge there has been no previous attempts to systematically synthesize the evidence available on the effects of acute or regular exercise on BP measures in patients with RH. Under this context, we aimed to summarize current evidence of the effects of acute or regular exercise on ABP measures in patients with RH.

METHODS

Data Sources and Search Strategy

The review protocol is registered in PROSPERO (International Prospective Register of Systematic Reviews) (https://www.crd.york.ac.uk/PROSPERO/; Unique identifier: CRD42021287788). Two researchers (GSL, PLV) independently conducted a systematic search — first by title and abstract, and then by full-text — in PubMed, Cochrane Library and Web of Science from inception to 3rd November 2021 using the following search strategy: ("exercise" OR "physical activity" OR "training") AND ("blood pressure" OR "BP" OR "SBP" OR "DBP") AND ("resistant hypertension" OR "resistant hypertensive"). This search was supplemented by a manual review of reference lists from relevant publications. We did not search abstracts, posters, and workshop presentations.

Study Selection

Eligibility criteria were defined in accordance with the Population, Intervention, Comparison, Outcome and Study Design (PICOS) approach (21). We included studies that met each of the following inclusion criteria:

- Population: Adults diagnosed with RH.
- Intervention: Physical exercise, including both a single acute exercise bout and/or regular exercise training (i.e., for several weeks/months). No restrictions were made regarding the frequency, duration, or length of the exercise interventions.
- Comparison: The comparator was a control condition where participants performed no physical exercise.
- Outcomes: Office or ABP.
- Study design: There were no exclusion criteria regarding the study design.

When two studies included part of the same patients' cohort, only data from the study with more participants were included in the meta-analysis.

Data Extraction

Two reviewers (GSL, PLV) independently identified for each study the number and characteristics of participants, exercise intervention details, endpoints, and results. Data were extracted as mean (standard deviation) when available. When data were provided as intervention effects or using other measures of dispersion (e.g., standard error, 95% confidence interval), the required information was estimated following published guidelines (22). A specific software (WebPlotDigitizer 4.2, San Francisco, CA) was used to extract data provided as a figure in one study (18).

Quality Assessment

Two authors (GSL, PLV) independently assessed the methodological quality of the different studies using the Tool for the Assessment of Study Quality and Reporting in Exercise (TEXTES) for chronic exercise interventions (23). For studies assessing the short-term effects of a single bout of acute exercise, we used a modified version of the TEXTES scale as proposed elsewhere (24).

Statistical Analyses

We performed meta-analyses when a minimum of two studies assessed the effects of either acute or regular exercise on a given outcome. A random-effects (DerSimonian and Laird) meta-analysis was performed to assess the mean difference between exercise and control groups using baseline and post-intervention data. Because none of the included studies provided information on the correlation between baseline and post-intervention BP, we used a Pearson's correlation coefficient (r) value of 0.8, in consistence with previous research (25, 26). Publication bias and heterogeneity across studies was assessed with the Begg's test and the I^2 statistic, respectively. Sensitivity analyses were performed by removing one study at a time. Analyses were conducted using Comprehensive Meta-analysis 2.0 (Biostat; Englewood, NJ) with $\alpha = 0.05$.

RESULTS

Included Studies

Ten studies ($N = 380$ participants, 51% female, age range 52 to 67 years) were included in the review, of which four (15, 16, 27, 28) ($N = 58$, 50% female) assessed the short-term (≤24 h) effects of acute physical exercise and six (17, 18, 20, 29–31) ($N = 322$, 51% female) assessed the mid-term (up to 6 months) effects of exercise training intervention (**Table 1**, Flowchart available as

TABLE 1 | Main characteristics of the included studies.

Study	Number of participants analyzed (mean age, % female)	Exercise intervention	Design	Main intervention effects on office and/or ABP
Exercise training intervention (regular exercise)				
Blumenthal et al. (29)	C-LIFE: *N* = 90 (∼54 years, 48% female) SEPA: *N* = 50 (∼52 years, 48% female)	**C-LIFE** Diet Behavioral weight management **Supervised exercise**: **Modality**: aerobic training (bicycling and/or walking and eventually jogging) **Total duration**: 4 months **Frequency**: 3 sessions/week **Duration per session**: 50–65 min [10 min of warm-up exercises, 30–45 min of bicycling and/or walking (and eventually jogging)], and 10 min of cool-down exercises **Intensity**: 70-85% of heart rate reserve **SEPA (control condition)** Educational session DASH diet materials, weight loss targets (i.e., ∼ 1 lb/week) **Exercise goal**s (i.e., ≥150 min/week of aerobic exercise). Patients in SEPA did not participate in the intensive, structured C-LIFE program	RCT (parallel study)	↓ Office SBP ↓ 24-h and daytime ABP (SBP & DBP) ↓ Nighttime ABP (SBP)
Carvalho et al. (31)	Exercise (1): *N* = 5 (∼58 years, 80% female) Exercise (2): *N* = 6 (∼61 years, 67% female)	**Modality**: strength exercises (1): neutral rowing, squatting, dumbbell supine, knee extension with ankle weights, dumbbell development, dumbbell curl, knee flexion with ankle weights, standing plantar flexion, triceps pulley, and trunk flexion); aerobic exercises (2): stationary cycling elliptical ergometer, and upper-body cycle ergometer) **Total duration**: 12 weeks **Frequency**: 3 sessions/week **Duration per session**: 50-60 min **Intensity**: 50% of HRmax and 11-13 on the Borg's RPE scale	RCT (parallel study)	↓ 24-h and daytime ABP (SBP & DBP) with (2) — but not with (1)
Cruz et al. (18)	Exercise: *N* = 28 (∼54 years, 50% female) Control: *N* = 16 (∼52 years, 44% female)	**Modality**: resistance (callisthenic exercises against water resistance) + aerobic (walking) exercises **Total duration**: 12 weeks **Frequenc**y: 3 sessions/week **Duration per session:** 60 min **Intensity**: 11-13 on the Borg's RPE scale	RCT (parallel study)	↓ Office BP and 24-h ABP (SBP & DBP).
Dimeo et al. (20)	Exercise: *N* = 22 (∼62 years, 54% female) Control: *N* = 25 (∼67 years, 61% female)	**Modality:** aerobic exercise (treadmill walking) **Total duration**: 8–12 weeks **Frequency**: 3 sessions/week **Duration per session**: 30-36 min, including intervals of 3-15 min interspersed with 3-min walking intervals **Intensity**: slightly above the aerobic threshold	RCT (parallel study)	↓ 24-h and daytime ABP (SBP & DBP)
Guimaraes et al. (32)	Exercise: *N* = 16 (∼55 years, 50% female)	**Modality:** resistance (callisthenic exercises against water resistance) + aerobic (walking) exercises **Total duration**: 2 weeks **Frequency**: 3 sessions/week **Duration per session**: 60 min **Intensity**: HR between the anaerobic threshold and respiratory compensation point, and 11–13 on the Borg's RPE scale	Non-randomized controlled trial	↓ Office SBP ↓ 24-h and daytime ABP (SBP & DBP) ↓ Nighttime ABP (DBP)
Guimaraes et al. (19)	Exercise: *N* = 16 (∼55 years, 50% female) Control: *N* = 16 (∼52 years, 63% female)	**Modality:** resistance (callisthenic exercises against water resistance) + aerobic (walking) exercises **Total duration**: 12 weeks **Frequency**: 3 sessions/week **Duration per session**: 60 min **Intensity**: 11–13 on the Borg's RPE scale	RCT (Parallel study)	↓ Office SBP and DBP ↓ 24-h, daytime, and nighttime ABP (SBP & DBP)

(Continued)

TABLE 1 | Continued

Study	Number of participants analyzed (mean age, % female)	Exercise Intervention	Design	Main intervention effects on office and/or ABP
Kruk et al. (30)	Exercise: $N = 27$ (~55 years, 59% female)	Recommendations concerning diet and healthy lifestyle including physical activity (lifestyle modification) **Total duration**: 6 months	Non-randomized controlled trial	↓ Office SBP and DBP at 3 months ↓ Office DBP at 6 months
Lopes et al. (17)	Exercise: $N = 26$ (~59 years, 46% female) Control: $N = 27$ (~61 years, 44% female)	**Modality:** aerobic exercise (cycling and/or walking) **Total duration**: 12 weeks **Frequency**: 3 sessions/week **Duration per session**: 60 min **Intensity**: 50 to 70% of VO_{2max} (11-14 on the Borg's RPE scale)	RCT (parallel study)	↓ Office SBP ↓ 24-h and daytime ABP (SBP & DBP)
Acute exercise				
Pires et al. (16)	Exercise: $N = 10$ (~60 years, 60% female)	**Modality:** strength (air squat, vertical bench press, seated knee raises, seated row, dorsiflexion and plantar flexion, and shoulder abduction); aerobic (walking); combined exercise (aerobic + strength) **Duration:** 6 exercises with 4 sets of 12 submaximal repetitions and a 1-min interval between sets and exercises (strength); 45 min (aerobic); 25 min of aerobic exercise plus 6 exercises with 2 sets of 12 submaximal repetitions (combined) **Intensity**: moderate intensity (3-5 on the adapted Borg scale) (strength); 50–60% of HRmax (aerobic); 50–60% of HRmax and moderate intensity according to the modified Borg scale (combined).	RCT (cross-over study)	↓ 24-h ABP
Ribeiro et al. (27)	Exercise: $N = 19$ (~58.7 years, 47% female)	**Modality:** aerobic exercise walking **Duration:** 10 min **Intensity:** 3 km/h	Non-randomized controlled trial	↑ Central and peripheral SBP ↓ Central and peripheral DBP
Santos et al. (15)	Exercise: $N = 20$ (~53.8 years, 60% female)	**Modality:** aerobic exercise (cycling, light intensity); aerobic exercise (cycling, moderate intensity) **Duration:** 45 min **Intensity:** 50 and 75% of HRmax (or Borg's RPE equivalent for patients receiving beta-blockers)	RCT (cross-over study)	↓ 19-h ABP (DBP, with borderline significance ($p = 0.053$) for SBP) ↓ Daytime and nighttime ABP (SBP & DBP)
Ukena et al. (28)	Exercise: $N = 9$ (~64.9 years, 21% female) patients with RH without renal sympathetic denervation	**Cardiopulmonary exercise testing** (bicycle exercise in a 45° semi-supine position lying on a reclining ergometer)	RCT (parallel study)	No changes

ABP, ambulatory blood pressure; BP, blood pressure; C-LIFE, Center-Based Lifestyle Intervention; DASH, Dietary Approaches to Stop Hypertension; DBP, diastolic blood pressure; HR, heart rate; HRmax, maximum heart rate; RCT, randomized controlled trial; RPE, rating of perceived exertion; SBP, systolic blood pressure; SEPA, Standardized Education and Physician Advice; VO_{2max}, maximal oxygen uptake. ↑, increase; ↓, decrease.

Supplementary Figure 1). Participants of two studies (19, 32) were enrolled in a larger RCT (18). Therefore, we only considered the study with more participants (18).

One study was excluded because the same patients had also participated in previous published research (33). In addition, another study was excluded because analyses were solely focused on the BP effects of exercise training cessation (34).

Exercise Intervention

Studies assessing the short-term effects of a single acute exercise bout applied sessions of ~10–45 min of strength exercise [moderate intensity, corresponding to 3–5 on the adapted Borg' 0–10 scale of rating of perceived exertion (RPE)] (16), aerobic [50-75% of maximum heart rate (HRmax) (15), 50–60% of HRmax (16), walking at a speed of 3 km/h (27), incremental cycling test (28)], or combined exercise (aerobic exercise at 50–60% of HRmax and strength exercise at moderate intensity, corresponding to 3–5 on the adapted Borg's 0–10 RPE scale) (16).

As for regular exercise, training programs lasted 2 to 24 weeks and included 3 weekly sessions of ~30-60 min duration. Interventions included aerobic [at an intensity of 70-85% of heart rate reserve (29), 50-70% of peak oxygen uptake (17), or slightly above the aerobic threshold (20)] or combined training (i.e., calisthenics and walking against water resistance in a 30–32°C–heated pool at an intensity corresponding to 11–13 on the Borg's 0–20 RPE scale) (18). Three studies reported adherence to the intervention, which averaged 89–100% (17, 18, 29). No major adverse events were noted (e.g., no excessive hypertensive/hypotensive response) in any of the studies (17, 18, 20).

Quality Assessment

Both the studies assessing the effects of acute (**Supplementary Table 1**) and regular exercise (**Supplementary Table 2**) were of overall good quality (median total score = 6.5 and 11, respectively; quality score = 3 and 3.5; reporting score = 6.5 and 7.5).

Synthesis

Three of the four included studies that assessed the short-term effects of a single bout of acute exercise found a beneficial effect on at least one BP measure. Two RCT found significant benefits on ABP measures after acute exercise (15, 16). One study lacking a control group found benefits of acute exercise on central and peripheral DBP — but not on SBP (27). Finally, one study failed to report a significant reduction in SPB following cardiopulmonary exercise testing in patients with RH who had not undergone renal sympathetic denervation (28).

As for regular exercise, all six studies (17, 18, 20, 29–31) found significant reductions in office BP or ABP measures after exercise training intervention. Five studies showed significant benefits to 24-hour or daytime ABP measures (17, 18, 20, 29, 32), and one found significant benefits to nighttime ABP measures (29). Four studies (17, 18, 29, 30) reported a significant reduction in office BP measures. Three RCT could be meta-analyzed ($N = 144$; 50% female; mean participants' age ranging from 52 to 67 years; weighted average office BP and ABP of 148/83 mmHg and 134/77 mmHg, respectively) (17, 18, 20). Pooled analyses indicated that exercise training tended to decrease office SBP (p=0.059) while significantly reducing office DBP as well as all the different ABP measures (24-h, daytime, and nighttime SBP/DBP, respectively) with no sign of publication bias (all Begg's test $p > 0.15$) (**Table 2**). The results of 24-h and daytime ABP remained significant in sensitivity analyses. Due to the differences in study designs (i.e., no control group) (30, 31), inclusion of nutritional interventions together with exercise training (29, 30), and the fact that some participants were also enrolled in a larger RCT (19, 32), we could not meta-analyze more studies.

TABLE 2 | Pooled analysis of the effect of exercise training intervention on blood pressure (BP) measures in patients with resistant hypertension.

Outcome	MD (95% CI)	*p*-value	I^2 (%)	Significance remains in sensitivity analyses
Office BP				
SBP	−17.8 (−36.2, 0.6)	0.059	0.0	No
DBP	−6.1 (−11.7, −0.5)	0.032	4.2	No
Ambulatory BP				
24-h SBP	−9.9 (−15.4, −4.4)	<0.001	24.0	Yes
24-h DBP	−5.0 (−7.0, −3.0)	<0.001	0.0	Yes
Daytime SBP	−11.7 (−17.8, −5.7)	<0.001	25.9	Yes
Daytime DBP	−7.4 (−11.9, −2.9)	<0.001	10.7	Yes
Nighttime SBP	−9.9 (−19.6, −0.2)	0.045	19.8	No
Nighttime DBP	−4.5 (−8.0, −1.1)	0.010	0.2	No

Results are shown as absolute mean difference (MD, in mmHg) along with 95% confidence interval (CI).
DBP, diastolic blood pressure; SBP, systolic blood pressure.

DISCUSSION AND CONCLUSION

This is the first systematic review and meta-analysis of the exercise effects on BP in patients with RH. Our findings overall suggest that a single bout of acute exercise might reduce BP in the short-term (i.e., within ∼24 h) in these patients, although no meta-analysis could be performed. Moreover, "chronic" exercise training interventions (e.g., three sessions/week for up to 6 months) seem to induce significant reductions in office and ABP measures. These results might therefore support the role of exercise as an effective co-adjuvant treatment in patients with RH. This finding is of clinical relevance, particularly when considering that these individuals are at high risk of cardiovascular complications (1). In fact, subjects with elevated resting and/or exercise BP show a worse cardiorespiratory fitness — a strong predictor of CVD and associated mortality — than those with normal BP levels (35), and BP reductions considerably lower than those reported here (e.g., −1.0−2.0 mmHg) have been associated with a reduced risk of cardiovascular complications in people with hypertension in general (36, 37).

In line with our findings, a recent meta-analysis showed that a single bout of acute aerobic exercise induces short-term reductions on ABP measures in patients with hypertension (8). To the best of our knowledge, only four studies to date have analyzed the short-term effects of acute exercise on BP in patients with RH (15, 16, 27, 28), although results seem overall promising. Two randomized cross-over studies found a beneficial effect on ABP after different types of acute exercise in patients with RH (15, 16), and Ribeiro et al. found a significant reduction of central and peripheral DBP — but not SBP — after walking for only 10 min using a non-RCT design in a group of patients with RH (27). It must be noted, nonetheless, that Ukena et al. found no significant effects on SPB after cardiopulmonary exercise testing in patients with RH who had not undergone renal sympathetic denervation (28). Unfortunately, due to the differences in study designs and the paucity of available studies, we could not meta-analyze the effects of acute exercise on BP. Further research is thus needed to confirm whether the benefits of acute exercise previously corroborated in hypertensive patients in general also apply to patients with RH specifically.

The reductions of BP observed in the present study in individuals with RH after exercise training intervention are overall in line with those reported by us in a recent meta-analysis, in which we observed that exercise interventions with a duration of eight to 24 weeks decrease 24-h (average reduction of −5.4 and −3.0 mmHg for SBP and DBP, respectively), daytime (−4.5 and −3.2 mmHg), and nighttime ABP (−4.7 and −3.1 mmHg), respectively, in patients with hypertension in general ($N = 910$) (6). However, greater reductions of ABP seem to occur in patients with RH. These differences might be due to the so-called Wilder's principle (38) — that is, exercise induces larger effects in those patients with higher BP at baseline, such as those with the most severe hypertension phenotypes, notably RH. Other factors can

also be involved in these differences, notably the lower number of studies included in the present meta-analysis, which could have partly confounded our results, along with the fact that in one study exercise was performed in a heated pool, which can magnify the hypotensive effects of exercise *per se* (18).

Some limitations must be acknowledged, notably the limited number of studies meta-analyzed, which precluded us from performing sub-analyses attending to variables such as the characteristics of the interventions (in terms of exercise modality or total duration of the exercise training programs) or of the participants (notably, in terms of age, sex or medication status). More research is needed in order to identify the most effective exercise characteristics (modality, intensity, duration) for reducing office BP/ABP in patients with RH, as well as to confirm whether exercise training *per se* might allow reducing the number and/or dosage of drugs needed to manage BP in patients with this condition. The latter question is important because a reduction in medication is associated with lower mortality in individuals with RH (39). Finally, the long-term (i.e., more than 6 months) effects of exercise training intervention also remain to be determined.

In conclusion, our results suggest that exercise training interventions (8–12 weeks, 3 sessions per week, ideally combining aerobic activities at light-moderate intensities such as walking or cycling) as well as muscle strengthening sessions (such as light-moderate intensity weight lifting or calisthenics) decrease both "office" and ABP measures, with even a single bout of acute exercise potentially reducing BP within the following ∼24 h. Although further high-quality research (e.g., using a RCT design) is needed to confirm these findings as well as to corroborate the beneficial effects of a single bout of acute exercise on BP, physical exercise appears as an overall effective option to induce meaningful BP reductions in patients with RH.

AUTHOR CONTRIBUTIONS

AL, GS-L, and PV: study concept and design, methodology, supervision, interpretation of data, and drafting of the manuscript. PV: statistical analysis. All authors critically revised the manuscript for important intellectual content and approved 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.2022.893811/full#supplementary-material

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CASE REPORT
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Cardiovascular Effects of Whole-Body Cryotherapy in Non-professional Athletes

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Objectives: The study aimed to investigate changes in heart rate, blood pressure, respiratory rate, oxygen saturation, and body temperature in non-professional trained runners during whole body cryotherapy (WBC).

Methods: Ten middle-distance runners received 3 once-a-day sessions of WBC. Subjects underwent BP measurements and ECG recorded before and immediately after the daily WBC session. During WBC we recorded a single lead trace (D1) for heart rhythm control. In addition, the 5 vital signs Blood pressure, heart rate, respiratory rate, oxygen saturation, and body temperature were monitored before, during, and after all WBC session.

Results: We did not report significant changes in ECG main intervals (PR, QT, and QTc). Mean heart rate changed from 50.98 ± 4.43 bpm (before) to 56.83 ± 4.26 bpm after WBC session ($p < 0.05$). The mean systolic blood pressure did not change significantly during and after WBC [b baseline: 118 ± 5 mmHg, changed to 120 ± 3 mmHg during WBC, and to 121 ± 2 mmHg after session ($p < 0.05$ vs. baseline)]. Mean respiratory rate did not change during WBC as well as oxygen saturations (98 vs. 99%). Body temperature was slightly increased after WBC, however it remains within physiological values

Conclusion: In non-professional athletes WBC did not affect cardiovascular response and can be safely used. However, further studies are required to confirm these promising results of safety in elderly non-athlete subjects.

Keywords: cardiovascular systems, vital signs, heart rate, respiratory rate, oxygen saturation, whole-body cryotherapy, blood pressure

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INTRODUCTION

Whole body cryotherapy (WBC), short exposure to dry air at cryogenic temperatures, has recently been applied to recovery after injury during sports and to counteract the inflammatory response due to specific diseases, characterised by high levels of inflammation such as rheumatoid arthritis (1–3).

The use of cryotherapy as an alternative or in association with immersion in cold water is widespread among professional athletes and is also spreading among non-professional athletes. However, the latter carry out the treatment WBC without medical supervision. Consequently, it is important to know the effects of cold temperature on cardiovascular parameters, especially on blood pressure in order to define the level of safety of the procedure. WCR results in rapid and especially short-term exposure to low temperatures.

Recent reports suggest that one or more WBC sessions can induce anti-inflammatory effects (4). In a previous study, we analysed a large panel of cytokines, haematological, and hormonal parameters, as well as circulating mitochondrial DNA (1, 5). We found that in non-professional athletes, WBC induced beneficial immunological and metabolic responses and seems to promote tissue repair (1).

To our knowledge little is known about the effect of cryogenic temperature during WBC on cardiovascular parameters.

Using state of the art technologies, we investigated changes in heart rate, blood pressure, respiratory rate, and oxygen saturation in non-professional trained runners. In addition, we also evaluated changes in electrocardiogram immediately after WBC and after acute exposure.

METHODS

Subjects

Ten volunteer middle-distance non-professional runners were recruited by dedicated sport clubs for consecutive, 2-min WBC sessions, proposed over a 3-day schedule. The mean age was 38 ± 12 years. Subjects with known injuries or inflammatory diseases were excluded. During the study, the athletes' training programs were maintained from previous weeks: specifically, runners trained once a day (average 60 min/run). We selected a group of runners belonging to the same non-professional group who were used to training together. The training of runners was scheduled for alternating a day of 20-min run with an easy warm-up plus aerobic repeats and a day of 40/70 min of endurance running. No change in the running program was performed during the study. Training sessions were in the evenings. WBC sessions (as well as blood and urine collection) were conducted at lunchtime.

Lifestyle and cardiovascular risk factors were investigated. Specifically cardiovascular risk factors included: familiarity, blood lipid levels, smoking, hypertension, diabetes, body mass index. Caffeine consumption was evaluated: we investigated frequency and quantity of coffee (espresso coffee, cappuccino), tea and caffeinated drinks (including energy drinks and sports drinks).

The local Ethics Committee approved the study (Area Vasta Nord Emilia Romagna #88/2018/SPER/AUSLMO) and each subject provided written informed consent. Volunteers were involved in the reporting and dissemination of our research.

ECG

Subjects underwent BP measurements and ECG recorded before and immediately after the daily WBC session. During WBC we recorded a single lead trace (D1) for heart rhythm control. The following parameters were measured and compared before and after WBC session: heart rate (bpm), rhythm, QT and QTc intervals (msec), PR interval (msec), number of supraventricular ectopic beats (SE), number of ventricular ectopic beats (VB).

The study's workflow has been previously published (1).

Vital Signs and Cardiovascular Parameters

Non-invasive hemodynamic assessment will be determined by recording the 5 WHO recommended vital signs through electrocardiography and photo plethysmography signals, acquired from the subjects' hands, carefully calibrates the data according to mathematical models. ButterfLife® is a non-invasive patented medical device that records the 5 vital signs [heart rate (bpm), blood pressure (mmHg), respiratory rate (rpm), oxygen saturation (%), and body temperature (°Celsius)] simultaneously and provides an output of behaviour of the signs that can be easily analysed in real time or by remote clinical staff in telemedicine model. Every 5 s the software emits the 5 vital parameters in addition to the signals visible on the ECG monitor and photo plethysmography.

Thanks to the integrated artificial intelligence, the system acquires and sends data every 5 s and creates a trend of the parameters, allowing a reliable and customizable detection of the parameters over time, comparable with the previously recorded health data. An Integrated artificial intelligence algorithm elaborates parameter of Heart Rate Variability (HRV). The time-domain parameters of HRV evaluated were SD of RR intervals, root mean- squared difference in successive RR intervals, and percentage of successive RR intervals 50 ms different from one another. The frequency domain parameter of HRV evaluated will be high-frequency power (0.15 to 0.40 Hz). Sympathovagal balance will be assessed by low-frequency power/high-frequency power ratio. Vital signs recording allows for a simple assessment of the patient's underlying health conditions in order to proceed with safe and tailored exercise. It also allows the monitoring of clinical conditions during the WBC and changes of the hemodynamic function (6, 7).

Statistical Analysis

Quantitative variables were compared between pre- and post-WBC by the Wilcoxon matched pairs signed rank test or by two-way ANOVA and Sidak's multiple comparisons test. Correlations between values recorded with traditional methods and recorded with BF were explored with linear regression analysis. Multivariate analysis was performed to exclude potential confounding factors. Due to the correlation between heart rate and blood pressure these variables were analysed separately.

Potential confounders included cardiovascular risk factors and lifestyle habits, i.e., smoking habits, intake of energy drinks, and caffeinated beverages.

P-values < 0.05 were considered statistically significant. Statistical analyses were performed using Prism 6.0 (Graphpad Software Inc., La Jolla, USA).

TABLE 1 | Baseline characteristics of athletes.

Nr of subjects	**10**
Mean age (years)	38 ± 12
Mean BMI (kg/m2)	19.5 ± 2
Cardiovascular risk factors	
Hypertension nr of subjects and (%)	0 (0)
Type II Diabetes nr of subjects and (%)	0 (0)
Hypercholesterolemia nr of subjects and (%)	1 (10)
Smoking habitus (active or previous) (nr of subjects and (%)	7 (70)
Obesity (BMI > 30 Kg/m^2)	0 (0)
Energy drinks consumption (nr of subjects and (%)	4 (40)
Habitual coffee consumption	
(nr of subjects and (%)	6 (60)
Cardiovascular drugs	0 (0)
Beta-blockers	0 (0)
Lowering lipid drugs	0 (0)
Blood analytical chemistry	
Glucose (mg/dL)	80.60 ± 12.66
Urea (mg/dL)	35.40 ± 6.15
Creatinine (mg/dL)	0.90 ± 0.10
Cholesterol (mg/dl)	205.80 ± 51.85
HDL cholesterol (mg/dl)	66.80 ± 13.38
LDL (mg/dl)	125.40 ± 38.52
Triglycerides (mg/dl)	100.00 ± 43.52
GOT (U/L)	28.20 ± 8.11
GPT (U/L)	23.90 ± 13.49
GGT (U/L)	26.90 ± 21.28
CK (U/L)	262.30 ± 157.20
Amylase (U/L)	84.70 ± 21.03
Sodium (mEq/L)	139.50 ± 1.08
Potassium	4.30 ± 0.38
Iron (mEq/L)	100.70 ± 40.54
Cardiovascular vital signs	
Heart rate (bpm)	50.98 ± 4.43
Systolic Blood Pressure (mmHg)	118 ± 6
Diastolic blood pressure (mmHg)	76 ± 2
Respiratory rate (rpm)	14.5 ± 2
Oxygen saturation (%)	98%

HDL, high-density lipoprotein.

RESULTS

Clinical characteristics and blood analytical chemistry parameters of subjects are shown in **Table 1**. No change in the running program was performed during the study. Subjects were asymptomatic during all WBC sessions.

Changes in ECG Parameters

ECG was recorded before and after WBC session. We did not report significant changes in ECG main intervals (PR, QT, and QTc). Mean heart rate changed from 50.98 ± 4.43 bpm (before) to 56.83 ± 4.26 bpm after WBC session ($p < 0.05$). During WBC we recorded rare supraventricular ectopic beats in 2 subjects. No ventricular ectopies were registered during WBC sessions.

Changes in Vital Signals Parameters

The mean heart rate before WBC was 51.75 ± 4.56 bpm, changed to 57.23 ± 5.12 bpm during WBC ($p < 0.01$) and to 61.5 ± 3.67 bpm after session ($p < 0.05$). The trend was an increase of the heart rate during exposure to very low temperature, however values remain within normal range. This trend reduced from the first to the last sessions (**Figure 1**).

The mean systolic blood pressure did not change significantly during and after WBC (baseline: 118 ± 5 mmHg, changed to 120 ± 3 mmHg during WBC and to 121 ± 2 mmHg after session ($p <$ 0.05 vs. baseline). **Figure 2** shows changes in systolic and diastolic blood pressure during the WBC sessions. All subjects showed an increase of values after WBC however changes were small and values remained within normal range.

Mean respiratory rate did not change during WBC (before 14.5 ± 2 rpm changed to 15 ± 1 rpm) as well as oxygen saturations (98% vs. 99%) (**Figure 3**).

Body temperature was slightly increased after WBC; however, it remains within physiological values. After the completion of the WBC treatments, the skin temperature normalised very quickly.

Due to the small number of subjects included in the study and the homogeneous characteristics of population we could only include smoking habits and the intake of energy drinks and caffeinated drinks as confounding factors. We found no significant differences in results after analysing the results according to these variables.

DISCUSSION

The current study evaluates the cardiovascular effects of WBC treatment in non-professional male runners. The main feature of the present study was that WBC did not change cardiovascular parameters.

WBC has been shown to be very effective on human health especially in its action on inflammation and muscle damage related to high exercise. The effects on inflammatory biomarkers (IL-6, IL 9 etc) are reported in several studies as well as the effects on the lipid and hormonal structure (1–3). The use of cold to reduce the inflammatory response triggered by strenuous physical activity is widespread among high intensity professional and non-professional athletes (1, 8). According to that reported in previous studies, WBC had an overall beneficial effect of on lipid, glucose, and protein metabolism (1). The effects on lipid levels were reported after at least 10 WBC sessions. In a previous study, we found an improvement of HDL after 3 sessions of WBC suggesting a sub-acute effect (9, 10). WBC also acts on skeletal muscle contraction and fatigue (11, 12). Furthermore, one of the most frequent complications in athletes, especially in the elderly, are cramps. Muscle cramp is a sudden, severe, and involuntary muscle contraction or excessive shortening. Symptoms range from mild to severe pain to paralysis-like immobility (13).

Several hypotheses have been advanced to explain the origin of muscle cramp induced by exercise, i.e., dehydration and

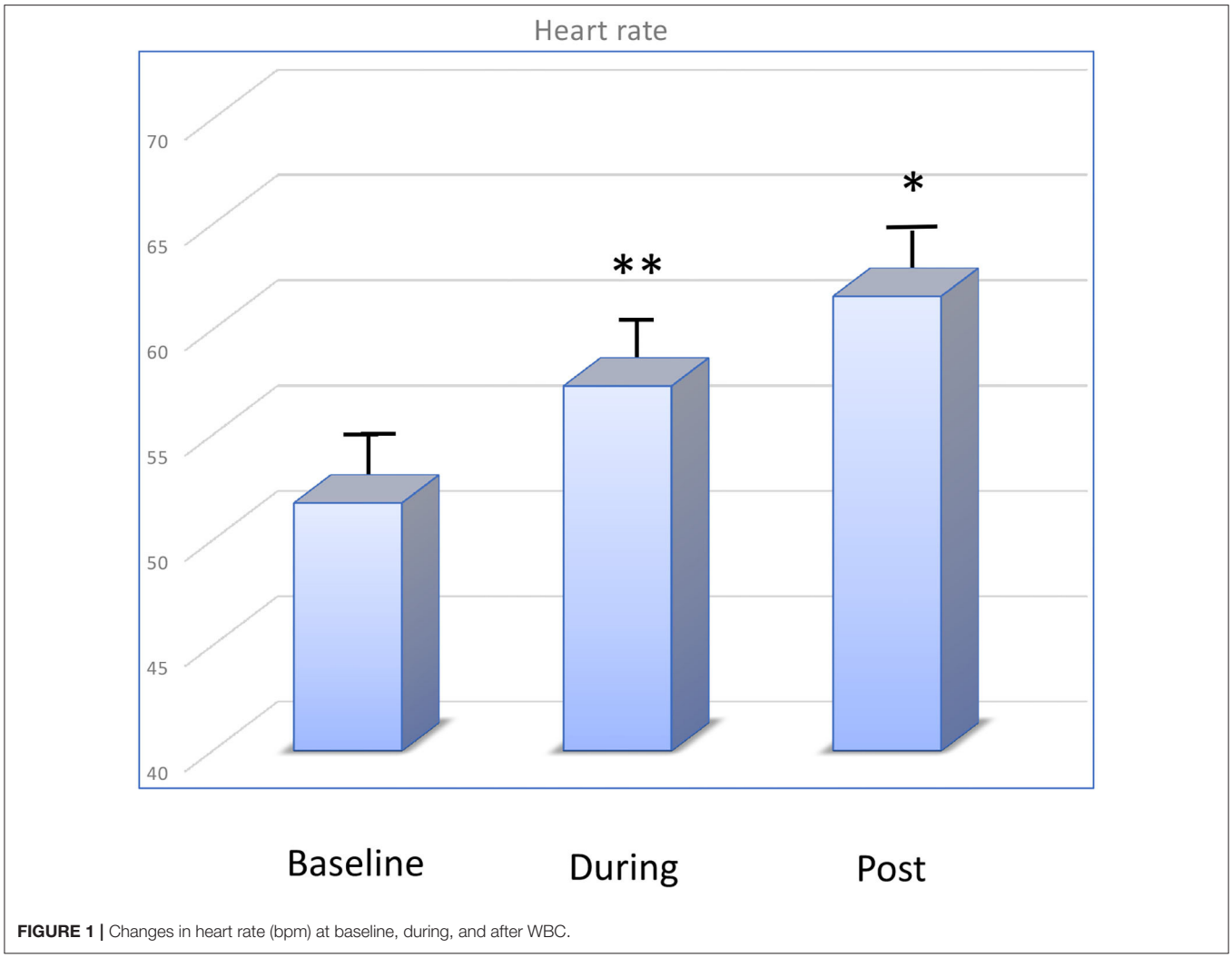


FIGURE 1 | Changes in heart rate (bpm) at baseline, during, and after WBC.

electrolyte depletion hypothesis and neuromuscular hypothesis (13). In both cases a trigger for muscle cramps is high-humidity environment and elevated heat conditions. Although there is no evidence that WBC has beneficial effects on cramps, the climatic conditions generated by exposure to cold could counteract the appearance of exercise-induced cramps. This hypothesis is at the moment theoretical and to be proved but certainly compelling.

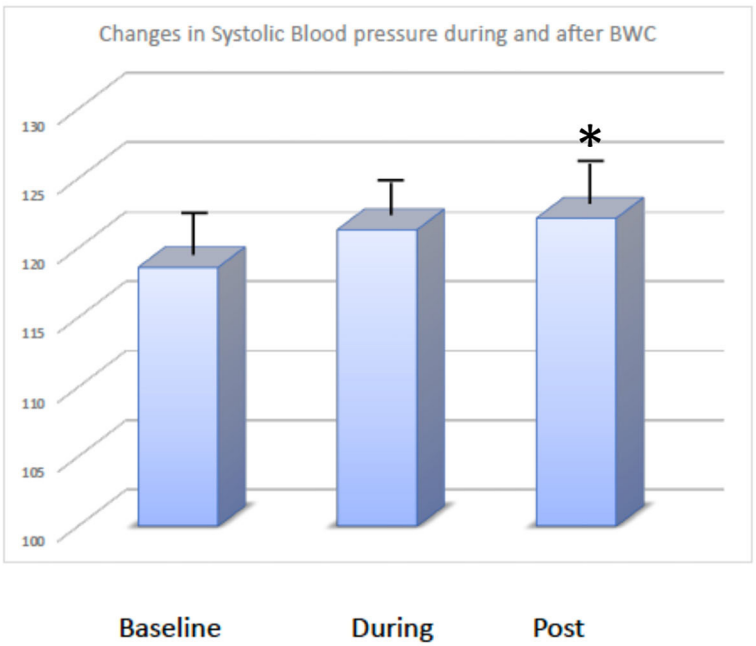
Little is known about the cardiovascular effects of WBC. Previous studies have reported an increased risk of myocardial infarction, stroke, and blood pressure when the external temperature decreases (14–16). The mechanisms proposed to explain this association are systemic inflammation, thrombosis, and vasoconstriction (17). However, most of the studies refer to the external temperature; on the contrary, the evidence on the cardiovascular effects of rapid exposure to cold is scarce. BMI and fat could influence cardiovascular effects induced by exposure to cold temperature. Young runners usually have a low BMI with high muscle and low fat. However, BMI is not a good measure for athletes because it does not allow evaluating differences in lean body mass and fat mass. Conventional Bioelectrical Impedance Analysis or Bioelectrical Impedance Vector Analysis can give more reliable details about body composition differences in competitive and non-competitive subjects, outlining a progressive decline in ECW and increase in ICW without affecting TBW composition of athletes (18, 19).

Nonetheless, exposure to cold through WBC is a habit that is spreading for selective reduction of adipose tissue, anti-ageing, and as a release of stress (20–23).

Wiecek and colleagues found that repeated whole-body exposure to cryogenic temperature increased inducible nitric oxide synthase (iNOS) concentration in senior subjects, regardless of their physical activity level (22).

We evaluated cardiovascular safety of WBC through measurements of vital signs during sessions. The new patented and certified system we used allow us to get data during all treatment exposure. The average and standard deviation of vital parameters calculated for both the ButterfLife and the reference methods show an accurate and repeatable accordance between the devices (Data showed in **Supplemental Materials**). Systolic, diastolic, and mean blood pressure showed a small change

A



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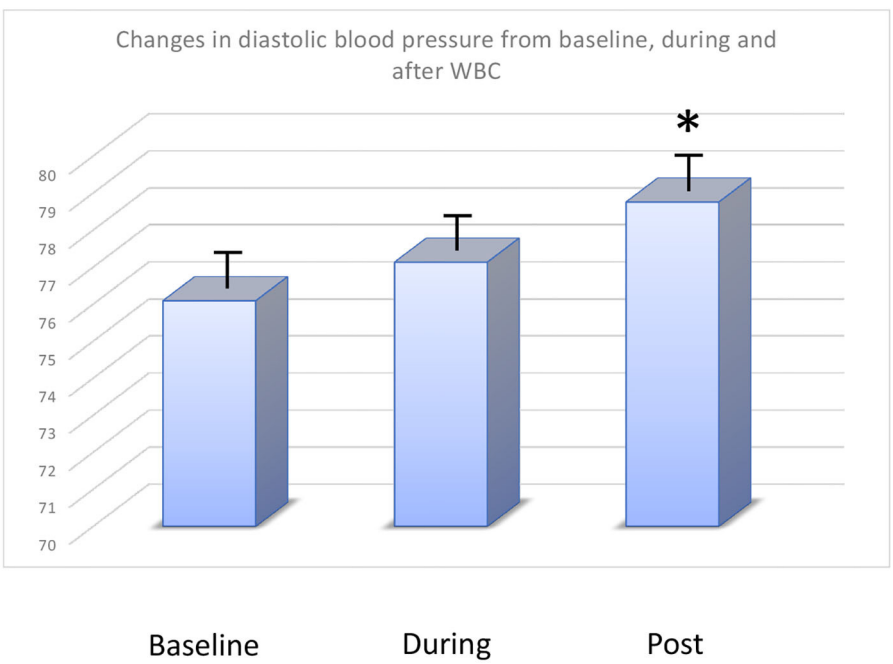

FIGURE 2 | (A) Changes in systolic blood pressure (mmHg) at baseline, during, and after WBC. **(B)** Changes in diastolic blood pressure (mmHg) at baseline, during, and after WBC.

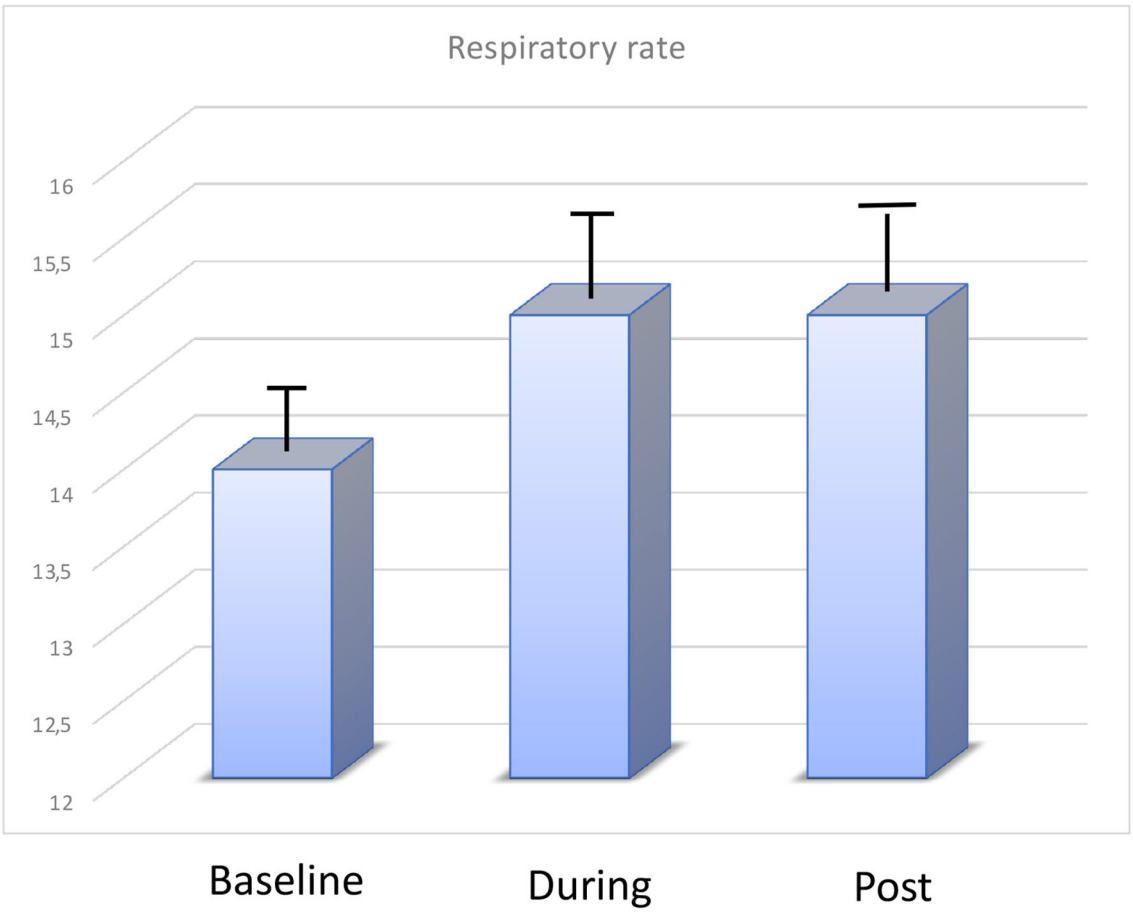

FIGURE 3 | Changes in respiratory rate (rpm) at baseline, during, and after WBC.

during WBC and these changes attenuates during repetitive exposure supporting the hypothesis that the first value recorded during the first exposure are induced by sympathetic activation. Similarly, heart rate and respiratory rate showed small changes during cold exposure and come back to previous values quickly. Oxygen saturation did not change during WBC. All these data suggest that WBC can be used safely in young athletes.

Limitation of the study. The main limitation of the study is the low number of subjects included in the study. The selection of patient populations was very strict to avoid bias, as previously stated the runners belong to the same non-professional group who were used to training together. A second limitation is the young age of the study subjects, which makes it difficult to transfer the results to the population of older non-professional athletes.

However, from a practical clinical point of view, the knowledge of the effects of acute cold on cardiovascular parameters is important to prevent unexpected and dangerous events, especially due to the widespread diffusion of physical activity and sports even in non-professional subjects. WHO guidelines suggest increased physical activity as a way to prevent non- communicable diseases, but when it comes to adults and elderly, it is important to expand our knowledge on safety (24–28).

Further investigations are needed to evaluate its safety in elderly non-professional athletes and also in elderly non-athletes.

CONCLUSIONS

As a whole, a main conclusion can be drawn from the present study. In non-professional athletes WBC did not affect cardiovascular response and may be a protagonist in promoting a safety process of tissue repair. However, further studies are required to confirm these promising results of safety in elderly non-professional athletes and also in elderly non-athlete subjects.

INTEREST IN THE FIELD

Whole body cryotherapy (WBC) seems to have a beneficial effect on tissue repair, innate, and adaptive immune systems in non-professional male athletes. In recent years, WBC has also spread to non-professional athletes and adult/elderly subjects for its anti-inflammatory and anti-aging effects. It becomes essential to verify the safety of this method especially at the cardiovascular level.

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 (Area Vasta Nord Emilia Romagna #88/2018/SPER/AUSLMO). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

FC, MN, AC, AM, VS, and GZ contributed to the conception and the design of the work. MN, AM, and PL contributed to the draught and the final approval of the manuscript. FC, MN, AC, and AM contributed to the interpretation of data. RD'A, PL, GS, and FT enrolled the subjects for the study. All authors contributed to manuscript revision, read, 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.2022.905790/full#supplementary-material

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OPINION
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Teaching Gender Differences at Medical School Could Improve the Safety and Efficacy of Personalized Physical Activity Prescription

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INTRODUCTION

The most recent scientific evidence on gender medicine indicates that the teaching of gender medicine is fundamental in the training of doctors and health professionals. This opinion paper aims to focus attention on the benefits of systematic teaching of gender medicine to improve the safety and efficacy of prescribing personalized physical activity and sport.

The practice of physical activity and sport has become extremely widespread in the elderly adult population also following the indications of the WHO Global Action Plan on Physical Activity 2018–2030 which indicates the prescription of physical activity for the prevention of non-communicable diseases (1).

A recent manuscript points out that implicit prejudice education is effective in raising awareness of prejudice regardless of personal beliefs (2).

Raising awareness of bias is one of many steps toward creating a positive learning environment and a more equitable healthcare system (2).

GENDER MEDICINE

Gender bias in medicine persists and affects patient care, trainee assessment, and organizational climate (3).

Cardiovascular (CV) diseases are an important example because they have different characteristics in both symptoms and prognosis in women and men (4).

The study of gender medicine in the CV field has led to the identification of specific CV risk factors for women related to hormonal life and hormonal changes over time.

Risk factor analysis is an example of how gender medicine can modify CV risk stratification. Traditional risk factors have been studied on predominantly male populations inducing the erroneous belief that the only relevant risk factor in women is menopause. Indeed, menopause acts as an important risk factor because it is associated with a series of modifications of traditional risk factors such as obesity. With menopause, there is a change in obesity that becomes visceral obesity and the appearance of the phenomenon known as sarcopenic obesity (5).

Other specific risk factors for women have been identified: i.e., hypertension and gestational diabetes. In addition to this, the same traditional risk factors are known to carry a different weight in women than in men. An important role is also the social and economic conditions.

Throughout a woman's life, hormonal variations affect exposure to different sex-specific risk factors at different ages. The best-known example is menopause, which marks an increase in the CV risk in women caused by the modification of the hormonal and metabolic balance (4). The menopausal woman develops visceral obesity, an important CV risk factor. During the fertile period, pregnancy is a critical moment. In recent years it has emerged that the onset of diseases, such as gestational diabetes and hypertension, affects a future risk of developing atherosclerosis (4, 6).

An independent risk factor for maternal and neonatal morbidity and mortality is pre-pregnancy obesity (7). Maternal obesity is associated with a higher risk of gestational diabetes, hypertension, preeclampsia, and adverse birth outcomes with an increased risk of cesarean delivery and wound complications (7).

Physical activity is an excellent tool to fight against obesity, and women must use it both during pregnancy and after menopause. The World Health Organization (WHO) recommends that "women who, before pregnancy, habitually engaged in a vigorous-intensity aerobic activity or who were physically active, can continue these activities during pregnancy and the postpartum period" (8). Additionally, encouraging pregnant women to engage in exercise programs is crucial in managing their weight gain and maintaining a healthy lifestyle (9).

Women are less likely to engage in physical activity and sports from an early age affected by an ancient social role (10). A sedentary lifestyle is more common in women and appears to have a greater CV effect in women than men. The recent pandemic has shown that women have suffered from increased stress, which has been reflected in poor diet, reduced physical activity, and increased sedentary lifestyle (11, 12). Psychosocial disadvantages (e.g., unemployment, chronic stress, insufficient social support, and social isolation) are more common in women than in men, which contributes to increased depression and anxiety (13). Moreover, the situation worsened significantly during the pandemic (13, 14).

Socio-economic factors affect CV risk with different effects in women and men. The knowledge of these differences would determine an adequate stratification of the risk to introduce tailored prevention actions (13, 14).

Many factors contribute to the gender bias in diagnosis and management of CVD: gender disparity in clinical evidence studies, which have a low percentage of women, the lack of CV disease research specifically dedicated to women, insufficient education specifically aimed at women on CV risk factors specific to women, underestimation by the national health system the prevalence of CVD among women, under evaluation of symptoms, and poor perception of subjective risk (15, 16) (**Table 1**).

The lack of gender-specific clinical guidelines can adversely affect patient care, particularly for women with hypertension or diabetes, for whom therapy often fails to meet its goals (17).

A recent position paper underlines that sex and gender should be incorporated into the design of prospective trials to ensure that outcomes and the implementation of findings are broadly and appropriately applicable to patient care (17).

In recent years, medical awareness of CV risk in women has increased, somewhat reducing the phenomenon of underdiagnosis of CVD. However, most healthcare professionals and female patients themselves still tend to underestimate the CV risk in women (4).

Although the same proportion of women and men present with chest pain of CV origin in ambulatory care, there is a strong sex bias in their management; men were 2.5 times more likely to be referred to a cardiologist than women. These data suggest that effort must be made to assure equality between men and women in medical care (18).

Moreover, several studies have shown that the perception of CV risk in women themselves has not changed, despite intense information and prevention campaigns (19). Sex-specific mechanisms in the pathophysiology of CV disease in women remain poorly understood.

Gender-dependent differences in morphological and functional aspects of body composition, as well as the well-recognized sexual dimorphisms in metabolic substrates, not only influence the risk, diagnosis, and therapeutic management of CVD, but also cardiac rehabilitation, e.g., after coronary artery bypass grafting (CABG) (20, 21).

Gender, besides body composition and age, strongly affects cardiac rehabilitation; older women post-cardiac surgery are characterized by a higher disability index in relation to tolerance to physical stress in comparison with men of the same age (21).

All these subjective, as well as objective, factors contribute to invalidating efforts in the field of prevention and in encouraging the adoption of healthy lifestyles and therapies (22).

How to counter these established and unhealthy habits? An effective strategy must include a different approach in women than in men and the basis for this strategy must include the systematic teaching of gender medicine.

GENDER BIAS IN MEDICAL EDUCATION

In a review of gender bias in resident physician assessment, five out of nine studies found that gender bias potentially influenced the assessment of resident physicians (23).

Medical schools now average approximately 50% female students, yet a disproportionate number of women continue to choose non-surgical over surgical specialties (23, 24). Once in training, studies indicate that pervasive gender stereotypes, sexism, and harassment negatively affect female surgeons (24).

Gender bias leads to negative experiences for women trainees in a surgical specialty, and women trainees in the male-dominated specialty are more prone to leave medicine and retire early (18). Previous studies have offered theories as to why women do not enter surgical specialties or assume leadership roles (23, 24). These include a paucity of role and family models' responsibilities (25). However, these studies did not take into account the influence of gender discrimination in

TABLE 1 | Gender differences in the cardiovascular field that could be corrected by teaching gender medicine.

1. Cardiovascular diseases are underdiagnosed and undertreated in women.
2. Women experience an inappropriate reduction in the dosage of cardiovascular drugs, especially if they are elderly.
3. Women are less likely to be screened for cardiovascular risk factors for prevention.
4. The pathophysiological mechanisms for cardiovascular disease in women and sex-specific cardiovascular risk factors are poorly studied.
5. The impact of psychosocial and socioeconomic factors on cardiovascular risk burden in women is underestimated.
6. There is a reduced perception of cardiovascular risk in women.

discouraging women from pursuing surgery or surgical subspecialty (25).

Furthermore, men continue to outnumber women in most medical specialties, and in some of the larger specialties, there are three times as many men as women. As an example: in cardiology, 82% of doctors are men, as well as in gastroenterology and hepatology where 73% of doctors are men (26). Overall, 58% of consultants and higher specialization trainees (aged 3–8) are men, although in some major specialties, there is a more uniform gender division (26).

GENDER MEDICINE IN SPORTS AND PHYSICAL ACTIVITY

Specific information on the different structures of muscle and joints, the different responses of the muscle to physical activity, and the different musculoskeletal pathology in women and men help to create a culture of personalized non-pharmacological prescriptions for physical activity.

The effectiveness of the systematic teaching of a procedure has been extensively studied in cardiopulmonary resuscitation where the spread of teaching resuscitation maneuvers has resulted in an improvement in response and survival in out-of-hospital cardiac arrest (27, 28).

Several studies showed that men and women adapt differently to endurance exercise (29, 30). Nonetheless, relative to body size, men and women can achieve comparable gains in strength and fitness after exercise training (27, 30). However, the mechanisms driving sex-specific adaptation to exercise are largely unknown.

It is also well-known that men and women differ in substrate utilization during endurance exercise. Many studies have shown that women rely less on carbohydrate and protein sources and more on fat sources to support substrate oxidation during endurance exercise (31). These sex differences may partly be explained by estrogen concentration and activity (32).

Moreover, there are sex differences in fiber type distribution and cross-sectional area in many muscle groups (33).

Women tend to have a higher percentage of slower type I and IIA fibers compared with men. This reflects the lower contractile velocity and the enhanced fatigue resistance of women, as oxidative fibers allow for enhanced endurance and recovery. Despite the multitude of research conducted on exercise genomics, there is still a lack of knowledge on specific genes. The reason is that exercise-related phenotypes are polygenic and influenced by many other factors, which make it challenging to identify genes with large effect sizes (33). Sex-based differences in exercise muscle metabolism strongly impact exercise and nutritional strategies: all these parameters/conditions are to be taken into account to optimize not only performance in women but also, and more importantly, the overall women's health (20).

Gender medicine is not yet widespread in medical education; however, it is essential to move in this direction (34).

The increase in knowledge will lead to a more effective approach. Moreover, one of the risks of spontaneous physical activity is CV safety. The stratification of the risk level of developing events must also be based on the different weight of traditional CV risk factors, on the assessment of emerging risk factors, and on the different pathophysiological responses of the musculoskeletal system in the two sexes (35). Similarly, inflammatory and immunologic responses are different in the two sexes.

It is also well-known that there are differences in the development of arrhythmias and the epidemiology of channelopathy. Cellular electrophysiological sex differences have been found for the action potential sodium, calcium, and potassium currents, which affect both depolarization and repolarization cycles (9).

Women have a higher risk of drug-related arrhythmia from drugs that block potassium currents in the cardiomyocyte channel. These drugs include not only antiarrhythmic drugs but also CV and non- CV drugs, such as antidepressants, antifungals, and antihistamines (9).

It is essential that sports and health professionals know these differences to identify early the subjects at risk; assuming that the different risk between men and women is determined not only by the influence of hormones but also by the environment and genetics (36).

The recent pandemic has led to important developments in teaching and distance learning, as well as in university and post-graduate training (37, 38).

With the rise of innovative virtual learning solutions, medical educators will need to leverage technology to develop e-learning materials that facilitate effective adult learning. This approach should include all issues relevant to medical education including gender medicine. The use of technology-based training solutions has been approved in several guidance documents for CV medicine trainees in several countries (39). Recommendations have been published to better address the challenges of digital health implementation in CV medicine (40). These experiences, gained during such a dramatic moment for public health, must be adapted to the post-pandemic reality in order not to lose valuable tools for learning.

A new frontier will be health and safety for transgender athletes. The gender-affirming medical and surgical treatments and the unique ways the musculoskeletal system could be

affected by each, such as impaired bone health, changes in ligament function, and the potential increased risk of deep venous thromboembolism, are essential for providing optimal musculoskeletal care for transgender athletes (41, 42).

CONCLUSION

We must act promptly with a series of actions on medical school programs adapted to sex differences in medical practice in order to reduce the gap between men and women. Physical activity therapy prescription should be personalized and take into account gender differences in muscle and joint structure to optimize the outcome.

AUTHOR CONTRIBUTIONS

AM, MN, MP, and CP contributed to the conception, design of the work, draft, and the final approval of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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Holter-determined arrhythmias in young elite athletes with suspected risk: Insights from a 20-year experience

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Purpose: We assessed the occurrence of rhythm alterations in elite athletes with suspected risk using Holter monitoring, and the association of Holter-determined rhythm alterations with echocardiographic findings.

Methods: A large cohort of Spanish elite athletes (N = 6,579, 34% female) underwent in-depth cardiological examination (including echocardiographic evaluation, and resting and exercise electrocardiogram [ECG]) between 01/02/1998 and 12/31/2018. Holter monitoring was performed in those reporting cardiovascular symptoms, with suspicion of cardiac structural abnormalities potentially associated with dangerous arrhythmias, or with resting/exercise ECG features prompting a closer examination. We assessed the occurrence of cardiac rhythm alterations, as well as the association between echocardiography-determined conditions and rhythm alterations.

Results: Most athletes (N = 5925) did not show any sign/symptom related to arrhythmia (including normal resting and exercise/post-exercise ECG results) whereas 9.9% (N = 654; 28% female; median age, 24 years [interquartile range 19–28]; competition experience [mean ± SD] 10±6 years) met the criteria to undergo Holter monitoring. Among the latter, sinus bradycardia was the most common finding (present in 96% of cases), yet with a relatively low proportion of severe (<30 bpm) bradycardia (12% of endurance athletes during night-time). Premature atrial and ventricular beats were also common (61.9 and 39.4%, respectively) but sinus pauses ≥3 s, high-grade atrioventricular blocks, and atrial fibrillation/flutter were rare (<1%). Polymorphic premature ventricular contractions (PVC, 1.4%) and idioventricular rhythm (0.005%) were also rare. PVC couplets were relatively prevalent (10.7%), but complex ventricular arrhythmias were not frequent (PVC triplets: 1.8%; sustained ventricular tachycardia: 0.0%; and nonsustained ventricular tachycardia: 1.5%). On the other hand, no associations were found between arrhythmias (including

their different morphologies) and major cardiac structural alterations (including mitral prolapse). However, an association was found between mild mitral regurgitation and supraventricular (odds ratio 2.61; 95% confidence interval 1.08–6.32) and ventricular (2.80; 1.15–6.78; $p = 0.02$) arrhythmias, as well as between mild or moderate mitral regurgitation and ventricular arrhythmias (2.49; 1.03–6.01).

Conclusions: Irrespective of the sports discipline, "dangerous" ventricular arrhythmias are overall infrequent even among young elite athletes who require Holter monitoring due to the presence of symptoms or abnormal echocardiographic/ECG findings, and do not seem to be associated with underlying serious cardiac structural pathologies.

KEYWORDS

cardiac rhythm, ECG, sports, echocardiography, Holter monitoring

Introduction

Elite athletes represent the top tier in competitive sports, and their long-term strenuous training regimes induce unique physiological adaptations, particularly at the cardiovascular level (1). This includes changes not only in cardiac dimensions (such as left ventricular hypertrophy) but also in electrical activity (mainly sinus bradycardia) (2, 3). In this regard, although regular moderate exercise confers protection against cardiac (including fatal) arrhythmias, principally by improved autonomic balance (4), concerns exist as to whether strenuous—especially endurance—exercise might have the opposite, nonphysiological effect, with elite athletes potentially at high risk of arrhythmias (5–7), including dangerous arrhythmias. Several studies have reported the prevalence of ventricular arrhythmias and sinus pauses in athletes of different training levels (8–11), but relatively scarce data are available in highly competitive (i.e., "elite") athletes based on Holter monitoring (9, 11–16), the method that provides more information for detection of cardiac rhythm alterations than resting 12-lead electrocardiogram (ECG) recordings.

In the present study, we analyzed the occurrence of cardiac rhythm alterations in a large group of elite athletes who underwent Holter monitoring due to suspected risk. We also assessed the potential association between Holter-determined cardiac rhythm alterations and echocardiography-determined cardiac abnormalities. Our main hypothesis was that cardiac rhythm alterations are very infrequent in elite athletes.

Materials and methods

Study design and participants

The present study follows the "Strengthening the Reporting of Observational Studies in Epidemiology" (STROBE) guidelines. The study was conducted at the Cardiology Department of the 'Consejo Superior de Deportes' (CSD, Madrid, Spain). In this center, Spanish elite athletes of different disciplines who are part of the national team in their specialty and compete in major international events (e.g., Olympic Games, European or World championships) undergo in-depth cardiological evaluation (≥1 per year). The study was approved by the local Ethics Committee (IRB #1385226-1) and complies with the Declaration of Helsinki and its later amendments. Oral or written consent was obtained from all participants.

All cardiological evaluations performed between January 2nd, 1998 and December 31st, 2018 were retrospectively reviewed. During this period, each elite athlete underwent at least one complete evaluation that included medical history, physical examination, resting 12-lead resting ECG, and echocardiography evaluations (see below), and exercise testing for cardiorespiratory fitness (maximum oxygen uptake, VO_2max) determination together with 12-lead ECG recordings, as detailed by us elsewhere (17, 18). Echocardiography evaluations were conducted using a Toshiba SSH-140A system (Toshiba Medical Systems, Tochigi, Japan) equipped with 2.5- and 3.75-MHz probes, or a Phillips Sonos 7500 system (Advance Diagnostics, Palo Alto, CA) equipped with a color, tissue Doppler, multifrequency 2-4 MHz transducer. All measurements were taken independently by two experienced sonographers (A.B. [>30-year experience] and M.E.H. [>15-year experience], 15 years working together), with all the evaluations ultimately supervised by the same researcher (AB). Ventricular and atrial dimensions were measured using two dimensional (2D)-guided M-mode imaging and 2D imaging, respectively, following American Society of Echocardiography recommendations (19). Left ventricular diastolic function was assessed by measuring transmitral flow rate (pulsed-wave Doppler, apical four-chamber view) and determining E and A wave velocities, also following ASE recommendations (20). All participants were assessed under resting conditions (i.e., during

morning hours or early afternoon, after a rest period from the last exercise training session of at least 12 hours).

In addition, Holter monitoring was conducted in those athletes meeting one or more of the following criteria at any given time point during the aforementioned period: family history of sudden cardiac death and/or cardiomyopathy, reporting cardiovascular symptoms (palpitations at rest, syncope, dizziness, chest pain); reaching abnormally/unexpectedly high heart rates during training sessions; suspicion of cardiac structural abnormality potentially associated with an increased risk of dangerous arrhythmias (i.e., cardiomyopathies of any type); showing resting and/or exercise ECG features prompting a deeper examination (i.e., bradycardia <40 bpm in resting ECG or sinus pauses, atrioventricular [AV] and fascicular blocks); atrial fibrillation (AF) or flutter, Wolf-Parkinson-White syndrome, paroxysmal supraventricular tachycardia, frequent premature ventricular contractions (PVC) in resting (i.e., ≥ two in 10 s) or exercise/post-exercise ECG (isolated, couplets or triplets), or long QT in resting ECG. Holter monitoring ECG recording was performed continuously for 24 h (or 48 h in those athletes with long QT or suspected cardiomyopathy) by means of a 3-channel, 7-lead SEER Light recorder (GE Healthcare, Milwaukee, WI), using MCL1 to determine PVC morphology (i.e., left [LBBB] or right bundle branch block [RBBB]), III to determine PVC axis, and CM5 to corroborate PVC morphology and to assess the potential presence of ischemia. The totality of Holter data were analyzed by the same researcher that supervised all the echocardiographic evaluations (i.e., A.B.). using GE MARS PC Holter software (GE Healthcare). Each Holter record was subjected to beat-to-beat inspection for artifact removal and cardiac rhythm classification. Participants used a diary to register any symptoms and also their waking up and sleeping times. The following outcomes were determined for each evaluation: bradycardia, atrial rhythms (premature atrial beat, AF/flutter, wandering pacemaker, supraventricular tachycardia), junctional rhythms (premature junctional beat, idioventricular rhythm), ventricular rhythms (PVC, ventricular tachycardia), sinus pauses above 2 or 3 s, AV blocks (1st, 2nd, high-grade and 3rd degree, respectively), isolated PVC (1–99, 100–999, ≥1,000, and the different PVC morphologies).

Statistical analysis

Data are presented as mean (standard deviation) for continuous variables (and as mean [interquartile range] for age) or as frequency (percentage) for categorical variables unless otherwise stated. In those athletes with more than one Holter evaluation, only data from the evaluation showing cardiac rhythm alterations was used (or alternatively the most recent evaluation in the case that no alterations were found). The normal distribution of the data was assessed with the Shapiro-Wilk test and confirmed by visual inspection. Unpaired Students' *t* test was used to compare the main characteristics of athletes undergoing or not, respectively, Holter evaluations. In those athletes undergoing Holter evaluation, a one-way analysis of variance was used to assess differences between types of sport (i.e., skill, power, mixed or endurance). The Greenhouse-Geisser correction factor was applied when the assumptions of sphericity were violated. When a significant group (i.e., "main type of sport discipline") effect was found, the Bonferroni test was used *post hoc* for pairwise comparisons. The chi-squared test (or Fisher's exact test if >20% of the cells in the cross-table had an expected frequency <5) was used for the analysis of categorical variables. Logistic regression analysis was used to assess the potential association between arrhythmias and echocardiography-determined abnormalities. Analyses were conducted using SPSS 20.0 (IBM, Armonk, NY) and significance was set at $p < 0.05$.

Results

A total of 19,662 in-depth cardiological evaluations were performed during the 20-year study period in 6,579 elite athletes, with each athlete undergoing on average three complete evaluations and 63% of athletes undergoing two or more evaluations. There were no missing data. The main characteristics of the study cohort were as follows: age median age 24 years (19–28), 34 % female, body mass index 22.6 ± 16.2 $kg{\cdot}m^{-2}$, training volume 19 ± 9 h/week, 8 ± 5 years in competition, and VO_2max 53.7 ± 9.4 $ml{\cdot}kg^{-1}{\cdot}min^{-1}$.

Of the total sample, 654 athletes (9.9% of total, 28% female) underwent Holter monitoring at least once as part of their cardiological evaluation (see more details in Figure 1). Most of these athletes (81%) underwent a single Holter evaluation whereas 83 (13%) and 39 (6%) underwent two and three or more evaluations, respectively, with all evaluations including at least one hard training session. The main characteristics of the athletes who underwent or not Holter monitoring, respectively, are shown in Supplementary Material. The former group had a lower proportion of women, a higher proportion of endurance athletes, a younger age (with less years in elite competition), higher VO_{2max} values and resting ECG-determined heart rate, and overall larger cardiac dimensions.

The descriptive characteristics of study participants undergoing Holter evaluation attending to the main type of sport discipline are shown in Table 1. Concisely, resting ECG-determined heart rate as well as Holter-determined average day and night-time heart rate values ranged in the following order: skill > power > mixed > endurance. The opposite trend was found for VO_2max levels.

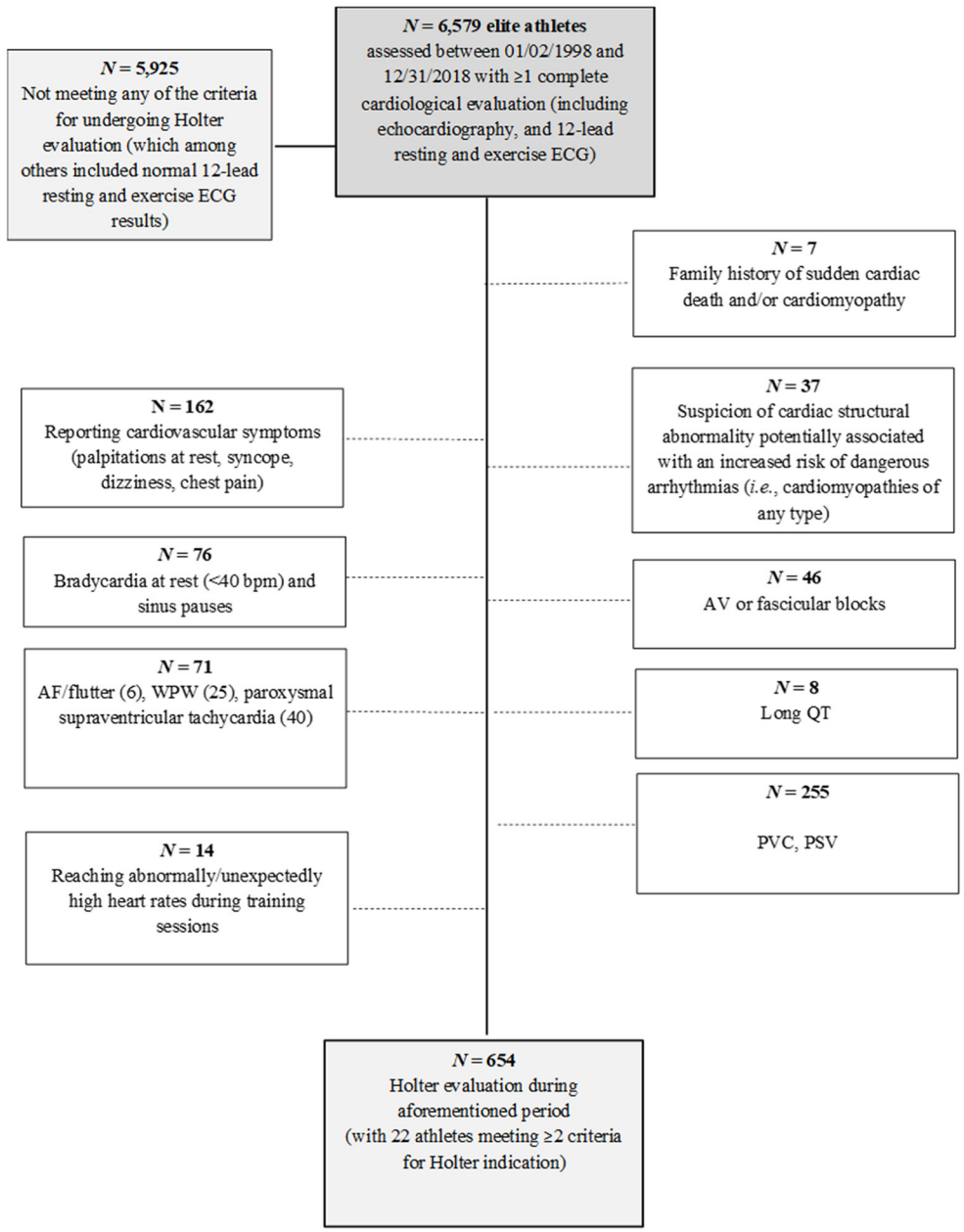

FIGURE 1
Participant flow chart.

Holter results are shown in Table 2. Sinus bradycardia was the most frequent condition (present in the great majority of athletes during Holter monitoring), with the highest proportion of severe — including both daytime and nighttime — bradycardia in endurance athletes. Two-second pauses were mainly detected during night-time (22 vs. 6% for daytime), with 3-s pauses found only in one endurance athlete (long-distance runner). AV blocks were also overall more frequent during night-time, but no differences were found attending to the different sports disciplines. Third-degree AV blocks (both during day- and night-time) were detected only in one athlete (i.e., complete congenital AV block) whereas high degree AV blocks during night-time were found in seven athletes (a wrestler, a soccer player, three basketball players, a cyclist, and an endurance runner), of whom two (the wrestler and the runner) also showed this condition during daytime. Premature atrial beats were prevalent (62%), with the highest prevalence observed among endurance

TABLE 1 Demographics and training characteristics of the participants who underwent Holter monitoring.

	Overall $N = 654$	Skill $N = 43$	Power $N = 135$	Mixed $N = 179$	Endurance $N = 297$	*p*-value
Age (years)	24 (19–28)	21 (17–27)	22 (18–26)[d]	23 (18–28)	25 (20–29)[b]	0.018
Training regimen (hours/week)	19 ± 8	20 ± 11	19 ± 7[c]	16 ± 7[b,d]	21 ± 8[c]	<0.001
Years in competition	10 ± 6	9 ± 4	9 ± 5	11 ± 7[d]	9 ± 6[c]	0.015
VO_2max (ml/kg/min)	56.7±10.1	48.2 ± 8.5[c,d]	50.6 ± 9.1[d]	53.4 ± 7.1[a,d]	62.3 ± 9.0 [a,b,c]	<0.001
ECG heart rate (bpm)	56 ± 13	68 ± 14[b,c,d]	59 ± 13[a,d]	57 ± 12 [a,d]	53 ± 12[a,b,c]	<0.001
Holter heart rate, daytime (bpm)*						
Average	74 ± 12	81 ± 13[c,d]	77 ± 12[d]	75 ± 12[a,d]	70 ± 11[a,b,c]	<0.001
Maximum	167 ± 23	165 ± 22	164 ± 24	169 ± 23	167 ± 23	0.287
Minimum	45 ± 8	50 ± 10[c,d]	47 ± 8[d]	45 ± 7[a,d]	43 ± 8[a,b,c]	<0.001
Holter heart rate, night-time (bpm)						
Average	52 ± 9	59 ± 11[c,d]	55 ± 9[d]	53 ± 9[a,d]	50 ± 8[a,b,c]	<0.001
Maximum	92 ± 14	98 ± 16[c,d]	96 ± 12[d]	92 ± 15[a,d]	90 ± 13[a,b]	<0.001
Minimum	37 ± 7	42± 8[c,d]	40 ± 6[c,d]	37 ± 6[a,b,d]	36 ± 6[a,b,c]	<0.001

Data are mean ± SD, except for age (median [intequartile range]). The main different types of sports in each discipline were [attending to recent classification (21)]: archery, motor driving, golf, jet skiing, motorcycling, and table tennis for "skill" disciplines; alpine skiing, artistic gymnastics, boxing, karate, snowboarding, track and field sprint/throwing/jumping events, weightlifting and wrestling for "power"; badminton, basketball, handball, field hockey, fencing, kickboxing, rugby, soccer, squash, taekwondo, tennis, volleyball, and water polo for "mixed"; and canoeing, cycling, mountaineering/trail running, mid/long distance swimming, mid/long distance running, and triathlon for "endurance" disciplines. *All daytime recordings included at least one hard training session.

Post hoc for pairwise comparisons: [a]significantly different from skill; [b]significantly different from power; [c]significantly different from mixed; and [d]significantly different from endurance.

athletes. AF/flutter, wandering pacemaker, supraventricular tachycardia, and junctional rhythms (premature junctional beats or idioventricular rhythm) were uncommon findings (all <1% except for supraventricular tachycardia [4.0%]). Isolated PVC were found in 39.4% of the athletes undergoing Holter monitoring, ranging between 1 and 99 in 31.2% athletes (with most of them [21%] in the 1–10 range), 100 and 999 in 6.3% and ≥1,000 in 2.0%, with the most frequent morphology (29.7%) being monomorphic PVC (i.e., LBBB [16.0%], RBBB [12.4%], or QS pattern in MCL1, III and CM5 with superior axis [1.2%]), followed by two morphologies (8.4%) and polymorphic morphology (1.4%, with 6 of the 9 cases being endurance athletes). On the other hand, PVC couplets were relatively frequent (10.7%) but complex ventricular arrhythmias were not frequent (PVC triplets: 1.8%; sustained ventricular tachycardia: 0.0%; and nonsustained ventricular tachycardia: 1.5%).

Echocardiographic findings in the athletes that underwent Holter monitoring are shown in Table 3. No statistical associations were found between arrhythmias (including the different PVC morphologies) and echocardiography-determined variables and cardiac structural conditions (including mitral valve prolapse) (all p > 0.1). On the other hand, an association was found between mild mitral regurgitation and supraventricular (odds ratio [OR] 2.61; 95% confidence interval (CI), 1.08 to 6.32; $p = 0.03$) and ventricular (OR 2.80; 95% CI, 1.15 to 6.78; $p = 0.02$) arrhythmias, as well as between mild or moderate mitral regurgitation and ventricular arrhythmias (OR 2.49; 95% CI, 1.03 to 6.01; $p = 0.04$). A trend ($p = 0.06$) was also found for an association between mild or moderate mitral regurgitation and supraventricular arrhythmias (OR 2.12; 95% CI, 0.98 to 5.65).

Discussion

The main finding of our study was the low proportion of dangerous cardiac arrhythmias (e.g., PVC triplets, nonsustained or sustained ventricular tachycardia, polymorphic PVC, high-degree atrioventricular block or idioventricular rhythm) irrespective of the sports discipline, in young elite athletes who required Holter monitoring due to the presence of symptoms or abnormal echocardiographic/ECG findings. Also, the presence of arrhythmias or the detection of ≥1,000 PVC during Holter monitoring was not associated with underlying major structural alterations. Furthermore, with the exception of bradycardia no overall differences were found in Holter findings attending to the main type of sports discipline. Participation in endurance sports was not associated with a higher risk of major cardiac rhythm alterations compared to the other types of sports, including those with a comparatively low cardiovascular demand (i.e., "skill" sports such as shooting events).

Most elite athletes (96%) undergoing Holter evaluation—and particularly endurance athletes during night-time (i.e., 99% of them)—presented with sinus bradycardia, thereby reflecting

TABLE 2 Cardiac rhythm alterations during Holter monitoring.

	Overall $N = 654$	Skill $N = 43$	Power $N = 135$	Mixed $N = 179$	Endurance $N = 297$	*p*-value
Mean daytime rhythm						
Sinus rhythm	629 (96.2%)	42 (97.7%)	131 (97.0%)	172 (96.1%)	284 (95.6%)	0.853
Sinus bradycardia	625 (95.6%)	37 (86.0%)	126 (93.3%)	173 (96.6%)	289 (97.3%)	**0.004**
Daytime bradycardia						
Mild	136 (20.8%)	17 (39.5%)	39 (28.9%)	39 (21.8%)	41 (13.8%)	**<0.001**
Moderate	319 (48.8%)	15 (34.9%)	64 (47.4%)	97 (54.2%)	143 (48.1%)	0.135
Severe	164 (25.1%)	5 (11.6%)	22 (16.3%)	34 (19.0%)	103 (34.7%)	**<0.001**
Extreme	6 (0.9%)	0	1 (0.7%)	3 (1.7%)	2 (0.7%)	-
Night-time bradycardia						
Mild	21 (3.2%)	6 (14.0%)	6 (4.4%)	4 (2.2%)	5 (1.7%)	**<0.001**
Moderate	192 (29.4%)	19 (44.2%)	57 (42.2%)	55 (30.7%)	61 (20.5%)	**<0.001**
Severe	381 (58.3%)	15 (34.9%)	67 (49.6%)	106 (59.2%)	193 (65.0%)	**<0.001**
Extreme	56 (8.6%)	2 (4.7%)	4 (3.0%)	14 (7.8%)	36 (12.1%)	0.068
Atrial rhythms						
Premature atrial beat	405 (61.9%)	25 (58.1%)	76 (56.3%)	108 (60.3%)	196 (66.0%)	**<0.001**
AF/flutter	3 (0.5%)	1 (2.3%)	0	2 (1.1%)	0	-
Wandering pacemaker	5 (0.8%)	0	4 (3.0%)	1 (0.6%)	0	**0.010**
Supraventricular tachycardia	26 (4.0%)	1 (2.3%)	6 (4.4%)	6 (3.4%)	13 (4.4%)	0.875
Junctional rhythms						
Premature junctional beat	4 (0.6%)	0	0	0	4 (1.3%)	0.255
Idioventricular rhythm	3 (0.5%)	0	0	2 (1.1%)	1 (0.3%)	-
Daytime sinus pauses						
≥2 seconds	42 (6.4%)	1 (2.3%)	5 (3.7%)	10 (5.6%)	22 (7.4%)	0.327
≥3 seconds	1 (0.2%)	0	0	1 (0.6%)	1 (0.3%)	-
Night-time sinus pauses						
≥2 seconds	146 (22.3%)	7 (16.3%)	25 (18.5%)	38 (21.2%)	76 (25.6%)	0.264
≥3 seconds	1 (0.2%)	0	0	1 (0.6%)	3 (1.0%)	-
Daytime AV block						
1st degree	53 (8.1%)	3 (7.0%)	8 (5.9%)	10 (5.6%)	32 (10.8%)	0.230
2nd degree type I	38 (5.8%)	2 (4.7%)	3 (2.2%)	10 (5.6%)	23 (7.7%)	0.168
2nd degree type II	4 (0.6%)	0	0	1 (0.6%)	3 (1.0%)	-
High degree	2 (0.3%)	0	1 (0.7%)	0	1 (0.3%)	-
3rd degree	1 (0.2%)	0	0	1 (0.6%)	0	-
Night-time AV block						
1st degree	85 (13.0%)	7 (16.3%)	11 (8.1%)	22 (12.3%)	45 (15.2%)	0.283
2nd degree type I	95 (14.5%)	5 (11.6%)	10 (7.4%)	29 (16.2%)	51 (17.2%)	0.072
2nd degree type II	22 (3.4%)	1 (2.3%)	1 (0.7%)	9 (5.0%)	11 (3.7%)	0.208
High degree	7 (1.1%)	0	1 (0.7%)	4 (2.2%)	2 (0.7%)	0.341
3rd degree	1 (0.2%)	0	0	1 (0.6%)	0	-
PVC						
Frequency						
1–99	204 (31.2%)	14 (2.1%)	39 (5.9%)	57 (8.7%)	94 (14%)	0.665
100–999	41 (6.3%)	4 (9.3%)	8 (5.9%)	12 (6.7%)	17 (5.7%)	0.823
≥1,000	13 (2.0%)	2 (4.7%)	3 (2.2%)	4 (2.2%)	4 (1.3%)	0.514
Morphology						
LBBB	105 (16%)	10 (23.3%)	22 (16.3%)	27 (15.1%)	46 (15.5%)	0.065

(Continued)

TABLE 2 Continued

	Overall $N = 654$	Skill $N = 43$	Power $N = 135$	Mixed $N = 179$	Endurance $N = 297$	*p*-value
Inferior axis	53 (8.1%)	9 (20.9%)	10 (7.4%)	15 (8.4%)	19 (6.4%)	
Superior axis	50 (7.6%)	1 (2.3%)	11 (8.1%)	12 (6.7%)	26 (8.8%)	
Horizontal axis	2 (0.3%)	0	1 (0.7%)	0	1 (0.3%)	
RBBB	81 (12.4%)	8 (18.6%)	16 (11.9%)	20 (11.2%)	37 (12.5%)	0.832
Inferior axis	43 (6.6%)	3 (7.0%)	7 (5.2%)	14 (7.8%)	19 (6.4%)	
Superior axis	31 (4.7%)	4 (9.3%)	8 (5.9%)	5 (2.8%)	14 (4.7%)	
Horizontal axis	7 (1.1%)	1 (2.3%)	1 (0.7%)	1 (0.6%)	4 (1.3%)	
QS pattern in MCL1, III, and CM5 with superior axis	8 (1.2%)	1 (2.3%)	2 (1.5%)	4 (2.2%)	1 (0.3%)	0.261
Two morphologies	55 (8.4%)	1 (2.3%)	9 (6.7%)	20 (11.2%)	25 (8.4%)	0.884
LBBB + RBBB	48 (7.3%)	1 (2.3%)	8 (5.9%)	18 (10.1%)	21 (7.1%)	
LBBB + QS pattern	7 (1.1%)	0	1 (0.7%)	2 (1.1%)	4 (1.3%)	
Polymorphic	9 (1.4%)	0	1 (0.7%)	2 (1.1%)	6 (2.0%)	0.908

Data are N (%). No cases were found of Brugada syndrome, neither of short or long QT. Eleven athletes had Wolf-Parkinson-White, none of whom showed reentry tachycardia (neither orthodromic or antidromic). AF, atrial fibrillation; AV, atrioventricular; LBBB, left bundle branch block; PVC, premature ventricular contraction; RBBB, right bundle branch block. Significant p-values for group (i.e., type of sport) effect are in bold. Details for degrees of bradycardia: mild, 59–50 bpm; moderate, 49–40 bpm; severe, 39–30 bpm; extreme, ≤29 bpm. The bold values indicate the significant *p*-values (< 0.05).

the well-documented exercise (and mainly endurance) training-induced vagotonic effect with a decrease in the intrinsic firing rate of the sinoatrial node (1). Sports-associated bradycardia therefore seemed to represent an essentially physiological "healthy" adaptation, at least in our large population sample. In fact, extreme bradycardia (<30 bpm) was an uncommon finding during daytime (<1%) and infrequently identified relatively at night (9%), and was not related to any underlying cardiac condition. Sinus pauses lasting ≥3 s and 2nd degree type II and 3rd degree AV blocks were also infrequent (<1%). In line with our findings, previous studies have reported a very high prevalence of sinus bradycardia (up to 94%) among athletes and a very low prevalence of extreme bradycardia, with the latter not related to any underlying cardiac condition (22, 23). Our findings are also in agreement with a study in 120 competitive athletes in whom only 14 presented with ≥3-s pauses, and no deaths were registered during a mean follow-up of 7.5 years (24). The authors concluded that the presence of ≥3-s pauses should not exclude sport participation, which is also supported by the present findings. High-grade AV blocks were also rarely identified in the present study (<1%), which is in agreement with previous reports (25, 26) except for Viitsalo et al. (27), who described the presence of AV blocks in 20% of 37 young athletes followed by Holter monitoring.

AF/flutter was an uncommon finding among the elite athletes who underwent Holter monitoring in the present study (3 of 654 athletes), which is in line with our previously published findings (11) and with the results reported in a similar cohort of Italian athletes (28). There is, however, conflictive data regarding the effects of regular exercise on the development of AF. For instance, there is evidence that regular leisure-time physical activity is not associated with the prevalence of AF and can even reduce the risk of this condition (29, 30), which is in accord with the overall antiarrhythmogenic effect of regular exercise at least at the non-elite level (4). Yet, sports participation seems to be associated with a higher prevalence of AF (29, 31). In particular, strenuous endurance exercise might trigger the occurrence of arrhythmias (predominantly, but not only, AF) through several mechanisms such as myocardial fibrosis and inflammation (32). Aagaard et al. (33) recently reported a higher prevalence of AF in former professional football players than in the general population, which was associated with slowed cardiac conduction. Andersen et al. (5) assessed 52,755 long-distance cross-country skiers and observed a higher incidence of AF among those who were faster or completed more races. The potential causes for AF occurrence, especially in young athletes, remains to be determined, although atrial remodeling toward "sphericity" (*i.e.*, enlargement mainly in the horizontal axis) might be involved (11). In any case, AF is a condition associated with age, including in elite athletes (11), which decreases the likelihood of encountering this condition in a cohort of young elite athletes such as that assessed here.

The prevalence of premature atrial and ventricular beats has been commonly reported as 40–90% in the general population (34, 35) and 6–70% in athletes (36). In the present study, premature atrial and ventricular beats were quite common (61.9% and 39.4%, respectively) among elite athletes who underwent Holter monitoring, although these figures represent a small percentage of the entire sample (6.2 and 3.9%, respectively). By comparison, Ben Halima et al. (8) reported the presence of PVC in resting ECG in 42 of 5,789 athletes, with three cases of hypertrophic cardiomyopathy, one of arrhythmogenic cardiomyopathy, one of compression of the right ventricle due to pectus excavatum, and two of ventricular

TABLE 3 Echocardiography findings in elite athletes that underwent Holter monitoring ($n = 654$).

Valvular regurgitations	
Mild aortic regurgitation	21
Moderate aortic regurgitation	9
Severe aortic regurgitation	0
Mild pulmonary regurgitation	124
Moderate pulmonary regurgitation	19
Severe pulmonary regurgitation	0
Mild mitral regurgitation	165
Moderate mitral regurgitation	14
Severe mitral regurgitation	1
Mild tricuspid regurgitation	218
Moderate tricuspid regurgitation	15
Severe tricuspid regurgitation	0
Cardiomyopathies*	
Hypertrophic cardiomyopathy	6
Dilated cardiomyopathy	2
Arrhythmogenic cardiomyopathy	2
LV non-compaction cardiomyopathy	8
Ischemic cardiomyopathy	1
Congenital heart diseases	
Mitral prolapse**	69
Ventricular septal defect	2
Atrial septal defect	1
Patent *foramen ovale*	6
Partial mitral clef	1
Atrial septal aneurysm	4
Tricuspid prolapse	1
Aortic disease	7
Bicuspid aortic valve	7
Idiopathic dilatation of pulmonary artery	2
Anomalous systemic venous drainage	1
Ebstein anomaly	1
LV myocardial cleft	1
Atrial myxoma	1

Data are *N* (%).
LV, left ventricular.
All the aforementioned conditions were diagnosed through echocardiographic evaluation by the same experienced cardiologist (A.B.) *All cardiomyopathies were corroborated with cardiac resonance imaging. **No case of mitral annular disjunction was found. The severity (mild, moderate, or severe) of valve regurgitations was determined following the recommendations of the Spanish society of cardiac imaging (https://ecocardio.com/documentos/valores-referencia/371-criterios-de-cuantificacion-de-valvulopatias.html).

tachycardia episodes, and with five athletes excluded from sports participation. Also, Biffi et al. (9) reported the presence of PVC in 355 (2.2%) of 15,899 competitive athletes. Cardiac pathology was detected in 7% of cases and one death was described due to arrhythmogenic cardiomyopathy while training against medical advice. In the present study, mitral valve prolapse was the most frequent congenital heart disease among those athletes undergoing Holter monitoring. Similarly, Biffi et al. (9) reported mitral valve prolapse as the most common cardiac abnormality in athletes, with this condition associated with the number of PVC. In our study, however, we found no association between any of the analyzed arrhythmias (including the dangerous arrhythmias) and echocardiographic findings other than mild or moderate mitral regurgitation. Further research is needed to determine the potential mechanisms linking mitral regurgitation and arrhythmias in elite athletes. In this regard, intense exercise training induces a significant dilation of annular dimensions and increases leaflet tenting of the mitral valve, potentially leading to mild mitral regurgitation (37). Indeed, mild mitral regurgitation was frequent among those athletes undergoing Holter evaluation (i.e., present in one-fourth of them). Our findings suggest the need for close monitoring of those cases with mild or moderate mitral regurgitation, as this condition might reflect an "insufficient" geometrical adaptation of the mitral annulus to regular, intense exercise (37). On the other hand, the prevalence of mitral regurgitation in those athletes undergoing Holter evaluation is overall comparable to that reported for young non-athletic populations (e.g., 24% in people aged 20 to 39 years) (38).

The main limitations of the present study are its retrospective design with no subsequent follow-up, the young age of most elite athletes (<30 years on average, albeit with a mean 10-year competition experience), which precludes making potential inferences on potential sequelae of sports participation in the longer term, and the Holter analysis of only part (~10%) of the total sample (i.e., those with family history, reporting cardiovascular symptoms, with suspicion of cardiac structural abnormalities potentially associated with dangerous arrhythmias, or with ECG features prompting a closer examination). Thus, while the remainder of athletes showed normal ECG and cardiovascular results (including echocardiographic evaluations, with a mean of three assessments per athlete) and no self-reported symptoms over the years, we might still have missed the occurrence of some cases of arrhythmias (i.e., silent cases or athletes unwilling to recognize cardiovascular symptoms). In addition, it is quite possible that athletes competing in a national team had been previously screened in their local/regional team, which minimizes the risk of reaching the elite competition level with an undiagnosed major structural or electrical cardiac abnormality. Moreover, it is unlikely that those individuals with severe structural or arrhythmic diseases could reach a very high, elite performance level. On the other hand, the use of cardiac magnetic resonance in all the athletes undergoing Holter monitorization [at least in those showing ventricular arrhythmias, as done in recent research (12, 13, 15, 16)] might have allowed to perform accurate myocardial tissue characterization and a more precise diagnosis of some cardiac abnormalities, as opposed to the echocardiographic evaluation we conducted. Notably, isolated nonischemic left-ventricular (LV) late gadolinium enhancement with a stria

pattern may be associated with life-threatening arrhythmias and sudden death in the athlete (12). In this effect, LV scar is often not detected by echocardiography owing to its subepicardial/midmyocardial location (12). In addition, we did not perform strain analysis because this technique was not available in our center during the start of the study period. In turn, the major strengths of our study are the large sample size analyzed (which to our knowledge is the largest elite athlete population evaluated by Holter monitoring so far), the inclusion of different types of sports disciplines (including specialties with a comparatively low cardiovascular demand vs. those with the highest demands) as well as of female athletes, and the comprehensive cardiac evaluation that all elite athletes underwent.

In conclusion, our results suggest that arrhythmias, especially dangerous ones (e.g., nonsustained ventricular tachycardia, frequently polymorphic PVC, high-degree atrioventricular block) are infrequent among young elite athletes, as detected with Holter monitoring due to the presence of symptoms, suspicious echocardiographic alterations, or abnormal ECG findings. Furthermore, the existence of cardiac structural conditions does not appear to increase the risk for cardiac rhythm alterations. Nonetheless, it would seem prudent to closely monitor the athlete in the event of mitral regurgitation.

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 Universidad Europea Miguel de Cervantes. The patients/participants provided their written informed consent to participate in this study.

Author contributions

Full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis: AB and M-EH. Concept, design, and supervision: AB and AL. Acquisition of data: AB, M-EH, FM-A, LD-G, MA-A, and SB-M. Data analysis: FM-A and AS-L. Drafting of the manuscript: AB, FM-A, PV, LD-G, AS-L, and AL. Interpretation of data and critical revision of the manuscript for important intellectual content: All authors. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.896148/full#supplementary-material

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Exercise-induced myocardial edema in master triathletes: Insights from cardiovascular magnetic resonance imaging

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Background: Strenuous exercise has been associated with functional and structural cardiac changes due to local and systemic inflammatory responses, reflecting oxidative, metabolic, hormonal, and thermal stress, even in healthy individuals. We aimed to assess changes in myocardial structure and function using cardiovascular magnetic resonance (CMR) imaging in master triathletes early after a full-distance Ironman Triathlon race.

Materials and methods: Ten master triathletes (age 45 ± 8 years) underwent CMR within 3 h after a full-distance Ironman Triathlon race (3.8 km swimming, 180 km cycling, and 42.2 km running) completed with a mean time of 12 ± 1 h. All the triathletes had a 30-day follow-up CMR. Cine balanced steady-state free precession, T2-short tau inversion recovery (STIR), tagging, and late gadolinium enhancement (LGE) imaging sequences were performed on a 1.5-T MR scanner. Myocardial edema was defined as a region with increased T2 signal intensity (SI) of at least two SDs above the mean of the normal myocardium. The extent of myocardial edema was expressed as the percentage of left ventricular (LV) mass. Analysis of LV strain and torsion by tissue tagging included the assessment of radial, longitudinal, and circumferential peak systolic strain, rotation, and twist.

Results: Compared with postrace, biventricular volumes, ejection fraction, and LV mass index remained unchanged at 30-day follow-up. Global T2 SI was significantly higher in the postrace CMR (postrace 10.5 ± 6% vs. follow-up 3.9 ± 3.8%, $P = 0.004$) and presented with a relative apical sparing distribution ($P < 0.001$) matched by reduction of radial peak systolic strain of basal segments ($P = 0.003$). Apical rotation and twist were significantly higher immediately after the competition compared with follow-up ($P < 0.05$).

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Conclusion: Strenuous exercise in master triathletes is associated with a reversible regional increase in myocardial edema and reduction of radial peak systolic strain, both presenting with a relative apical sparing pattern.

KEYWORDS

CMR, deformation imaging, master triathletes, Ironman, athlete's heart

Introduction

Exercise training and moderate-to-high levels of physical activity have been shown to improve health outcomes and reduce cardiovascular morbidity and mortality (1–3). Despite exercise being an efficacious therapy, there is an incomplete understanding of the entire dose-response relationship. A hypothesis that intense physical training may harm, causing significant myocardial injury, remains unproven (4). Following the initial reports of myocardial fibrosis in athletes about 10 years ago, several studies raised the hypothesis that chronic overload of the cardiovascular system and overtraining may be responsible for myocardial scarring and increased susceptibility to ventricular arrhythmias. However, other studies have outlined different findings questioning the existence of exercise-induced cardiomyopathy (5–7). Cardiovascular MR (CMR) has been used as an imaging technique to assess acute and chronic cardiac changes in endurance athletes, providing information on function and tissue characterization (7–11). CMR data are not entirely concordant about whether intense exercise is harmful to the heart, both in terms of functional abnormalities or myocardial damage. However, the presence of myocardial fibrosis appears to be higher in endurance athletes compared to controls. These data have been confirmed in a recent meta-analysis of CMR studies performed on endurance athletes, showing a higher incidence of myocardial fibrosis by late gadolinium enhancement (LGE) imaging in athletes than in controls, with a predominant non-ischemic LGE pattern at the interventricular insertions (11). In addition, the evidence of myocardial edema, after strenuous exercise, is questionable based on current published data (12–14).

Ironman Triathlon (3.8 km swimming, 180 km cycling, and 42 km running) is a strenuous sports discipline, combining dynamic and static components and causing relevant cardiac adaptations (15–17). We hypothesize that acute changes in cardiac function and myocardial tissue composition occurring after strenuous exercise are fully reversible and there is a relationship between structural and functional changes in the myocardium. Therefore, we used CMR imaging to assess longitudinal changes in myocardial structure and function occurring in master athletes early after completing an Ironmen Triathlon race and a 30-day follow-up.

Materials and methods

Study cohort

We enrolled 10 healthy, amateur, Ironman triathletes (9 males, age 45 ± 8 years), with a mean training time of 13 ± 9 years. The inclusion criteria for enrollment were: (i) experience with ultra-triathlon (swimming, cycling, and running) races with at least two completed competitions; (ii) well-trained (> 10 h of intense training per week); (iii) no known medical problems; (iv) no cardiovascular risk factors; and (v) no history of performance-enhancing drug use.

The research study design complied with the Declaration of Helsinki and was approved by the local Ethics Committee (Pisa, Italy, protocol number for study acceptance 2,805). After receiving the description of the procedures and potential risks, all the subjects gave their written informed consent.

Study design

Cardiovascular magnetic resonance was performed twice: (1) within 3 h following completion of the Ironman race (postrace) and (2) 30 days after the race (follow-up). The second CMR scan was performed in resting conditions, asking athletes not to exert physical activity for 2 days preceding the examination.

Cardiovascular magnetic resonance imaging

Cardiovascular magnetic resonance examinations were performed using a 1.5-T Signa CVI scanner (GE Healthcare, Milwaukee, WI, United States) with a cardiac phased-array 8-channel coil. Left ventricular (LV) and right ventricular (RV) volumes, mass, and function (including assessment of regional wall motion abnormalities) were derived using steady-state free precession [Fast Imaging Employing Steady-State Acquisition (FIESTA)], pulse sequence cine images from the short axis (from atrioventricular valve plane to the apex, 8-mm slice thickness, and no gap), and para-axial views

(from the diaphragm to the entire outflow tract, 5-mm slice thickness, and no gap). The following acquisition parameters were applied: 30 phases, 10–25 views per segment depending on heart rate, the number of excitation (NEX) 1, the field of view (FOV) 40 cm, a matrix of 224 × 224, a 45° flip angle, repetition time/echo time (TR/TE) equal to 3.5/1.5 s, and a bandwidth of 125 kHz. T2-STIR images were acquired using triple inversion recovery T2-weighted pulse sequence in short-axis views and two long-axis views (vertical and horizontal long-axis views) using the following parameters: TR = 2 RR, TE 70 ms, FOV 40 cm, phase FOV 1, and matrix 256 × 256. LGE images were acquired 10 min after administering gadolinium-diethylenetriaminepentaacetic acid (Gd-DTPA) (Magnevist, Schering AG) with a dosage of 0.2 mmol/kg. An inversion recovery T1-weighted gradient-echo sequence was used with the following parameters: FOV 40 mm, slice thickness 8 mm, no gap between each slice, TR 4.6 ms, TE 1.3 ms, flip angle 20°, matrix 224 × 224, reconstruction matrix 256 × 256, and an excitation number of 1. The appropriate inversion time was set to null for normal myocardium based on the Look-Locker scout sequence.

Myocardial tagging images for calculation of LV systolic longitudinal, radial, and circumferential strain for basal, middle, and apical segments of the LV were acquired with an electrocardiography-gated, segmented K-space, fast gradient recalled echo pulse sequence with spatial modulation of magnetization to generate a grid tag pattern. Non-selective radiofrequency pulses separated by spatial modulation of magnetization encoding gradients allowed tag separation of 5 mm. Two sets of orthogonally intersecting tag lines were acquired in short-axis views at basal, mid, and apical levels. The number of views per phase was optimized based on the heart rate. The following parameters were used: field of view 40 cm, slice thickness 5 mm, no gap between each slice, repetition time 8 ms, echo time 4.3 ms, flip angle 12°, bandwidth 31 Hz, 30 phases, matrix 256 × 256, reconstruction matrix 256 × 256, and an excitation number of 1.

Using dedicated software (Mass Analysis, MEDIS, Leiden, Netherlands), the following functional parameters were obtained from the short-axis images: RV and LV end-diastolic volume indexed to body surface area, indexed RV and LV end-systolic volume, indexed LV mass, RV and LV ejection fraction (EF), and RV and LV stroke volumes. The indexed RV and LV volumes were compared with the respective age- and sex-specific reference values (18). Myocardial edema was detected as a region with signal intensity > mean + 2 SD of normal myocardium. The extent of myocardial edema was expressed as a % of LV mass. LGE was visually evaluated and measured as a % of LV mass using the conventional mean + 5 SD technique. Tagged CMR images were exported and analyzed with previously validated software (Tagging Tool) (19), and the following LV functional parameters were obtained: global and regional (basal, mid, and apical) radial, longitudinal, and circumferential strain, basal rotation, apical rotation, and twist. All the analyses were performed by two EACVI CMR level 3 certified operators (FR and GA) who were blinded to any clinical information of the athlete and the results of the other examination. Any discrepancies were solved by a third investigator (AP).

TABLE 1 Characteristics of the study population (n = 10).

Age (years)	45 ± 8
Males, n (%)	9 (90)
Height (cm)	174 ± 11
Weight (kg)	70 ± 10
BSA (m^2)	1.9 ± 0.2

Data are mean ± SD, unless otherwise indicated. BSA, body surface area.

Statistical analysis

Data were expressed as mean ± SD or percentages as appropriate. Differences in immediate postrace vs. resting parameters of the follow-up scans were explored using the paired t-test and ANOVA for immediate postrace vs. resting interslice comparison. One-way intraclass correlation coefficients (ICCs) were obtained to assess inter- and intraobserver variability. We considered a 2-sided p-value of <0.05 as statistically significant throughout. We ran all the tests with the R statistical software version 3.4.3.[1]

Results

The demographic and physical characteristics of triathletes are shown in **Table 1**. Sufficient image quality was obtained in all the participants. Athletes completed the Ironman competition without any cardiovascular symptoms, either during or after the race, in a mean time of 12 ± 1 h.

Ventricular volumes and function

Postrace and resting structural and functional LV and RV parameters are shown in **Table 2**. All the athletes had normal resting LV and RV functions. Compared with follow-up resting conditions, end-diastolic volumes, stroke volumes, and RV ejection fraction were significantly lower immediately postrace ($P < 0.05$), whereas LV ejection fraction remained unchanged.

1 www.R-project.org

TABLE 2 Postrace and follow-up CMR imaging parameters.

Variables	Postrace ($n = 10$)	Follow-up ($n = 10$)	*P*-value
Heart rate, bpm	62 ± 5	58 ± 7	NS
LVEDVI, ml/m^2	87 ± 14	100 ± 16	NS
LVESVI, ml/m^2	33 ± 9	37 ± 11	NS
LVSVI, ml/m^2	54 ± 11	63 ± 8	NS
LVEF, %	62 ± 5	63 ± 5	NS
LVCI, L/min/m^2	3.4 ± 0.5	3.5 ± 0.5	NS
LV mass index, g/m^2	69 ± 13	68 ± 13	NS
LVSV/ESV	1.8 ± 0.8	1.8 ± 0.6	NS
RVEDVI, ml/m^2	88 ± 18	98 ± 22	NS
RVESVI, ml/m^2	36 ± 14	34 ± 14	NS
RVSVI, ml/m^2	52 ± 12	63 ± 13	NS
RVEF, %	59 ± 6	65 ± 6	NS
RVCI, L/min/m^2	3.2 ± 0.5	3.5 ± 0.7	NS
RVSV/ESV	1.6 ± 1	2 ± 0.6	NS
Edema, % of LV mass	12 ± 6	3 ± 3	<0.001
Edema, g	16 ± 7	4 ± 4	<0.001
LGE, n (%)	0 (0)	0 (0)	NS

CMR, cardiovascular magnetic resonance; ESV, end-systolic volume; HR, heart rate; bpm, beats per minute; LGE, late gadolinium enhancement; LVCI, left ventricular cardiac index; LVEDVI, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESVI, left ventricular end-systolic volume index; LVSV, left ventricular stroke volume; LVSV/ESV, left ventriculo-arterial coupling; LVSVI, left ventricular stroke volume index; RVCI, right ventricular cardiac index; RVEDVI, right ventricular end-diastolic volume index; RVEF, right ventricular ejection fraction; RVESVI, right ventricular end-systolic volume index; RVSV, right ventricular stroke volume; RVSV/ESV, right ventriculo-arterial coupling; RVSVI, right ventricular stroke volume index.

Myocardial strain

Postrace and follow-up myocardial deformation parameters are shown in Table 3. Compared to follow-up, apical rotation and twist significantly increased postrace ($P < 0.05$), whereas LV systolic basal radial strain significantly decreased postrace ($P < 0.05$) (Figures 1–3).

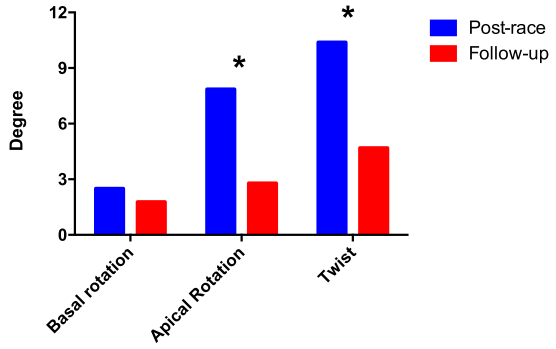

FIGURE 1
Left ventricular rotation and twist: Postrace vs. 30-day follow-up. *$P < 0.05$.

Tissue characterization

Immediate postrace and follow-up assessment of global, basal, middle, and apical LV myocardial edema are shown in Table 4. Compared with follow-up, the extent of myocardial edema was significantly higher immediately after the competition (postrace: 10.5 ± 6% LV mass vs. follow-up: 3.9 ± 3.8% LV mass, $P = 0.004$; Figure 4) and presented with a relative apical sparing distribution ($P < 0.001$) and a basal-to-apical gradient (Figures 5, 6). There was a significant inverse relationship between temporal changes in radial strain and myocardial edema, both tracking the basal-to-apical distribution of edema, or edema localized at basal LV segments (Figures 7, 8). In one case, increased T2-STIR signal intensity remained unchanged in midsegments and increased in the apical segments at follow-up assessment; however, the presence of breathing artifacts located at mid and apical levels is the most likely explanation for this isolated finding. No LGE was detected immediately postrace or during follow-up CMR for any of the triathletes.

TABLE 3 Regional distribution of myocardial edema: Postrace vs. follow-up.

Myocardial edema by T2W-STIR	Postrace	Follow-up	*P*-value[b]	*P*-value*	*P*-value[§]
Basal segments, % of LV mass	5.6 ± 4	1.6 ± 1.1	0.007	NS	<0.001
Mid-cavity segments, % of LV mass	3.8 ± 2	1.3 ± 1.8	0.007		
Apical segments, % of LV mass	1.0 ± 1	0.4 ± 0.7	NS		
Basal segments, g	7 ± 5	1.9 ± 1.3	0.006	NS	<0.001
Mid-cavity segments, g	4.9 ± 2.7	1.5 ± 2.3	0.004		
Apical segments, g	1.4 ± 1.4	0.4 ± 0.7	NS		
Base-to-apex gradient, % of LV mass	4.6 ± 4.3	1.2 ± 0.9	0.026	–	–
Base-to-apex gradient, g	5.6 ± 5.3	1.5 ± 1.1	0.027	–	–

[b] *t*-test post-race vs. follow-up; *ANOVA inter-slice comparison analysis at follow-up; [§] ANOVA inter-slice comparison analysis post-race.

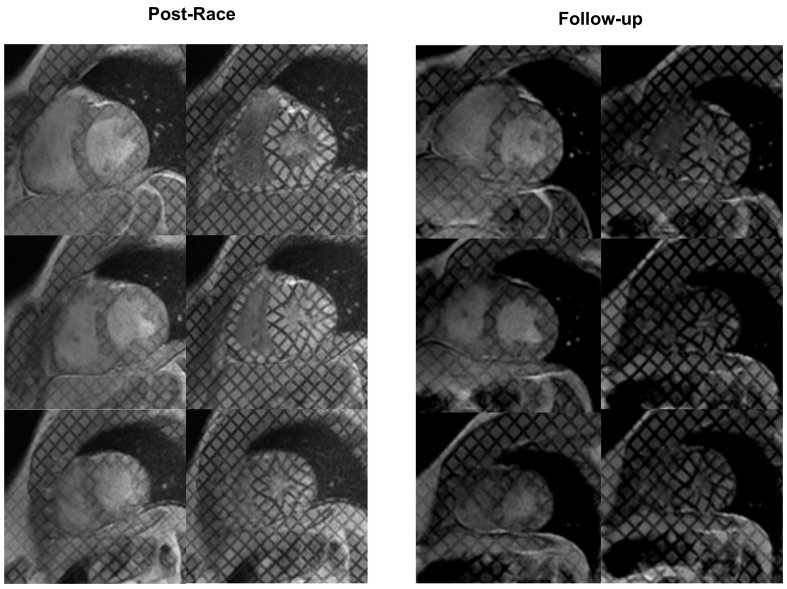

FIGURE 2
Myocardial tagging: Postrace vs. 30-day follow-up. The radial strain of the basal slice was lower in the postrace than at 30-day follow-up, as demonstrated by the deformation of the tag lines (top rows). Apical twisting was higher in the postrace (left panels) compared with 30-day follow-up (right panels).

Intra- and inter-observer variability

Good-to-excellent intra- and interobserver variabilities were observed for all the measurements, with an inter-rater correlation coefficient between 0.92 and 0.98 and an intra-rater correlation coefficient between 0.92 and 0.98.

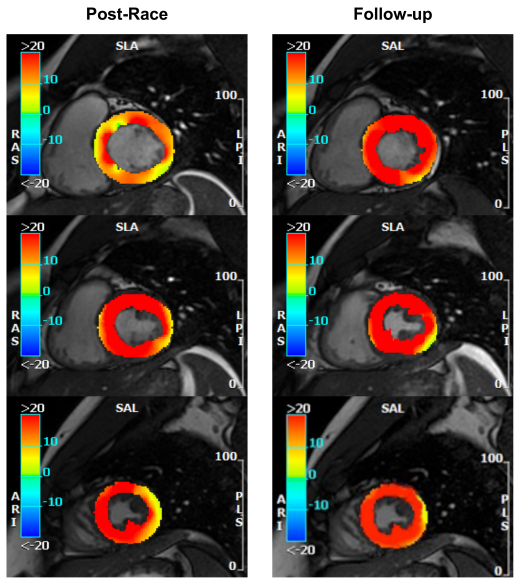

FIGURE 3
Radial strain: Postrace vs. 30-day follow-up. Feature tracking analysis confirmed tagging evidence of reversible reduction of basal radial strain in the same subject as **Figure 2**.

Discussion

In a small cohort of master triathletes, we demonstrated acute and reversible changes in ventricular function and myocardial tissue composition after a full-distance Ironman Triathlon competition. Immediately after an Ironman race, we observed the development of myocardial edema, but the regionality of myocardial edema distribution was noteworthy, mainly involving basal myocardial segments and yielding a relative apical sparing pattern. Notably, myocardial edema was associated with lower peak radial strain values with a similar pattern of regional distribution.

Myocardial edema

Previous experimental studies inducing edema in different conditions, such as coronary sinus hypertension, hypoproteinemia, lymphatic obstruction, or crystalloid cardioplegic solution, showed that edema was not always associated with a reduction in myocardial contractility, probably depending on the different methods used (20). In an experimental model of myocardial ischemia-reperfusion, myofibrillar edema was a mechanism of postischemic regional dysfunction (21). Interestingly, in patients with ST-elevation

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TABLE 4 Global and regional analysis of left ventricular strain and rotational mechanics.

Myocardial deformation parameters	Postrace	Follow-up	*P*-value[b]	*P*-value*	*P*-value[§]
Global radial strain, %	46 ± 7	51 ± 8	NS	–	–
Global longitudinal strain, %	−28 ± 9	−28 ± 5	NS	–	–
Global circumferential strain, %	−21 ± 4	−21 ± 3	NS	–	–
Basal radial strain, %	28 ± 7	47 ± 10	0.003	NS	<0.001
Mid-cavity radial strain, %	54 ± 12	57 ± 10	NS		
Apical radial strain, %	54 ± 6	49 ± 8	NS		
Basal longitudinal strain, %	−28 ± 12	−29 ± 5	NS	NS	NS
Mid-cavity longitudinal strain, %	−28 ± 7	−27 ± 5	NS		
Apical longitudinal strain, %	−27 ± 9	−27 ± 6	NS		
Basal circumferential strain, %	−20.6 ± 2.8	−20 ± 3	NS	NS	NS
Mid-cavity circumferential strain, %	−22.3 ± 2.8	−23 ± 2	NS		
Apical circumferential strain, %	−23.3 ± 3.5	−20 ± 3	NS		
Basal rotation, °	−2.4 ± 1.9	−1.8 ± 1.7	NS	–	–
Apical rotation, °	7.8 ± 2.2	2.8 ± 1.3	<0.001	–	–
Twist, °	10.2 ± 2.9	4.6 ± 2.2	0.009	–	–

[b]*t*-test post-race vs. follow-up; *ANOVA inter-slice comparison analysis at follow-up; [§]ANOVA inter-slice comparison analysis postrace.

acute myocardial infarction, the edematous peri-infarct myocardium had attenuated circumferential strain compared with the remote myocardium, and strain parameters improved after the resolution of myocardial edema (22). In the setting of sports cardiology, in a cohort of 20 recreational athletes undergoing CMR within 48 h after marathon completion, the presence of localized myocardial edema (with a per-segment myocardial T2-ratio increase of 11%) was associated with an impaired regional function (13). This finding contrasts with other studies documenting the absence of myocardial edema after a Triathlon race or a marathon (14, 23). These differences may be due to the choice of imaging modality used for edema detection. Similar to previous studies (13, 24), we used the T2-STIR sequence that remains one of the predominant CMR modes for assessment of myocardial edema, but not T2 mapping. Despite the two methods have usually good agreement in assessing myocardial edema (25), whole heart coverage is desirable. Tahir acquired only three short-axis slices for T2 and T1 mappings, covering only 20–30% of the myocardium (14), whereas we achieved a complete LV coverage, without any gap between slices (usually 10–13 short-axis slices). Then, in the study by Tahir, some myocardial regions of edema could have been missed. Moreover, the discrepancies in the results can also depend on the athlete's fitness level. Gaudreault found a larger amount of edema in athletes with relatively lower fitness. Furthermore, the extent of exertion may be a component of the development of myocardial edema. In our study, the athletes performed an Ironmen competition that was much more intense and demanding than the effort made by the athletes enrolled in the other studies. Indeed, exercise duration and fitness level are key determinants in the development of postexercise LV dysfunction (26).

A possible explanation for the relative apical sparing pattern distribution of myocardial edema observed in our cohort in the postrace period includes regional differences in density

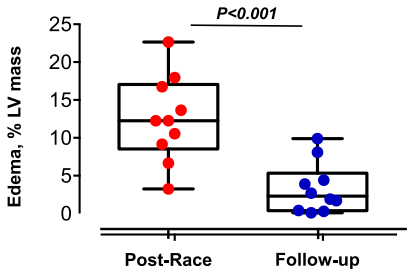

FIGURE 4
Reversible myocardial edema in master triathletes: Postrace vs. 30-day follow-up.

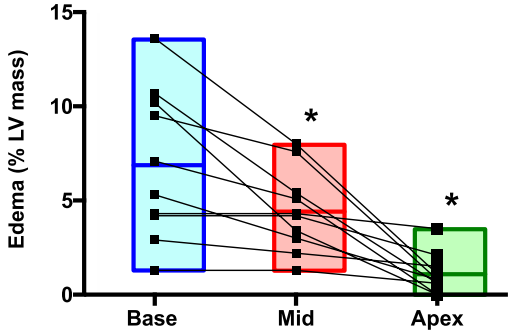

FIGURE 5
Regional distribution of myocardial edema in the postrace. *$P < 0.05$.

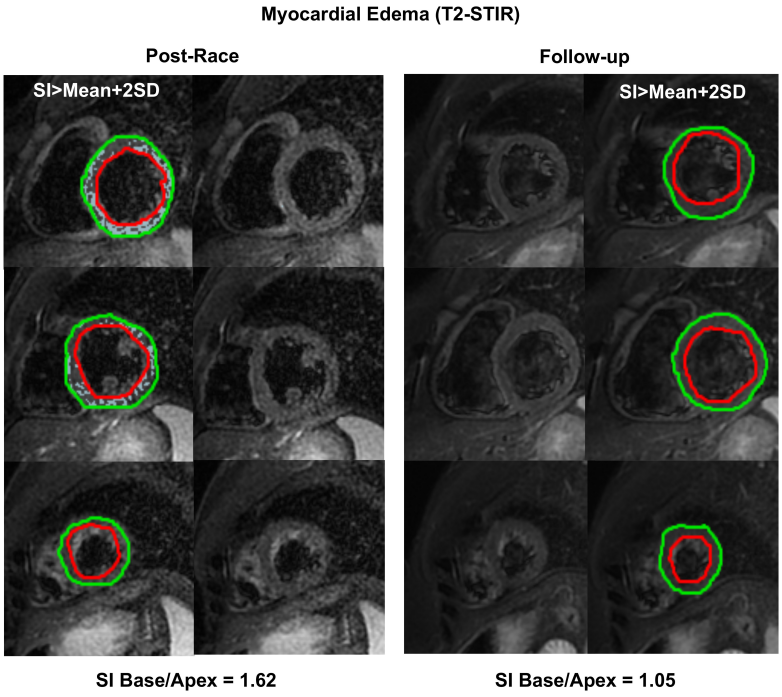

FIGURE 6
Myocardial edema: Postrace vs. 30-day follow-up. Example of postrace and 30-day follow-up resting T2-STIR images (basal, middle, and apical slices from the complete dataset of short-axis views). Edema was evaluated semi-quantitatively as signal intensity (SI) greater than mean + 2 SD. As shown in the left panels, edema was detected in the postrace acquisition and not at rest (right panels). Moreover, a basal-to-apex gradient was found as the SI ratio basal/apex was greater in postrace than at 30-day follow-up.

of cardiac sympathetic fibers and age-related differential β-adrenoceptors expression (27–30). Future studies investigating regional differences in adrenoreceptor reserve or the process of release and reuptake of neurotransmitters in the athletic population may help to further clarify this hypothesis.

Deformation imaging and rotational mechanics

The results of our study cannot ascertain the reason for the reduction in radial strain in the presence of myocardial edema. The complex three-dimensional architecture of the myocardium makes it much harder to explain the mechanisms underlying the observed transient reduction in cardiac contractility and to understand the role of adaptive or maladaptive response to strenuous exercise. As shown by MR diffusion tensor imaging, subepicardial fibers display an anticlockwise spiral pattern from inside to outside, and, with increasing distance from the epicardium, fiber orientation undergoes a continuous change in angulation with respect to an axis normal to the epicardium, thus the fibers are more circular at the middle layer, and more radial at the subendocardial portion of the myocardium (31). Therefore, there is no definite beginning or end of the contractile chain, but rather a fine three-dimensional meshwork inducing longitudinal and circumferential shortening, radial thinning, and shear strains (32, 33). In our study, beyond the reduction in the radial strain of the basal myocardial segments, we observed increased twisting and apical rotation in the apical LV segments, possibly representing a compensatory mechanism to preserve LV systolic function. Accordingly, there were no significant changes in global LV function between postrace and 30-day follow-up CMR scans. Several studies evaluated strain patterns in athletes after strenuous and prolonged exercise using echocardiography and CMR tagging techniques, yet delivering variable results. A recent study showed impaired LV global longitudinal strain (LVGLS) after a recreational ultramarathon at moderate altitude, in agreement with previous studies focusing on different types of exercise (34–36). Moreover, in the study of Champigneulle et al., the LVGLS reduction has been documented in athletes early after a speed ascent of the Montblanc (4,808 m), thus in the presence of gradual hypoxic conditions potentially worsening cardiac function (37). In the study of Jouffroy et al., in which athletes had run 80 km, LVGLS was already reduced at 53 km (early before the end of the race) and was found to be decreased in nearly 50% of athletes after race completion (36). However, other authors did not find any functional cardiac alteration after prolonged exercise. In the study of Hanssen et al. (28 males, age of 41 ± 5 years), no changes in radial, circumferential or longitudinal strain could

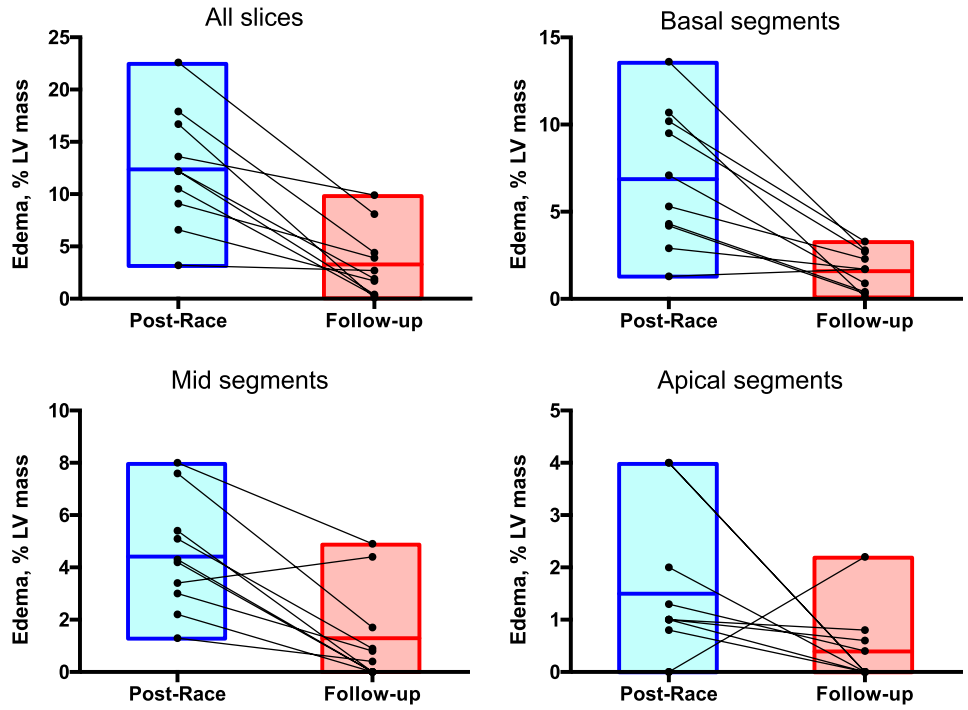

FIGURE 7
Regional distribution of myocardial edema: Postrace vs. 30-day follow-up. Myocardial edema was detected as a region with signal intensity > mean + 2 SD of normal myocardium. The extent of myocardial edema within each slice was expressed as % of the entire LV mass.

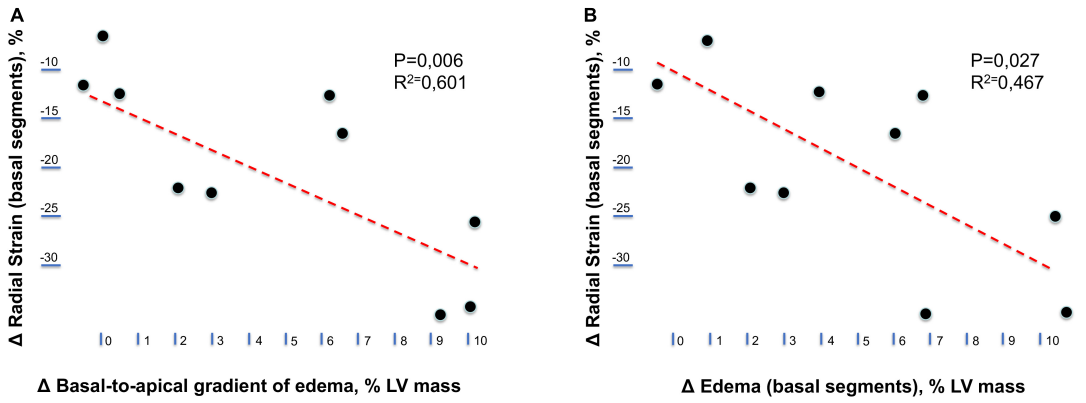

FIGURE 8
Relationship between longitudinal changes in radial strain and myocardial edema. **(A)** Relationship between temporal changes (postrace vs. follow-up) in the radial strain of left ventricular basal segments and the basal-to-apical gradient of myocardial edema. **(B)** Relationship between temporal changes (postrace vs. follow-up) in the radial strain and myocardial edema of left ventricular basal segments.

be identified by CMR tagging early after an amateur marathon race (38). In another cohort of 14 male non-elite runners, aged 32 ± 10 years, who completed the 42.2-km London marathon, only limited changes in strain, rotation, and torsion in both the subendocardial and subepicardial layers of the LV wall could be detected by speckle tracking echocardiography.

Based on the observation of functional adaptive changes of the heart, also matching an increase in biomarkers of myocardial injury (39), the term postexercise cardiac fatigue has been coined. Cardiac fatigue refers to functional and humoral alterations occurring after prolonged and strenuous exercises, which are transient and indicative of cardiac distress (40). In the 30-day follow-up scan, we documented the full reversibility of acute changes in myocardial tissue and function seen in the early postrace period.

Subclinical myocardial fibrosis

Beyond benign junctional pattern, LGE was negative in all of our master athletes. The prevalence and clinical significance of myocardial scarring in the athletic population are still debated (41, 42). Discordant findings may be due to various reasons, including limited sample size, training volume, age, number of races, frequency, intensity, time, and type of exercise, as well as individual susceptibility and genetic determinants of cardiac remodeling (43, 44). Moreover, gadolinium and myocardial washout might vary after strenuous effort because of acute modifications of blood volume or renal function. Interestingly, coronary artery calcifications have been associated with subclinical myocardial damage in athletes, thus recommending particular attention to cardiovascular risk stratification, mainly in veteran athletes (45).

Study limitations

Our study has a few limitations that must be addressed. First, the sample size was small, yielding a larger margin of error and limiting our ability to identify outliers. Second, we enrolled a cohort of amateur master triathletes with a net prevalence of men. Thus, the results cannot be generalized to elite triathletes and the female gender. Third, we did not perform a basal CMR acquisition because of limited athlete's availability and to avoid multiple administrations of gadolinium-based contrast agents in the same healthy subject; however, our objective was to assess the reversibility of any possible acute changes documented in the early postrace period. Fourth, we acknowledge the lack of important pieces of information such as 12-lead ECG, levels of cardiac biomarkers (cardiac troponin, natriuretic peptides), and detailed data about the frequency, intensity, time, and type of training that led up to the competition. Finally, tissue characterization was limited to conventional T2-weighted STIR [with its intrinsic technical limitations (46), including low signal-to-noise ratio, high dependency on magnetic field inhomogeneity, susceptibility to motion artifacts, and loss of signal secondary to cardiac motion across the plane in black blood preparation, subendocardial slow flow hyperintensity] and LGE sequences. Parametric T1 and T2 mapping and extracellular volume fraction data were not available at the time of enrollment.

Conclusion

The present study demonstrated significant early postrace changes in ventricular function and myocardial tissue composition and the full reversibility of these changes in a cohort of master Ironman triathletes. The results of this study add new insights regarding the acute cardiac response to strenuous and prolonged exercise on myocardial tissue component, function, and the reversible nature of these changes. In view of the variability of published results, larger multicenter studies are needed to confirm the presence, magnitude, and reversibility of myocardial functional and structural changes in order to help clarify the concept of cardiac fatigue and investigate the true prevalence of irreversible cardiac injury linked to intense and prolonged exercise.

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 involved human participants and has been reviewed and approved by the local Ethics Committee (Comitato Etico Locale dell'Azienda Ospedaliera Universitaria Pisana) of Pisa, Italy.

Author contributions

AP: full access to all the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. FR, GA, and AP: study concept and design. FR, GA, AP, CM, and SR: acquisition, analysis, or interpretation of data. FR, AP, and CD: drafting of the manuscript. FR: statistical analysis. GA: administrative, technical, or material support. SG and AP: study supervision. All authors critical revision of the manuscript for important intellectual content and approved the submitted version.

Conflict of interest

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

Publisher's note

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The effect of aerobic exercise on pulse wave velocity in middle-aged and elderly people: A systematic review and meta-analysis of randomized controlled trials

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A growing body of research examines the effect of aerobic exercise on pulse wave velocity (PWV) in middle-aged and elderly people, while findings of available studies were conflicting. The aim of this study was to explore the effect of aerobic exercise on PWV in middle-aged and elderly people. Searches were performed in PubMed, Web of Science, and EBSCO databases. Cochrane risk assessment tool was used to evaluate the methodological quality of the included literature. We included studies that satisfied the following criteria: (1) eligible studies should be randomized controlled trials (RCTs); (2) eligible studies should include both an intervention and a control group; (3) eligible studies should use the middle-aged or elderly people as subjects; and (4) eligible studies should use PWV as the outcome measure. From 972 search records initially identified, 11 studies with a total of 12 exercise groups (n = 245) and 11 control groups (n = 239) were eligible for meta-analysis. There was a significant effect of aerobic exercise on reducing PWV in middle-aged and elderly people [weighted mean difference (WMD), −0.75 (95% CI, −1.21 to −0.28), p = 0.002]. Specifically, a higher intensity [vigorous-intensity, −0.74 (−1.34 to −0.14), p = 0.02; moderate-intensity, −0.68 (−1.49 to 0.12), p = 0.10], a younger age [45 years ≤ age < 60 years, −0.57 (−0.78 to −0.37), p < 0.00001; age ≥ 60 years, −0.91 (−2.10 to 0.27), p = 0.13], a better health status [healthy, −1.19 (−2.06 to −0.31), p = 0.008; diseased, −0.32 (−0.64 to −0.01), p = 0.04], and a lower basal body mass index (BMI) [BMI < 25, −1.19 (−2.06 to −0.31), p = 0.008; 25 ≤ BMI < 30, −0.52 (−0.92 to −0.12), p = 0.01; BMI ≥ 30, −0.09 (−0.93 to 0.76), p = 0.84] were associatedwith larger reductions in PWV. Aerobic exercise, especially

vigorous-intensity aerobic exercise, contributed to reducing PWV in middle-aged and elderly people. The effect of aerobic exercise on improving PWV was associated with characteristics of the participants. Specifically, a younger age, a better health status, and a lower basal BMI contributed to more significant reductions in PWV.

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KEYWORDS

aerobic exercise, arterial stiffness, pulse wave velocity, middle-aged people, elderly people

Introduction

With aging, cardiovascular function gradually declines, especially in middle-aged and elderly people, which is mainly manifested as the aging of the cardiovascular and the decline of blood supply. Cardiovascular diseases (CVDs) are the primary chronic disease affecting human health and quality of life. In recent years, with the change of lifestyle, the prevalence and mortality of CVDs have increased year by year. At the same time, the onset age of CVDs also presents a younger trend. CVDs, such as atherosclerosis, congenital and rheumatic heart disease, and hypertension, are the leading cause of disability and death in middle-aged and elderly people, accounting for more than 40% of the deaths in people aged 65 years and above (1).

Arterial stiffness, which is considered to be one of the earliest pathophysiological processes in the progression of atherosclerosis-related metabolic diseases, is a prominent manifestation of vascular aging, and it has become an independent risk factor for atherosclerosis (2), coronary heart disease (3), diabetes (4), stroke (5), and other CVDs (6, 7). Increased arterial stiffness or decreased vascular elasticity can impair arterial function, leading to increased systolic blood pressure, left ventricular hypertrophy, and reduced ventricular diastolic function (8, 9), and thus increases the risk of arteriosclerosis and coronary artery disease (10, 11). Therefore, the prevention and treatment of arterial stiffness is crucial (1, 12).

Previous studies have shown that pulse wave velocity (PWV), especially carotid-femoral pulse wave velocity (cfPWV), has been recommended as the gold standard for assessing arterial stiffness as a non-invasive measurement (8, 11, 12). In addition, PWV is considered to be negatively correlated with vascular health (13). However, these results show more negative outcomes when the blood vessels are stiffer and the lumen is narrowed and thickened, suggesting increased arteriosclerosis, decreased vascular elasticity levels, arteriosclerosis, and an increased risk of coronary artery disease (9). Therefore, reducing PWV is one of the main goals for improving cardiovascular function (14, 15).

Exercise is considered to be an effective measure to prevent CVD and improve its prognosis. In recent years, a large number of studies on exercise and cardiovascular function have shown that appropriate exercise can effectively improve arterial stiffness and reduce the risk of CVDs (10, 12, 16). Older adults who are physically active have less decline in physical function and health and a lower incidence of CVDs than those who are inactive (17, 18). However, there is substantial evidence that high-intensity exercise may lead to CVDs (19). Furthermore, exercise can increase the risk of acute CVDs in sedentary older adults who are not used to sudden high-intensity exercise (19).

At present, there are various intervention methods for middle-aged and elderly people, such as aerobic exercise, resistance exercise, and combined exercise. Totosy de Zepetnek et al. (20) showed that combined exercise had no significant effect on cardiovascular function in middle-aged and elderly people, which is in line with a meta-analysis conducted by Zhang et al. (21). However, aerobic exercise is considered to be an effective method for improving arterial stiffness, whereas the results of resistance exercise are controversial (20). Among different types of intervention methods, aerobic exercise has a higher degree of freedom, is simpler and more convenient, and is more suitable for middle-aged and elderly people. Therefore, aerobic exercise is recommended as the preferred exercise for middle-aged and elderly people (11).

A growing body of research examines the effect of aerobic exercise on PWV in middle-aged and elderly people, while findings of available studies were conflicting. Many studies have confirmed that aerobic exercise can effectively reduce PWV in middle-aged and elderly people (13, 22, 23), while some studies have shown that aerobic exercise has no significant effect on the PWV (16, 19, 24–27). Therefore, we conducted a comprehensive

systematic review and meta-analysis of randomized controlled trials (RCTs) to explore whether aerobic exercises have a role in improving PWV in middle-aged and elderly people.

Methods

This systematic review and meta-analysis was conducted following the guidelines of the Cochrane Selection Manual (28) and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) (29). The protocol for this systematic review has been registered on PROSPERO (CRD42022337103).

Search strategy

For this systematic review and meta-analysis, we searched through PubMed, Web of Science, and EBSCO electronic databases from the inception of indexing until October 11, 2021. The initial search contained the following terms: (a) exercise, aerobic exercise, endurance exercise, aerobic training, endurance training, cardio training, physical endurance, physical exertion; (b) pulse wave velocity, PWV, pulse wave analysis, (analyses, pulse wave), (analysis, pulse wave), pulse wave analyses, (wave analyses, pulse), (wave analysis, pulse), pulse wave velocity, pulse wave velocities, (velocities, pulse wave), (velocity, pulse wave), (wave velocities, pulse), (wave velocity, pulse), pulse transit time, pulse transit times, (time, pulse transit), (times, pulse transit), (transit time, pulse), (transit times, pulse), pulse wave transit time; (c) elderly, aged, geriatrics, eldest, old, older, middle-aged, middle aged, middle age, elderly, aged, geriatrics, eldest, old, older, middle-aged, middle aged, middle age. We also hand-searched reference lists of all identified studies. We excluded studies based on the review of the title, abstract, and full text. Two authors (GL and YL) conducted the process independently using a standardized form. In case of any discrepancies between the two authors, a third author (LY) was involved in the discussion until a consensus was made.

Eligibility criteria

We included studies that satisfied the following criteria: (1) eligible studies should be RCTs; (2) eligible studies should include both an intervention and control group with the only difference between them being the addition of aerobic exercise in the intervention group; (3) eligible studies should use the middle-aged or elderly people as subjects; and (4) eligible studies should use cfPWV as the outcome measure. Non-English language publications, animal model publications, reviews, and conference articles were excluded from the analysis.

Data extraction

Two authors (GL and YL) of this study performed the data extraction independently using the same and standardized form created in Microsoft Excel. If there were any discrepancies between the authors in the extracted data, the accuracy of the information was rechecked in the studies. The extracted variables mainly included: (a) characteristics of included studies (first author's last name, year of study publication); (b) characteristics of aerobic exercise (type of exercise, intensity, duration of intervention, session duration, frequency); (c) participant's characteristics [n, age, gender, basal body mass index (BMI), basal systolic blood pressure (SBP), basal diastolic blood pressure (DBP), health status]; and (d) treatment effects [mean and standard deviation (SD) values reflecting the change in PWV from baseline to post-intervention in the aerobic exercise and control groups].

Methodological quality assessment

We assessed the methodological quality of the included studies using the Cochrane risk of bias criteria, which included seven items, namely, randomization sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other bias. Each item was judged as "low risk," "unclear risk," or "high risk" based on responses to the signaling questions, to make an overall bias judgment for the specific study outcome being assessed (28). Two reviewers (GL and YL) performed the methodological quality assessment independently. Disagreements in the assessments between the reviewers were resolved through discussion and consensus with a third author (LY).

Statistical analysis

The mean and SD values reflecting the change in PWV from baseline to post-intervention were extracted from each study for pooling effects. SD was calculated using a previously described formula for studies reporting standard error (SE) or 95% confidence intervals (CIs) (30). When the data could not be extracted or there was a dispute, two authors negotiated or contacted the author of the article to resolve it. Otherwise, the platform was used to extract the information (31).

The majority of included studies provided mean and SD values before and after the intervention. We calculated the changes in the mean and SD values for PWV. When analyzing whether aerobic exercise could improve the PWV of

middle-aged and elderly people, the Chi-square (χ^2) test was used. The negative value of I^2 was defined as zero, so the value of I^2 was between 0 and 100%. As mentioned by Chiarito et al. (32), an I^2 value of 0% indicates no observed heterogeneity, and larger values indicate increasing heterogeneity. The I^2 values of < 25%, 25–75%, and > 75% were considered to represent low, moderate, and high levels of heterogeneity, respectively (33). If there was a high level of heterogeneity ($I^2 \geq 50\%$), we used subgroup analyses to interpret the results (29). When I^2 is < 50%, data were pooled using fixed effects models to obtain the weighted mean difference (WMD) and 95% CIs; when I^2 is ≥ 50%, data were pooled using random effects models to obtain the WMD and 95% CIs. In the subgroup analyses, we tried to use intensities of aerobic exercise (moderate-intensity and vigorous-intensity), age of participants (45 years ≤ age < 60 years and age ≥ 60 years), basal BMI (BMI < 25, 25 ≤ BMI < 30, and BMI ≥ 30), and health status (healthy and diseased) to explore the impact on PWV. The analysis result, funnel plot, and forest chart were generated using the software RevMan.5. In terms of overall impact, $p < 0.05$ was considered statistically significant.

Results

Study selection

As shown in **Figure 1**, a total of 969 search records were preliminarily retrieved, and three records were identified through other sources. After excluding the duplicates, 740 studies were remaining, and 704 studies were not eligible for inclusion through the title and abstract screening. Twenty-five studies were excluded by reading the full text of 36 studies: (1) the experimental group combined with other treatments ($n = 5$); (2) outcomes were not relevant ($n = 15$); and (3) no control group ($n = 5$). Finally, 11 studies (13, 19, 22, 23, 25, 27, 34–38) examining the effect of aerobic exercise on PWV in middle-aged and elderly people were considered eligible for systematic review and meta-analysis.

Characteristics of the included studies

The main characteristics of the participants and exercise interventions are shown in **Supplementary Table 1**. The included studies involved 245 participants in the 12 exercise groups and 239 participants in the 11 control groups. One study (22) involved only women, and the other 10 studies (13, 19, 23, 25, 27, 34–38) involved both men and women. Three studies (22, 23, 27) involved healthy participants, and eight studies (13, 19, 25, 34–38) involved diseased participants. The average age of the participants was ranging from 45 to 74.3 years. Among them, seven studies (13, 22, 25, 34, 36–38) involved participants with an average age of < 60 years, and four studies (19, 23, 27, 35) involved participants with an average age of ≥ 60 years. There studies (22, 23, 27) involved participants with basal BMI < 25, five studies (19, 25, 34, 37, 38) involved participants with 25 ≤ BMI < 30, and two studies (13, 35) involved participants with BMI > 30.

According to the position statement of physical activity and training intensity (39), we adjusted the intensity classification of aerobic exercise according to the included research situation: 20% < maximal oxygen uptake (VO_{2max}) ≤ 40%, 40% < maximum heart rate (HR_{max}) ≤ 55%, or 20% < heart rate reserve (HRR) ≤ 40% were determined as light-intensity; 40% < VO_{2max} ≤ 60%, 55% < HR_{max} ≤ 70%, or 40% < HRR ≤ 60% were determined as moderate-intensity; 60% < VO_{2max} ≤ 85%, 70% < HR_{max} ≤ 90%, or 60% < HRR ≤ 85% were determined as vigorous-intensity. Among the included studies, the intensity of two studies (19, 36) could not be defined, two studies (13, 34) were defined as moderate-intensity, and seven studies (22, 23, 25, 27, 35, 37, 38) were defined as vigorous-intensity.

Risk of bias

Cochrane risk assessment tool was used to evaluate the methodological quality of the included literature, mainly from six aspects, namely, selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias. The quality score was determined according to three levels (low risk, high risk, and unclear). The quality of the included literature was divided into three levels from high to low, namely, high quality, medium quality, and low quality (see **Figure 2**). Publication bias was assessed visually by inspecting the funnel plot (see **Figure 3**).

Meta-analysis results

Effects of aerobic exercise on pulse wave velocity

After analyzing the data of all included studies, we found that compared with the control group, aerobic exercise had a significant effect on reducing PWV in middle-aged and elderly people [WMD, −0.75 (95% CI, −1.21 to −0.28), $p = 0.002$], while there was a high heterogeneity ($I^2 = 84\%$) (**Figure 4**). Therefore, we used subgroup analyses to interpret the results.

Subgroup analysis

Different results were shown when considering exercise intensity (see **Figure 5**). Specifically, compared with the control group, vigorous-intensity exercise significantly reduced PWV [WMD, −0.74 (95% CI, −1.34 to −0.14), $p = 0.02$, $I^2 = 91\%$], while moderate-intensity exercise had no significant effect on PWV in middle-aged and elderly people [WMD, −0.68 (95% CI, −1.49

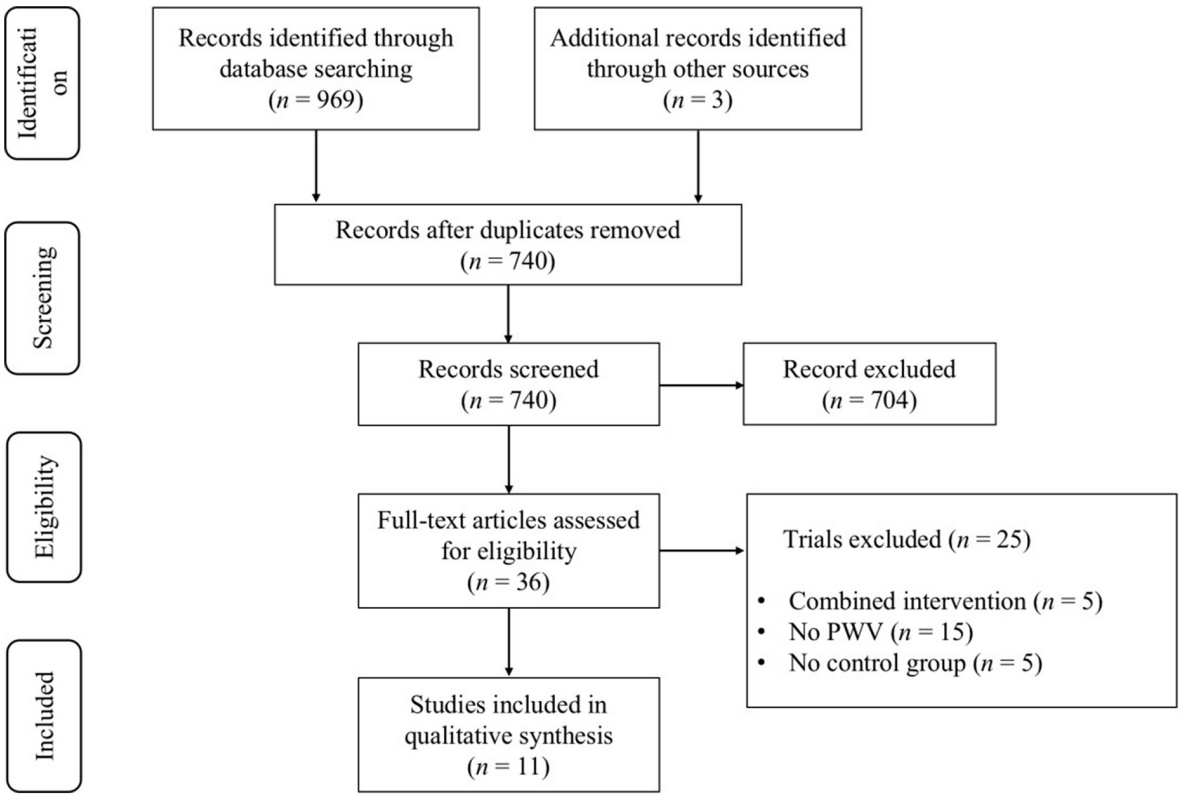

FIGURE 1
PRISMA flowchart of study selection.

to 0.12), $p = 0.10$, $I^2 = 0\%$]. Subgroup analysis indicated that a higher intensity was associated with larger reductions in PWV.

In addition, different results were shown when considering participants' characteristics. The subgroup analysis indicated that a younger age [45 years $\leq$ age $<$ 60 years, −0.57 (95% CI, −0.78 to −0.37), $p < 0.00001$, $I^2 = 0\%$; age $\geq$ 60 years, −0.91 (95% CI, −2.10 to 0.27), $p = 0.13$, $I^2 = 94\%$. see **Figure 6**], a better health status [healthy, −1.19 (95% CI, −2.06 to −0.31), $p = 0.008$, $I^2 = 94\%$; diseased, −0.32 (95% CI, −0.64 to −0.01), $p = 0.04$, $I^2 = 11\%$. see **Figure 7**], and a lower basal BMI [BMI $<$ 25, −1.19 (95% CI, −2.06 to −0.31), $p = 0.008$, $I^2 = 94\%$; 25 $\leq$ BMI $<$ 30, −0.52 (95% CI, −0.92 to −0.12), $p = 0.01$, $I^2 = 0\%$; BMI $\geq$ 30, −0.09 (95% CI, −0.93 to 0.76), $p = 0.84$, $I^2 = 36\%$. see **Figure 8**] were associated with larger reductions in PWV.

Discussion

Effects of aerobic exercise on pulse wave velocity

This systematic review and meta-analysis indicated that aerobic exercise had the potential to reduce arterial stiffness in middle-aged and elderly people, as manifested by a reduction in PWV. Previous studies were consistent with our results, for example, 10 weeks of shallow water aerobic exercise significantly reduced PWV in elderly people (40), 20 weeks of walking training significantly reduced PWV in elderly people (41), and 21 weeks of aerobic exercise effectively reduced PWV in kidney transplant recipients (25). However, the mechanism by which aerobic exercise improves arterial stiffness has not been fully revealed.

Many studies have shown that the lack of exercise may lead to fat accumulation and disorders of glycolipid metabolism (42–44). Adipose tissue produces the pro-inflammatory cytokine interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), plasminogen activator inhibitor, and adiponectin. Therefore, the accumulation of fat may be related to the increased inflammatory response during atherosclerosis, which is consistent with the study of Jennersjö et al. (45), and that the inflammatory response can accelerate the process of arteriosclerosis (46, 47). Previous studies have shown that regular aerobic exercise can reduce fat content and increase adiponectin secretion, which in turn reduces arterial stiffness (27, 30, 48). In addition, a previous study also showed that exercise can reduce risk factors for arterial stiffness associated with metabolic disorders (20). Metabolic syndrome, which can

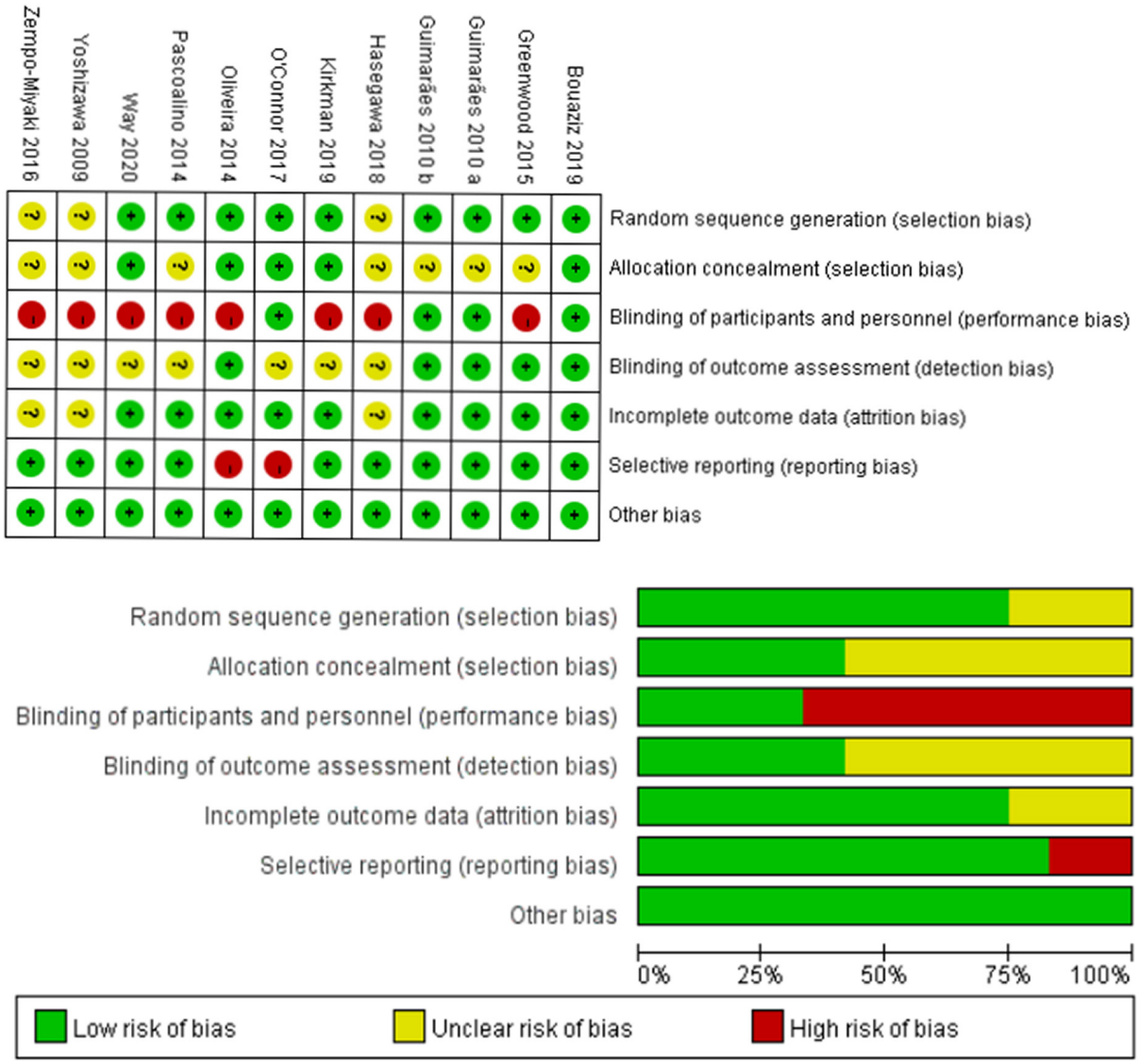

FIGURE 2
Results of Cochrane risk of bias tool.

lead to impaired glucose tolerance, hypertension, dyslipidemia, and abdominal obesity, has been reported to be associated with changes in the arterial system, mainly manifested by changes in vascular structure and function, including increased arterial wall thickness and increased vascular wall stiffness (46, 47, 49). Above all, metabolic disorders can accelerate arterial aging through elastin fiber fragmentation, increased pressure on the collagen fibers of the arterial wall (50), and vascular damage, ultimately leading to increased arterial stiffness (51, 52). Aerobic exercise has been shown to have a dampening effect on metabolic disorders (53). There is increasing evidence that aerobic exercise promotes the clearance of triacylglycerol and low-density lipoprotein cholesterol (54–56), thereby preventing oxidative stress, which in turn reduces arterial stiffness.

In addition, Beck et al. (57) found that an increase in PWV may be associated with a decrease in endothelial function. The increase in PWV is manifested by the decrease in the bioavailability of endothelial-derived nitric oxide (NO) (58). NO is produced by L-arginine through endothelial nitric oxide synthase (eNOS) in the vascular endothelium, which has the effect of dilating blood vessels. Maeda et al. suggested that exercise increases the bioavailability of NO and reduces PWV (58), which was in line with the report by Taddei et al. showing that regular exercise restores the utilization of NO after oxidative stress and prevents age-induced endothelial dysfunction. A previous study showed that NO increased and PWV decreased after 24 weeks of aerobic exercise, and a significant negative correlation between NO and PWV was

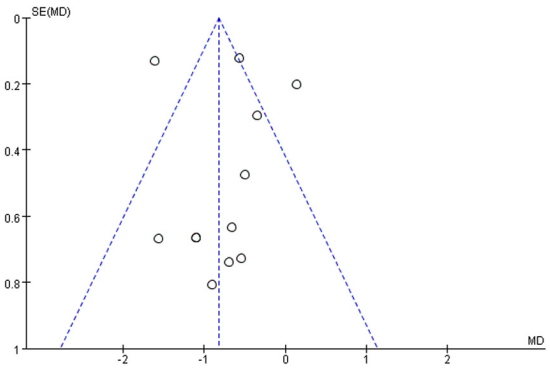

FIGURE 3
Funnel plot.

observed (59). Taken together, aerobic exercise in middle-aged and elderly people can increase the synthesis and bioavailability of NO, reduce circulating endothelin-1 (ET-1), increase flow-mediated dilation (FMD) of the brachial artery, improve the endothelial function, and ultimately reduce PWV (60).

In conclusion, aerobic exercise in middle-aged and elderly people can reduce fat accumulation and improve glycolipid metabolism and endothelial function, thereby reducing arterial stiffness and playing an important role in preventing arteriosclerosis.

Subgroup analysis

According to the studies we included, aerobic exercise significantly reduced PWV in middle-aged and elderly people, but the heterogeneity between groups was high. Therefore, we used subgroup analysis to interpret the results. In the subgroup analyses, we sought to determine the effects of exercise intensity and characteristics of the participants.

Previous studies have demonstrated that aerobic exercise has a positive effect on arterial stiffness (61–63). However, some studies have found that PWV does not always decrease with increasing aerobic exercise intensity, for example, Zempo-Miyaki et al. (23) showed that 8 weeks of aerobic exercise (60–70% peak oxygen uptake) significantly reduced PWV in middle-aged and elderly people, while Oudegeest-Sander et al. (64) reported that 12 months of cycling exercise (70–85% of individual HRR) had no effect on PWV in elderly people, suggesting that exercise intensity was a key factor affecting the impact of the intervention. Therefore, we divided the study into a moderate-intensity group and a vigorous-intensity group. Compared with the control group, vigorous-intensity exercise significantly reduced PWV, while moderate-intensity exercise had no significant effect on PWV. Previous studies have demonstrated that vigorous-intensity exercise may generate greater shear stress in endothelial cells, thereby improving endothelial function, reducing oxidative stress, and improving vascular function (25, 50, 65, 66), which is consistent with our study showing that vigorous-intensity exercise can significantly reduce the arterial stiffness in middle-aged and elderly people. However, recent studies have shown that exercise intensity definition based on percentages of peak HR and VO_2peak may misclassify the effective exercise intensity, and the discrepancy between the individually determined and the recommended exercise intensity is particularly relevant in cardiac patients. And a ventilatory threshold-based rather than a range-based approach is advisable to define an appropriate

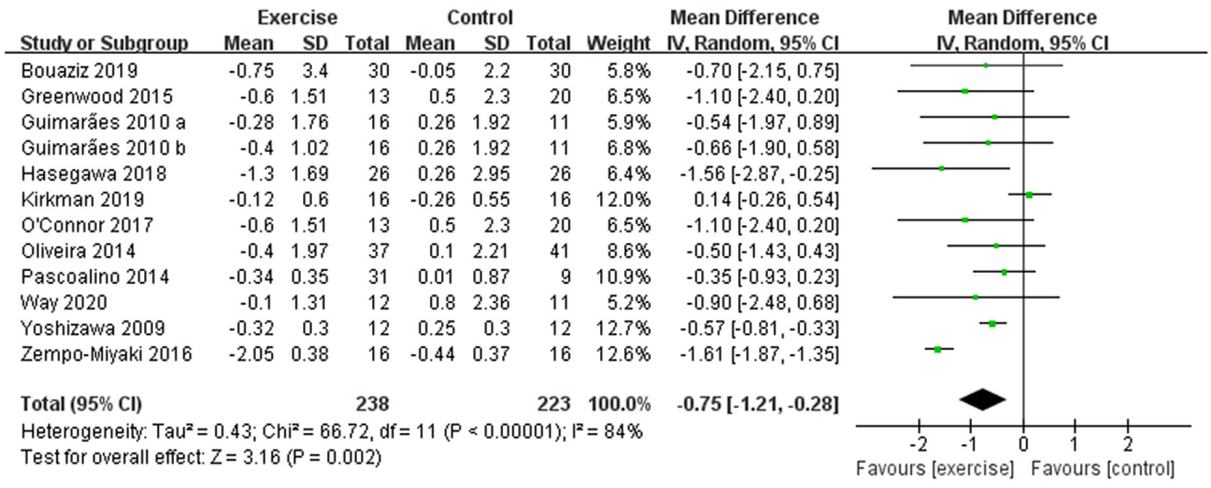

FIGURE 4
Meta-analysis results of the effect of aerobic exercise on the PWV of middle-aged and elderly people. The pooled estimates were obtained from random effects analysis. Diamonds indicate the effect size of each study summarized as WMD. The size of the shaded squares is proportional to the percentage weight of each study. Horizontal lines represent the 95% CI and the vertical line represents the overall effect.

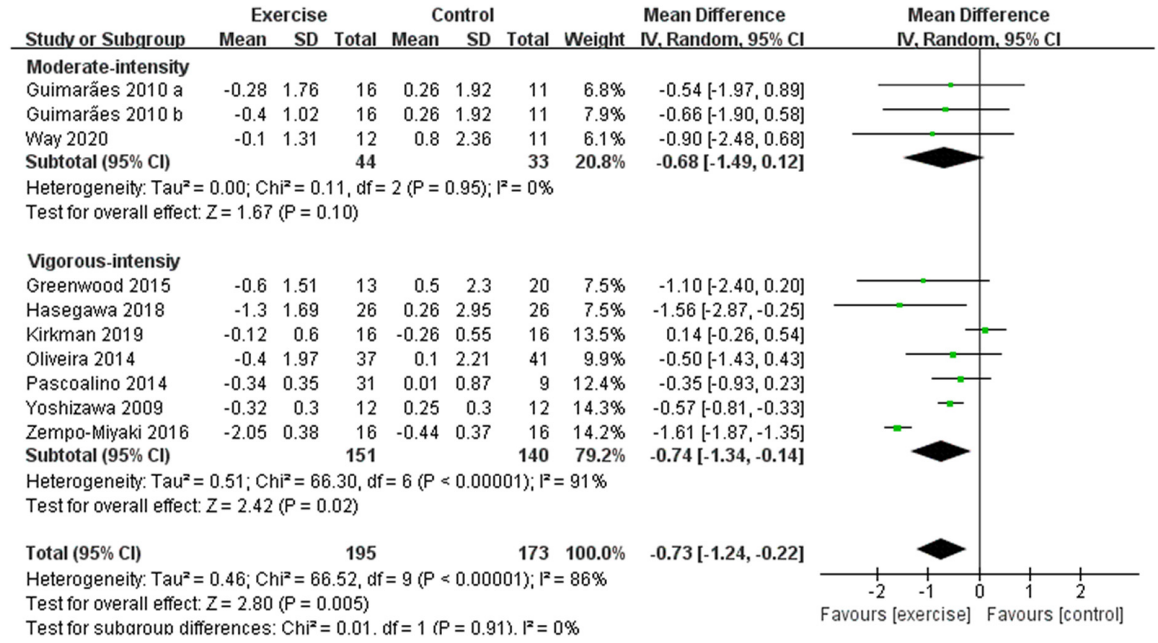

FIGURE 5
Meta-analysis results of the effect of different intensities of aerobic exercise on the PWV of middle-aged and elderly people. The pooled estimates were obtained from random effects analysis. Diamonds indicate the size of the effect of each study summarized as WMD. The size of the shaded square is proportional to the percentage weight of each study. Horizontal lines represent the 95% CI and the vertical dashed line represents the overall effect.

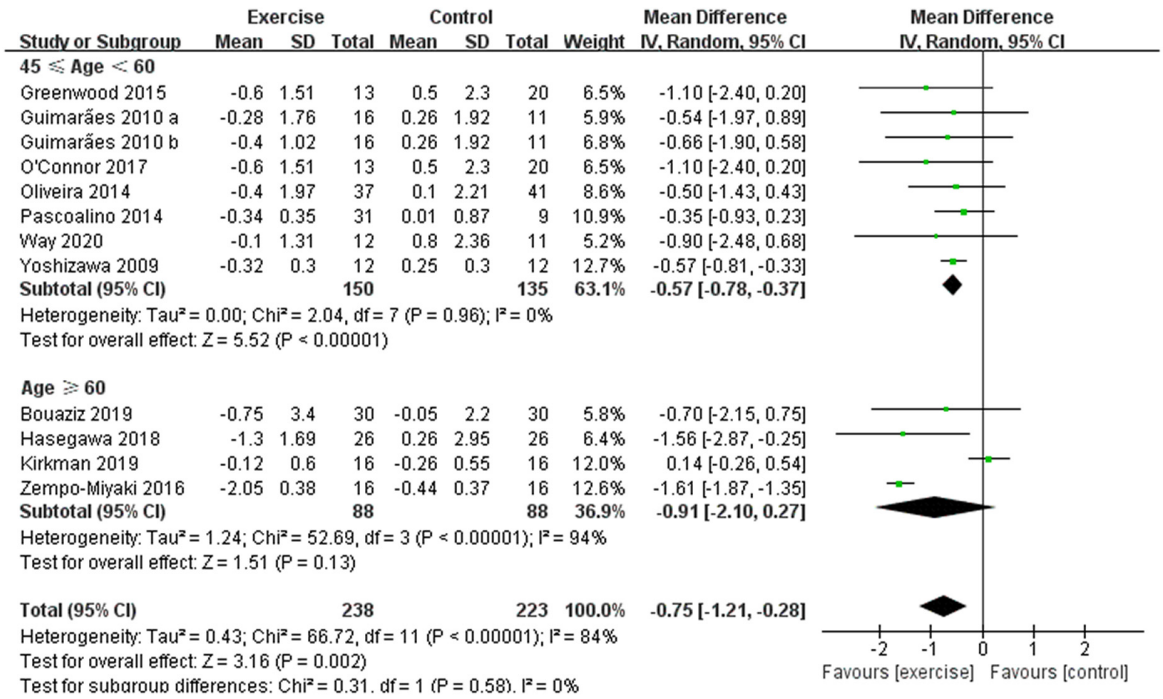

FIGURE 6
Meta-analysis results of the effect of aerobic exercise on the PWV of middle-aged people or elderly people. The pooled estimates were obtained from random effects analysis. Diamonds indicate the size of the effect of each study summarized as WMD. The size of the shaded square is proportional to the percentage weight of each study. Horizontal line represents the 95% CI and the vertical dashed line represents the overall effect.

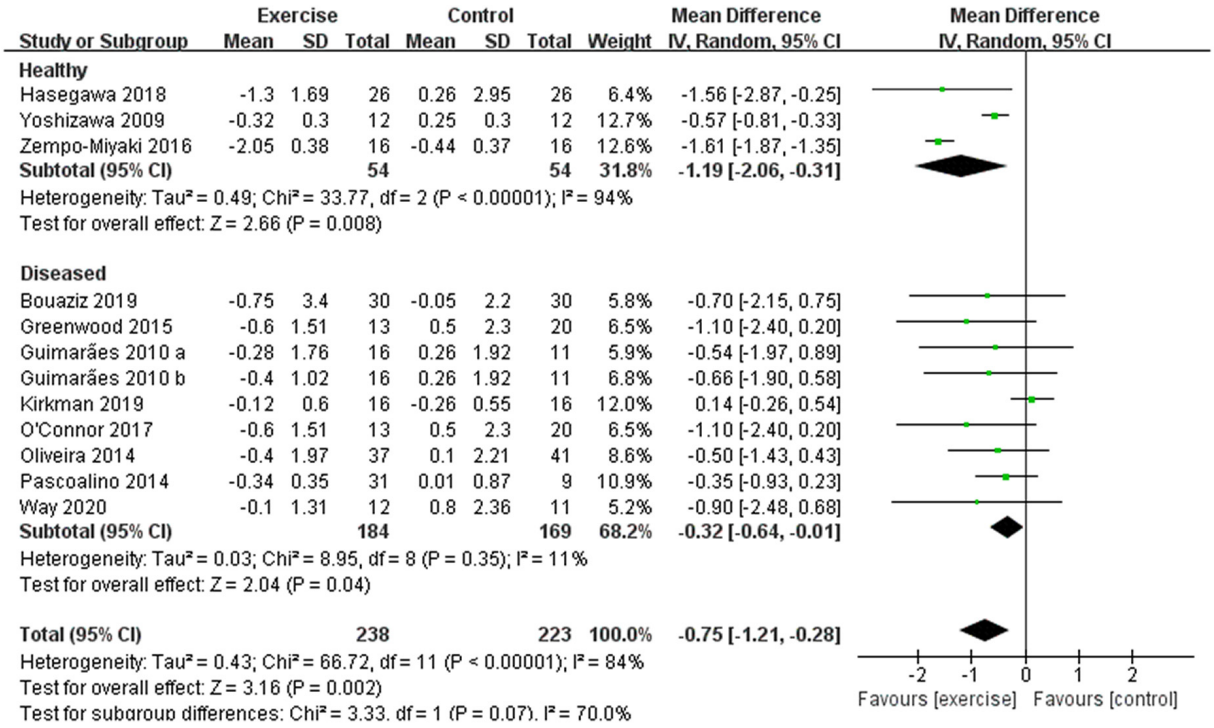

FIGURE 7
Meta-analysis results of the effect of aerobic exercise on the PWV of healthy or diseased middle-aged and elderly people. The pooled estimates were obtained from random effects analysis. Diamonds indicate the size of the effect of each study summarized as WMD. The size of the shaded square is proportional to the percentage weight of each study. Horizontal line represents the 95% CI and the vertical dashed line represents the overall effect.

level of exercise intensity (67, 68). In addition, according to the European Association of Preventive Cardiology (EAPC) position statement on the assessment and prescription of aerobic exercise intensity in cardiovascular rehabilitation, the assessment of ventilatory threshold 1 (VT1) and VT2 during cardiopulmonary exercise test (CPET) should be used for the determination of the aerobic exercise intensity in the majority of CVD patients (69). Therefore, since studies included in this systematic review and meta-analysis used HR and VO_2max to define the exercise intensity, those focused on CVD populations need to be cautious when referring to our finding.

A previous study showed that blood pressure increases more rapidly in adults after the age of 60 years, which is the critical point for a higher incidence of CVDs (70). Therefore, the included studies in this meta-analysis were divided into two subgroups by the age of participants, namely, middle-aged group and elderly group. Compared with the control group, aerobic exercise significantly reduced PWV in middle-aged people, while aerobic exercise had no significant effect on PWV in elderly people, indicating that aerobic exercise had a better effect on PWV in middle-aged people than in elderly people. Aging is an inevitable part of life, and aerobic exercise has a limited effect on improving vascular endothelial function. For example, Ha et al. (11) found that 12 weeks of aerobic exercise did not reduce PWV in women aged 70–80 years, which may be related to sex hormone levels of middle-aged and elderly people. Cross-sectional studies have also reported an age-related decline in sex hormones, with a sharp decline in sex hormones after the age of 65 years (71, 72). Additionally, a previous study reported that sex hormone levels may influence the effect of aerobic exercise on improving cardiovascular function (73). In addition, one study found that the benefit of aerobic exercise on vascular function was diminished in estrogen-deficient postmenopausal women, but in this group, estrogen treatment appeared to restore improvements in endothelial function (73). Furthermore, studies have shown that aortic PWV increases by approximately 0.10 m/s per year with age, with a weak annual increase in PWV (less than 0.10 m/s) in subjects before the age of 45 years, indicating a low rate of arteriosclerosis in young adults (74, 75). Therefore, the insignificant decline in PWV in the elderly may also be due to the insufficient effect of exercise against vascular aging.

In the abovementioned results, we suspected that the improvement of arterial stiffness by exercise was influenced by a variety of CVDs, so this report divided the included studies into two subgroups, namely, the healthy group and the diseased group. Compared with the control group, aerobic exercise significantly reduced PWV in both healthy and diseased

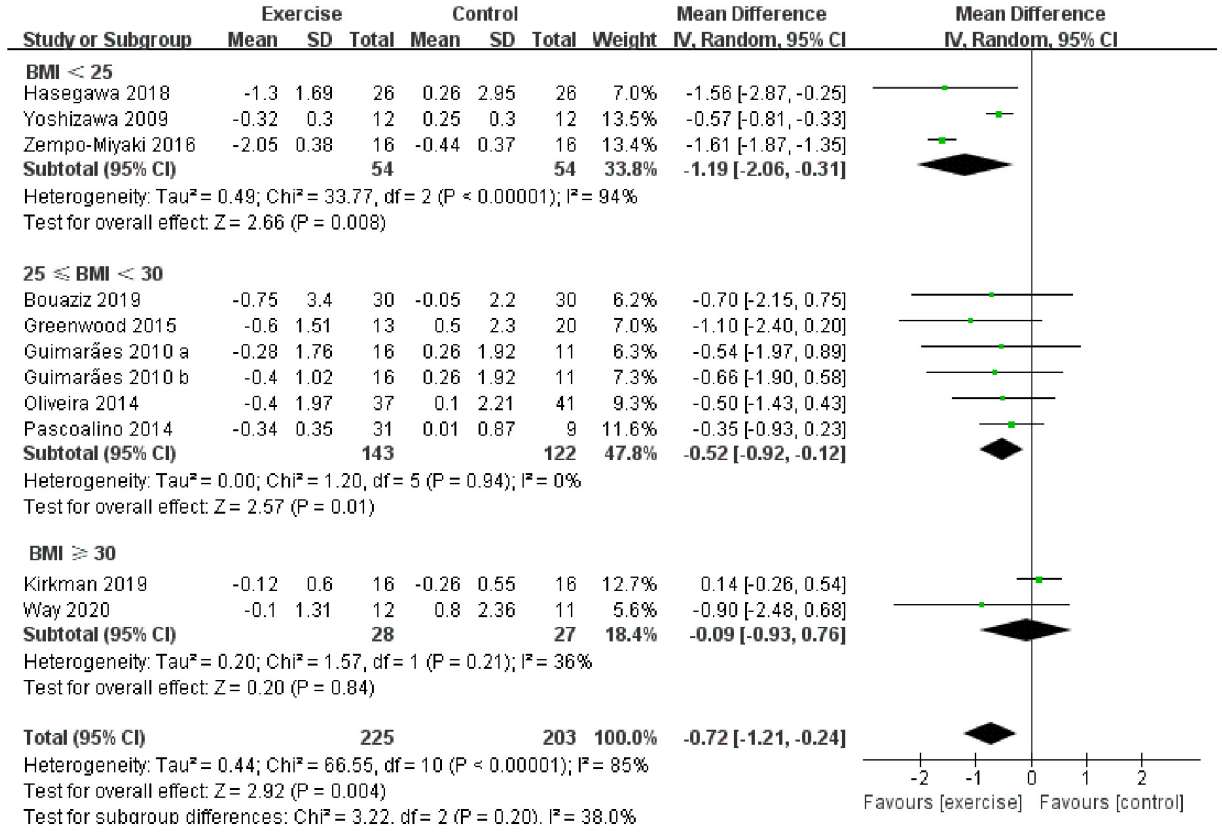

FIGURE 8
Meta-analysis results of the effect of aerobic exercise on the PWV of normal weight, overweight, or obese middle-aged and elderly people. The pooled estimates were obtained from random effects analysis. Diamond indicated the size of the effect of each study summarized as WMD. The size of the shaded square is proportional to the percentage weight of each study. Horizontal line represents the 95% CI and the vertical dashed line represents the overall effect.

individuals, while a better health status was associated with larger reductions, which was consistent with a previous study, showing that aerobic exercise had no long-term effect on arterial stiffness in older adults with cardiometabolic risk factors (76). Therefore, the lesser the number of risk factors for CVDs or the types of CVDs, the better the effect of aerobic exercise.

Obesity is an independent predictor of CVDs, and weight loss has been shown to improve many obesity-related risk factors; therefore, we divided the included studies into normal weight, overweight, and obese groups based on the basal BMI of the participants. Our results showed that compared with the control group, aerobic exercise significantly reduced PWV in normal weight and overweight people, whereas aerobic exercise had no significant effect on PWV in obese people. In addition, a lower BMI was associated with larger reductions in PWV, indicating that aerobic exercise had a better effect on PWV in lower BMI people than in higher BMI people, which was consistent with a previous study, showing that a mean weight loss of 8% resulted in a statistically and clinically significant PWV reduction of 0.6 m/s, suggesting that a lower BMI was associated with lower rates of arteriosclerosis (77). Therefore, arteriosclerosis in people with a higher BMI may be a major determinant of morbidity and mortality in this population.

Limitations of the review

Some potential limitations of this meta-analysis should be acknowledged. First, the included studies were all RCTs of aerobic exercise intervention, which could not be completely blinded. Therefore, in the quality evaluation process, subjective factors will cause a certain degree of deviation. Second, studies included in this systematic review and meta-analysis used HR and VO_2max to define the exercise intensity, and studies focused on CVDs populations need to be cautious when referring to our finding. Finally, although the included studies did not specify any adverse events associated with the aerobic exercise intervention, it is unclear whether the researchers attempted to comprehensively document all possible adverse events. Therefore, future studies with more detailed data describing possible injury, pain, and/or any other potential adverse effects

are encouraged, as this will expand our knowledge of the safety of aerobic exercise in middle-aged and elderly people.

Conclusion

Our analysis indicated that aerobic exercise, especially vigorous-intensity aerobic exercise, contributed to reducing PWV in middle-aged people. The effect of aerobic exercise on improving PWV was associated with characteristics of the participant. Specifically, a younger age, a better health status, and a lower basal BMI contributed to more significant reductions in PWV.

Data availability statement

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

Author contributions

GL wrote the manuscript. LY and YL contributed to the conception. GL and YL did the literature search. GL, YL, and LY extracted the data. QS and QY contributed to the acquisition. All authors have read and approved the final manuscript.

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Conflict of interest

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

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.960096/full#supplementary-material

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Hemodynamic and cardiorespiratory responses to submaximal and maximal exercise in adults with Down syndrome

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Introduction: The genetic disorder causing Down syndrome (DS) affects the cardiorespiratory and hemodynamic parameters. When exercising, sufficient blood flow is necessary for active muscles. Cardiac output (Q) must be proportional to the peripheral requirements. In case the stroke volume (SV) is lower, the heart rate (HR) will increase further in order to maintain an adequate blood flow in the active territories (HR compensatory response). People with DS have a lower HR response to maximal exercise. Nevertheless, the response of the hemodynamic and cardiorespiratory parameters during the submaximal phases of maximal exercise was not well studied.

Objective: to evaluate cardiorespiratory and hemodynamic parameters 1) during submaximal and 2) maximal metabolic treadmill test in individuals with and without DS.

Methods: fifteen adults with DS (age = 27.33 ± 4.98 years old; n = 12 males/3 females) and 15 adults without disabilities, matched by age and sex, participated in this cross-sectional study. Peak and submaximal cardiorespiratory and hemodynamic parameters were measured during a treadmill test. Linear mixed-effects models were used to analyse interactions between the variables. Post-hoc analyses were employed to assess within and between-group differences.

Results: The DS group showed lower peak values for ventilation (VE), respiratory exchange ratio (RER), tidal volume (V_T), ventilatory equivalent for O_2 ($VEqO_2$), end-tidal partial pressure for O_2 ($P_{ET}O_2$), O_2 uptake (VO_2) and CO_2 production (all $p < 0.050$), Q, SV, systolic and diastolic blood pressure (SBP, DBP), and HR (all $p < 0.050$). There were group-by-time interactions (all $p < 0.050$) for all ventilatory

submaximal values. Significant group and time differences were observed for VE; RER; respiratory rate (RR); $VEqO_2$; $P_{ET}O_2$; VO_2, and V_T (all $p < 0$ .050). There were also group-by-time interactions (all $p < 0$ .050) and group and time differences for SBP, mean arterial blood pressure (MAP) and HR (all $p < 0.010$).

Conclusion: During submaximal exercise, we verified a compensatory response of HR, and greater VE and VO_2 in the individuals with DS. In addition, we were able to observe that the DS group had a reduced SBP and MAP response to submaximal exercise. On the other hand, we found that adults with DS have lower peak hemodynamic and cardiorespiratory values, and a lower cardiac reserve. Further research is warranted to investigate the effects of these results on the general health of adults with DS and the impact of long-term exercise programs on these parameters.

KEYWORDS

down syndrome, cardiorespirarory fitness, blood preasure, exercice, hemodymamics

1 Introduction

Down syndrome (DS) is a chromosomal disorder that occurs in the human species, which has a variable and a wide range of impact and severity at an individual level. This genetic disorder influences physical and clinical characteristics, cardiorespiratory fitness, and intellectual disability (World Health Organization, 2000). European DS prevalence during 2011–2015 was estimated at 4.9 per 10,000 inhabitants, which corresponds to approximately 359,000 people with DS living in Europe, of whom 35% are under the age of 20 and 35% above 40 years old (De Graaf et al., 2018).

Down syndrome individuals' life expectancy and survival have increased significantly since the 1960s, with median life expectancy in the late 50 s (Englund et al., 2013; Glasson et al., 2016). This is secondary to better preventive health care, educational programs, curative surgical intervention on congenital and gastro-intestinal anomalies, and social support. Some predictors of life expectancy include race, sex, birth weight, gestational age at birth, and presence of heart defects and other structural anomalies (Yang et al., 2002; Englund et al., 2013). Infectious diseases, mainly pneumonia, followed by congenital heart defects, circulatory disease, and dementia, are the leading causes of death in individuals with DS (Englund et al., 2013). Also, one of the most significant studies analysing cardiovascular abnormalities in DS identified that 342 of 821 (42%) DS infants born from 1985 to 2006 had cardiovascular anomalies (Irving and Chaudhari, 2012).

Individuals with DS have a broad spectrum of cardiovascular disease, and multiple studies have found that their response to exercise is different from non-DS individuals (Mendonca et al., 2010; Fernhall et al., 2013). Baynard et al. (2008) reported that the peak oxygen consumption (VO_2peak) in adolescents and adults with DS was similar to 60-year-old non-disabled adults. Moreover, other studies have proposed that individuals with DS would have autonomic dysfunctions such as decreased responses to sympathetic nervous system stressors, altered baro-reflex sensitivity, cardiovascular chronotropic incompetence, and altered hormonal response to exercise (Heffernan et al., 2005; Bricout et al., 2008; Fernhall et al., 2013; Hilgenkamp et al., 2019). Interestingly, it was found that at rest, individuals with DS have higher parasympathetic activity than their peers without disabilities, but during the exercise these differences disappeared. Therefore, the authors suggest that low-intensity exercise may facilitate an adequate increase in heart rate (HR), and other variables may be responsible for the inability to increase HR as expected during maximal exercise (Baynard et al., 2004).

It is documented that at rest and during one set of light strength exercise, parameters such as cardiac output (Q), stroke volume (SV), and HR are lower in people with DS (Vis et al., 2012a). In addition, previous work shows that there are higher metabolic demands in people with DS versus non-DS at submaximal intensities of exercise, which makes DS persons less efficient when performing physical activities or exercise (Agiovlasitis et al., 2009).

We think that it is important not only to determine these parameters during maximal exercise, as other researchers have done, but also during submaximal exercise. As part of daily life, people perform physical activity at submaximal intensities. As Oppewal et al. (2020) indicate, even the performance of exercises whose energy expenditure corresponds to low intensities will benefit the health of persons with intellectual disabilities. Therefore, investigating the response of hemodynamic and cardiorespiratory parameters, not only during maximal exercise but also at submaximal intensities, can provide insight into the response and function of these parameters at magnitudes that are more representative of activities of daily living.

Thus, the main objectives of our study were to analyse and compare the responses of cardiorespiratory and hemodynamic

parameters during maximal and submaximal exercise in individuals with and without DS matched by age and sex.

2 Methods

2.1 Study design and participants

This cross-sectional study included three women and 12 men with DS (27 ± 5 years old) and 15 adults without disabilities (non-DS) with similar ages and sex. Participants with DS from three occupational day centers were invited for this study. Adults without DS were recruited from Universities' campuses. A previous study where cardiorespiratory parameters were assessed in adults with and without DS, showed a large effect size (Hilgenkamp et al., 2018). Therefore, after calculating the sample size (power = 0.80; $\alpha < 0.05$; effect size of $d = 1$), we determined that we needed to recruit at least 28 participants (14 in each group).

Interested persons between 18 and 35 years old with and without DS, matched by age and sex, were invited to the laboratory facilities. Before obtaining the informed consent of participants and parents/legal guardians, we explained the study protocol, benefits and risks. Next, all participants were given ample time to read the study protocol and ask all necessary questions. Finally, all volunteers undergo a physical examination to disclose any physical and/or cardiovascular pathology that would make maximal exercise contraindicated.

To be part of the present study, all participants needed to be able to walk without aids; be willing to perform a treadmill test; and parents/legal guardians and participants should have signed the informed consent. In addition, exclusion criteria were: taking medications that could affect physical performance or HR; having any cardiovascular disease or other contraindications to exercise.

This study was approved by the Institutional Review Board (CER URL 2017_2018_008) and complied with the principles of the Declaration of Helsinki (World Medical Association, 2013).

2.2 Testing procedure

We organized one to three familiarization sessions so that participants could become acquainted with the tests and equipment used in this study. All tests were performed during the morning, and all participants were requested to neither take part in moderate or vigorous exercise nor consume alcohol and/or caffeine for at least 24 h before the testing day.

2.2.1 Anthropometric measurements

We measured participants' height (Seca 225, Seca, Hamburg, Germany) and weight (Tanita MC-780U, Arlington Heights, IL, United States) to the nearest 0.1 cm and 0.1 kg, respectively. Finally, we calculated the body mass index (BMI) for every participant by using the equation weight (kg)/height (m^2).

2.2.2 Cardiorespiratory fitness assessment

Participants walked on a treadmill (Quasar model, HP Cosmos sports and medical gmbh, Nussdorf-Traunstein, Germany) at a constant speed (4 km/h), and the gradient increased 2.5% every 2 min until a grade of 12.5% was attained. From this point, grade remained constant, whereas speed was increased 1.6 km/h every minute up to exhaustion. This protocol was used by different authors to assess the cardiorespiratory fitness in persons with DS (Fernhall and Tymeson, 1987; Mendonca and Pereira, 2009; Boer and Moss, 2016; Hilgenkamp et al., 2018). Peak values were calculated from the average of the last 30 s of exercise. Peak effort was identified by a respiratory exchange ratio (RER) > 1.0, or HR and/or VO_2 plateau and when a participant could no longer continue. Values were recorded continuously, and every minute's average was used for the submaximal analysis. In this case, the highest submaximal workload was considered as the one exceeded by 90% of our participants.

We measured the respiratory gas exchange with an automatic gas analysis system (Metasys TR-plus, Brainware SA, La Valette, France) and using a two-way mask (Hans Rudolph, Kansas, United States). Before each test, we performed gas and volume calibrations. In addition, we used a 12-lead electrocardiogram to monitor the HR of the participants (CardioScan v.4.0, DM Software, Stateline, Nevada, United States).

2.2.3 Hemodynamic assessments

As in previous studies performed in our laboratory (Esquius et al., 2019; Oviedo et al., 2021), we used a finger cuff to obtain beat-to-beat hemodynamic and blood pressure (BP) information (Nexfin, BMEYE Amsterdam, Netherlands). Stroke volume and Q are derived by pulse contour method using the measured systolic pressure-time integral and the afterload of the heart (Wesseling et al., 1993). The finger cuff was placed around the middle phalanx of the left middle finger, and the arm was placed on a platform and secured with elastic straps to prevent any movement. We monitored the finger photoplethysmography continuously, and values were averaged every minute. Peak values were obtained from the last 30 s of the treadmill test. For the present analysis, all data obtained in each time point were visually inspected and values containing a variation higher or lower than two SD were eliminated.

2.3 Statistical analysis

Descriptive statistics were calculated for all variables. We used the Kolmogorov-Smirnov and Shapiro Wilk tests to check the normality of the data.

TABLE 1 Participants' characteristics.

	Non-DS (n = 15)			DS (n = 15)			*p*-value	Effect size
Characteristics								
Sex (male/female)	12/3			12/3			1.000	--
Age (years)	27.3	±	5.0	27.3	±	5.0	1.000	--
Weight (kg)	71.5	±	9.9	66.6	±	9.9	0.185	0.50
Height (m)	1.75	±	0.09	1.56	±	0.06	<0.001	2.40
BMI (kg/m^2)	23.3	±	1.6	27.4	±	4.3	0.002	1.28

values are mean ± standard deviation.
Abbreviations; DS (Down syndrome); BMI (body mass index).

TABLE 2 Participants' cardiorespiratory and hemodynamic values at rest.

	Non-DS (n = 15)			DS (n = 15)			*p*-value	Effect size
	Resting values			Resting values				
Cardiorespiratory data								
VE (L•min^{-1})	10.1	±	1.7	9.9	±	2.9	0.720	0.13
RER	0.88	±	0.04	0.85	±	0.05	0.416	0.30
RR (breath•min^{-1})	18.3	±	4.1	20.8	±	6.4	0.162	0.52
V_T (L)	0.50	±	0.13	0.48	±	0.11	0.171	0.51
$VEqO_2$	31.1	±	4.8	29.2	±	4.4	0.273	0.41
$VEqCO_2$	108.2	±	6.1	106.7	±	4.2	0.139	0.56
$P_{ET}O_2$ (mmHg)	37.8	±	5.7	34.8	±	4.9	0.581	0.20
VO_2 (ml•kg^{-1}•min^{-1})	4.5	±	0.9	5.0	±	1.1	0.208	0.47
VO_2 (L•min^{-1})	0.32	±	0.06	0.33	±	0.11	0.423	0.30
VCO_2 (L•min^{-1})	0.28	±	0.05	0.28	±	0.15	0.368	0.33
Hemodynamic data								
Q (L•min^{-1})	6.4	±	2.8	6.5	±	2.6	0.913	0.04
Stroke Volume (ml)	84.3	±	22.7	75.0	±	21.1	0.252	0.42
SBP (mmHg)	137.0	±	26.6	119.5	±	24.8	0.120	0.67
DBP (mmHg)	86.6	±	16.6	78.8	±	15.4	0.089	0.48
MAP (mmHg)	106.2	±	19.9	94.3	±	18.5	0.082	0.62
SVR (dyn•s^{-1}•cm^{-5})	1,447.5	±	531.1	1700.0	±	494.4	0.086	0.49
O_2 pulse (ml•beat^{-1})	4.37	±	2.74	4.08	±	2.78	0.773	0.10
HR (beat•min^{-1})	77.0	±	14.2	83.0	±	13.1	0.290	0.43

values are mean ± standard deviation.
Abbreviations: DS (Down syndrome); VE (minute ventilation); RER (respiratory exchange ratio); RR (respiratory rate); V_T: tidal volume; VE_qO_2: ventilatory equivalent for O_2; VE_qCO_2: ventilatory equivalent for CO_2; $PETO_2$ (end-tidal partial pressure for oxygen); VO_2 (oxygen uptake); VCO_2 (carbon dioxide production); Q (cardiac output); SBP (systolic blood pressure); DBP (diastolic blood pressure); MAP (mean arterial pressure); SVR (systemic vascular resistance); HR (heart rate).
p-value: between-group differences at rest.

The interactions between group (DS vs. non-DS) and condition (different workloads) were analysed using a linear mixed-effects model. In addition, post-hoc comparisons with Bonferroni correction were conducted to analyse within and between-group differences. Finally, to examine between-group differences in characteristics, cardiorespiratory and hemodynamic peak values, independent *t*-tests were conducted, and effect size (Cohen's *d*) was calculated when possible with 0.2; 0.5 and 0.8 indicating a small, medium and large effect, respectively (Cohen, 1988).

Statistical analyses were performed with the Statistical Package for the Social Sciences version 25.0 (IBM SPSS, Chicago, IL, United States). Statistical significance was set at an alpha level < 0.050 ($p < 0.050$).

TABLE 3 Participants' peak cardiorespiratory and hemodynamic values.

	Non-DS (n = 15)			DS (n = 15)			*p*-value	Effect size
	Peak values			Peak values				
Cardiorespiratory data								
VE ($L \bullet min^{-1}$)	123.9	±	23.3	53.7	±	14.5	<0.001	3.61
RER	1.14	±	0.03	1.12	±	0.03	0.043	0.77
RR ($breath \bullet min^{-1}$)	46.3	±	7.4	42.0	±	7.8	0.139	0.56
V_T (L)	2.47	±	0.59	1.15	±	0.22	<0.001	2.93
$VEqO_2$	33.9	±	3.8	28.2	±	2.6	<0.001	1.75
$VEqCO_2$	27.8	±	2.8	27.8	±	2.3	0.992	0.00
$P_{ET}O_2$ (mmHg)	112.4	±	3.8	107.5	±	3.0	0.001	1.42
VO_2 ($ml \bullet kg^{-1} \bullet min^{-1}$)	51.6	±	10.9	28.8	±	6.7	<0.001	2.53
VO_2 ($L \bullet min^{-1}$)	3.73	±	0.91	1.90	±	0.44	<0.001	2.55
VCO_2 ($L \bullet min^{-1}$)	4.26	±	0.98	2.12	±	0.54	<0.001	3.12
VO_2 max predicted (%)	123.1	±	16.3	77.9	±	10.7	<0.001	3.27
Respiratory reserve (%)	14.3	±	9.6	55.5	±	8.2	<0.001	4.50
Treadmill test duration (min)	16.6	±	2.0	12.5	±	2.1	<0.001	1.99
Hemodynamic data								
Q ($L \bullet min^{-1}$)	20.2	±	3.0	14.1	±	3.6	0.002	1.32
Stroke Volume (ml)	113.2	±	20.4	94.2	±	22.9	0.030	0.87
SBP (mmHg)	188.4	±	34.0	141.6	±	22.7	<0.001	1.56
DBP (mmHg)	106.0	±	21.5	85.6	±	17.2	0.016	0.97
MAP (mmHg)	141.6	±	26.8	107.5	±	22.0	0.001	1.36
SVR ($dyn \bullet s^{-1} \bullet cm^{-5}$)	794.4	±	315.2	916.3	±	463.8	0.431	0.30
O_2 pulse ($ml \bullet beat^{-1}$)	20.4	±	4.2	12.5	±	2.5	<0.001	1.96
HR ($beat \bullet min^{-1}$)	183.0	±	7.1	150.0	±	13.1	<0.001	3.04

Note: values are mean ± standard deviation.
Abbreviations: DS (Down syndrome); VE (minute ventilation); RER (respiratory exchange ratio); RR (respiratory rate); V_T: tidal volume; $VEqO_2$: ventilatory equivalent for O_2; $VEqCO_2$: ventilatory equivalent for CO_2; $P_{ET}O_2$ (end-tidal partial pressure for oxygen); VO_2 (oxygen uptake); VCO_2 (carbon dioxide production); Q (cardiac output); SBP (systolic blood pressure); DBP (diastolic blood pressure); MAP (mean arterial pressure); SVR (systemic vascular resistance); HR (heart rate).
p-value: between-group differences for peak values.

3 Results

The general characteristics of the participants are presented in Table 1. Both groups had similar weights. However, individuals with DS were shorter and had a higher BMI than the non-DS participants (all $p < 0.050$). Regarding cardiorespiratory and hemodynamic parameters at rest, we did not observe between-groups significant differences (Table 2).

3.1 Peak values

Compared to the peak values obtained by the non-DS group, individuals with DS had lower values for ventilation (VE; $p < 0.001$), respiratory exchange ratio (RER; $p = 0.043$), tidal volume (V_T; $p = < 0.001$), ventilatory equivalent for O_2 ($VEqO_2$; $p < 0.001$), end-tidal partial pressure for O_2 ($P_{ET}O_2$; $p = 0.001$), VO_2 ($p < 0.001$); CO_2 production (VCO_2; $p < 0.001$), achieved a lower percentage of the predicted VO_2 max ($p < 0.001$). The DS group had a higher percentage of the respiratory reserve at the end of the tests ($p < 0.001$). Finally, the test duration of the DS participants was shorter than the test duration of the non-DS group ($p < 0.001$) (Table 3). Regarding the hemodynamic parameters, the DS group had lower peak values for Q ($p = 0.002$), SV ($p = 0.030$), SBP ($p < 0.001$), DBP ($p = 0.016$), mean arterial BP (MAP; $p = 0.001$), O_2 pulse ($p < 0.001$), and HR ($p < 0.001$) than the non-DS group (Table 3).

3.2 Submaximal values

When analysing the ventilatory submaximal values (Figure 1A), significant interaction effects were observed for all variables ($p < 0.050$). In addition, significant group and time differences were observed for VE; RER; respiratory rate (RR); $VEqO_2$; $P_{ET}O_2$; VO_2, and V_T (all $p < 0.050$). However, for VCO_2 and $VEqCO_2$, we only found a significant difference in time ($p < 0.001$).

The analysis of the hemodynamic variables (Figure 1B) revealed significant interaction effects and group and time

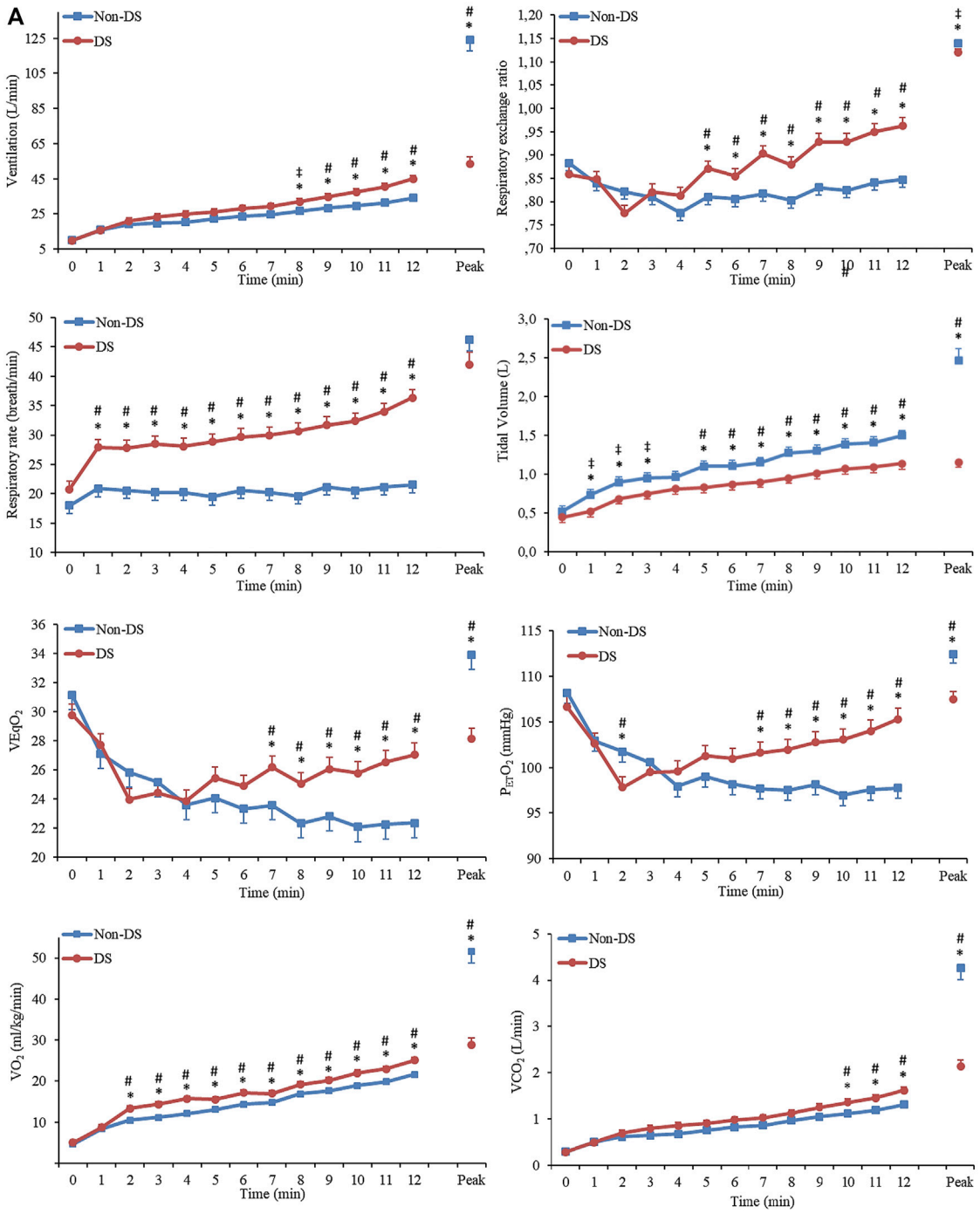

FIGURE 1
Cardiorespiratory and hemodynamic parameters in response to submaximal exercise in adults with and without Down syndrome. **(A)**: Cardiorespiratory parameters; **(B)**: Hemodynamic parameters. Abbreviations: DS (Down syndrome). Values are mean ± standard error. * Between-group differences ($p < 0.050$). ‡ Medium effect size. # Large effect size.

differences for SBP, MAP, and HR (all $p < 0.010$). Even though no significant interactions were observed for DBP, significant group and time differences were observed (all $p < 0.050$). We only found significant time differences for Q, SV, systemic vascular resistance (SVR), and O_2 pulse (all $p < 0.010$).

During the submaximal exercise, we found significant correlations between VE and VCO_2 for both groups (all $p < 0.001$) (Figure 2).

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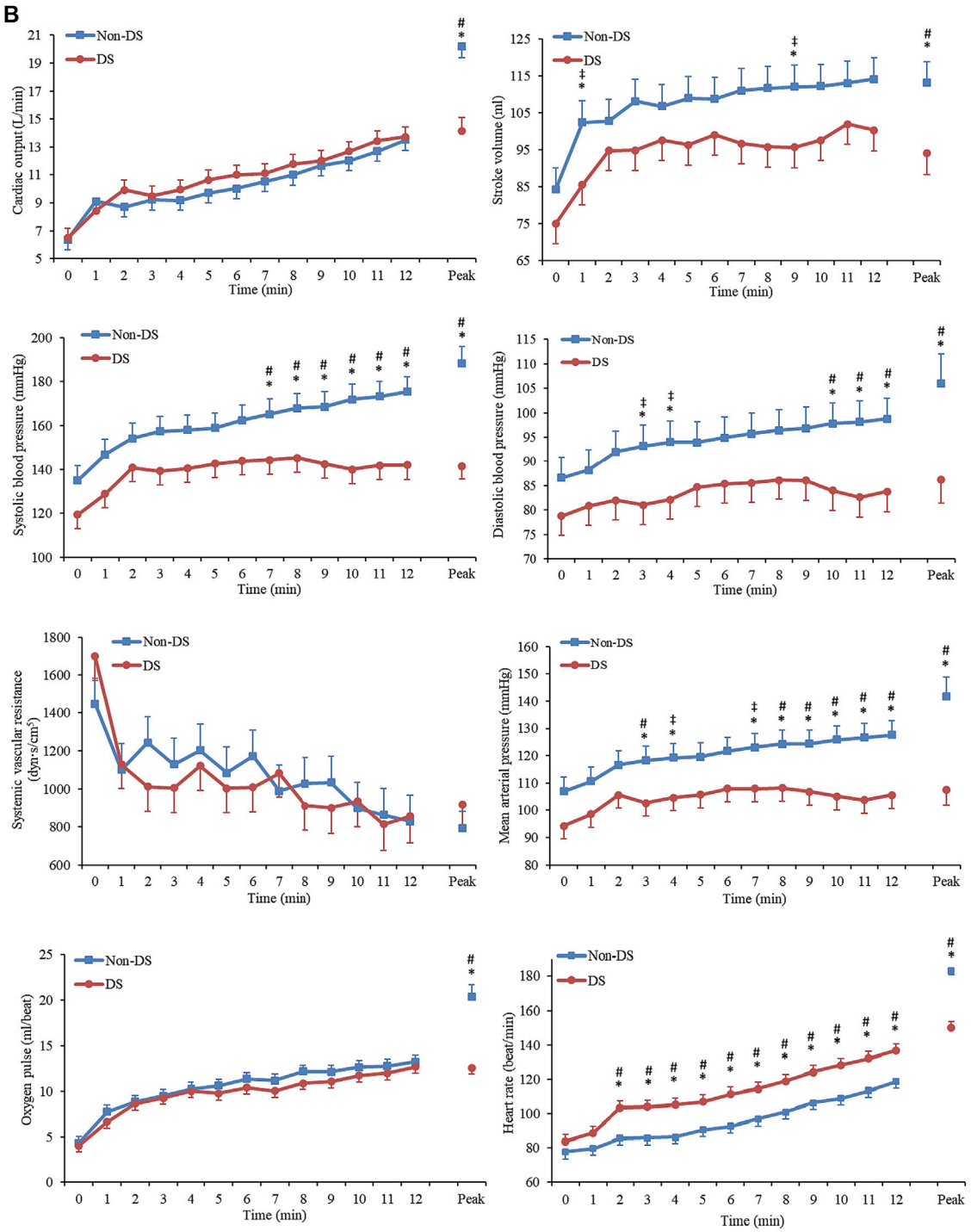

FIGURE 1
(continue).

4 Discussion

In the present study we observed differences in the cardiorespiratory response between the two groups (DS vs non-DS), both at submaximal and maximal intensities.

At submaximal effort, and comparing the same workloads performed by each group, we found that the response of cardiorespiratory parameters (VE; RER; RR; VO_2; HR) was higher in the DS group; while some hemodynamic parameters (SBP; DBP; MAP) were attenuated, or similar (Q; SV; SVR; O_2

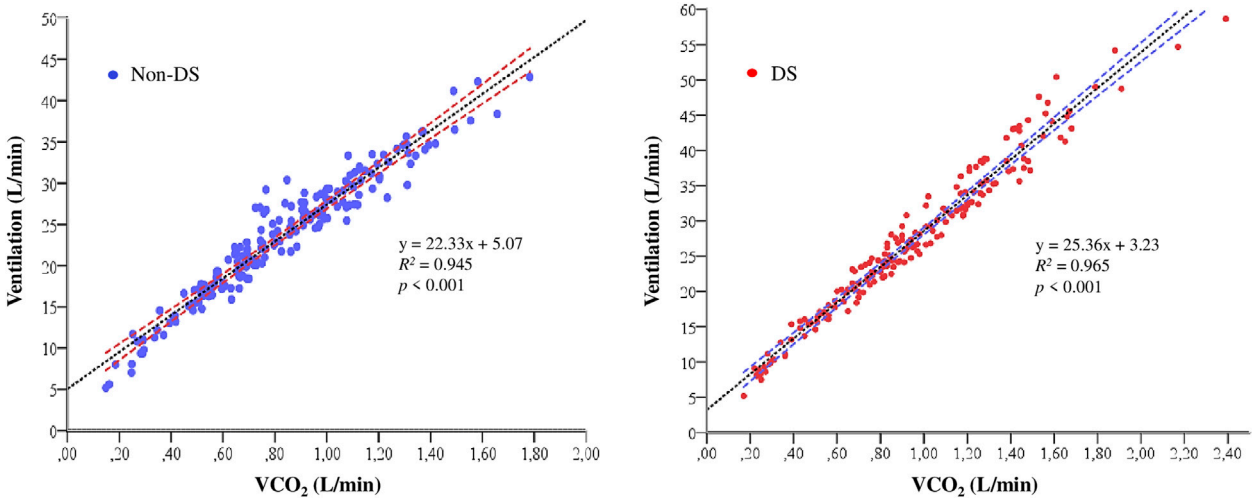

FIGURE 2
Relationship between ventilation (VE; L/min) and carbon dioxide production (VCO_2; L/min) during the submaximal phases of the treadmill test. Abbreviations: DS (Down syndrome).

pulse) compared with the non-DS group. A better understanding of specific characteristics and physiological demands that submaximal exercise represents for persons with DS, will help researchers, sports scientists, and physical therapists to better design exercise and rehabilitation programs by using adequate submaximal workloads, which are more representative of the metabolic cost and the intensities at which we moved during the activities of daily living.

As far as we know, this is the first time that a study examines and compares cardiorespiratory and hemodynamic parameters in response to maximal and submaximal exercise intensities in age- and sex-matched adults with and without DS. The results attained in our study during the peak exercise support and further substantiate previous studies showing that persons with DS have different physiologic and hemodynamic responses to maximal effort than peers without DS (Fernhall et al., 1996; Baynard et al., 2008; Fernhall et al., 2009; Fernhall et al., 2013).

4.1 Peak cardiorespiratory and hemodynamic responses

Concerning the peak cardiorespiratory values, our results reinforce the findings of previous reports, showing that adults with DS have lower peak cardiorespiratory fitness than non-DS adults (Baynard et al., 2008; Mendonca et al., 2010; Mendonca et al., 2011; Beck et al., 2021). The cause of these differences at peak exercise may include central and peripheral mechanisms (Fernhall et al., 2013). Moreover, as suggested by Fernhall et al. (2013), the autonomic dysfunction observed in DS persons may cause their reduced maximal HR.

In addition to lower peak HR, we also observed lower Q values, which negatively affect the peak VO_2 and the peak work capacity of individuals with DS. Furthermore, DS persons also present typical characteristics, such as micrognathia, tracheal stenosis, macroglossia (Bull, 2020), and impaired mitochondrial energy metabolism, among others (Valenti et al., 2018), limiting their maximal aerobic capacity. Among our participants, macroglossia was observed in all of them, which might have restricted peak ventilation and adversely affected the peak aerobic capacity.

Our results also allowed us to identify that our participants with DS had significant lower peak V_T than those without DS, which added to the fact that both groups present equal values for RR, made the quantities of air mobilized by the DS individuals considerably lower at peak intensities. Thus, negatively affecting O_2 supply and CO_2 elimination at peak workloads.

Concerning hemodynamic values, we also found that people with DS reached lower values of SV and Q during peak exercise. Different mechanisms could explain these differences. As indicated by Vis et al. (2012b), one of them is that adults with DS may have a smaller left ventricle compared to non-disabled adults. In addition to this, DS participants may have a lower venous return due to a blunted sympathetic control of blood flow (Hilgenkamp et al., 2018), affecting the preload conditions.

The peak values of the SBP, DBP, and MAP of the DS participants may be affected by a reduced peripheral vasoconstrictor control during the cardiopulmonary exercise test (Fernhall et al., 2013; Hilgenkamp et al., 2019). The effect of a lower MAP during the exercise could negatively affect the venous return, compromising the end-diastolic volume and the SV. If we add to all this that DS persons have lower peak HR (Guerra et al., 2003; Fernhall et al., 2013), the Q will be lower, as

we found in our results, thus compromising the correct blood volume distribution and the arrival of O_2 and nutrients needed to match the metabolic demands of peak workloads.

Cardiorespiratory fitness is a strong independent predictor of life expectancy (Strasser and Burtscher, 2018). Therefore, we believe that further research on these parameters are needed to analyse whether long-term increments in maximal exercise power may affect positively the mortality rate in DS persons.

Finally, we observed that peripheral vascular resistance at maximal loads was similar in both groups, and that the peak O_2 pulse, which reflects the myocardial O_2 supply and the cardiac functional reserve, was significantly higher in the non-DS. These data confirm that people with DS have a lower cardiac reserve and a much lower capacity than non-DS to increase it during maximal efforts.

4.2 Submaximal cardiorespiratory and hemodynamic responses

When performing an analysis of submaximal loads such as the one presented in our study, it is necessary to take into account the absolute workload used in each phase of the test (the need of energy for metabolic and mechanical work) and the duration of the effort. For this reason, we decided to carry out an innovative approach which allowed us to compare the responses of the parameters studied using the same absolute workloads and the same time of the test.

The data of our study showed a higher VO_2 at submaximal loads in the participants with DS. We hypothesize that there is a lower biomechanical efficiency of gait patterns in adults with DS; therefore, the participants with DS in our study may have higher needs of VO_2 when walking. Previous findings support this argument, suggesting that persons with DS have reduced walking economy and higher metabolic cost (Agiovlasitis et al., 2009; Mendonça et al., 2009; Agiovlasitis et al., 2015; Agiovlasitis et al., 2018). Unfortunately, the present protocol does not allow us to determine the causes of group differences in VO_2 when walking at submaximal intensities and compare them with the previous cited studies.

Our results showed that the individuals with DS had higher RR and lower V_T, which promoted a higher VE in the DS group. Undoubtedly, this produces a lower ventilatory efficiency, as shown by a higher $VEqO_2$ in the DS group. Furthermore, after analyzing the slopes of the relationship between VE and VCO_2 (DS = 25.36 points vs Non-DS = 22.33 points) (Figure 2), we may conclude that participants with DS have a lower ventilatory efficiency, which increases the energy expenditure required by the respiratory muscles for a given workload. On the other hand, the VE-to-VCO2 slopes for both groups are within the normal values, which range from 21 to 31 units (Sun et al., 2002; Naeije and Faoro, 2018), which indicates that the ventilatory response as a function of CO_2 production during submaximal exercise had a normal behavior in both groups. Together, this indicates that the DS group has a higher ventilatory work and, therefore, higher needs of O_2 because of a higher respiratory muscle activity, which may also justify the higher VO_2 at submaximal workloads (Figure 1A).

Moreover, higher RR in the DS group have several consequences, one of which is a higher HR at submaximal workloads compared to control individuals. This fact could explain the increase in HR despite having a lower sympathetic response (Fernhall et al., 2005). These results are consistent with Mendonca et al. (2011) study, where the authors found that DS persons have higher HR than non-DS adults at different submaximal workloads. On the contrary, Vis et al. (2012) found that the HR in DS individuals was lower after performing ten knee bends. Therefore, we hypothesize that in the study of Vis et al. (2012a), there was no compensation increase of the HR because of the short duration of the test (less than 45 s).

The increased ventilatory response could be of central origin and adaptive to the effort secondary to altered gait patterns (Agiovlasitis et al., 2015), neuromuscular abnormalities, and neurological impairments affecting stability and motor control (Zago et al., 2020). The physiological response of DS individuals may be disproportionate to the exercise performed. Moreover, and taking into account that Q is similar in both groups, and VO_2 is more significant in the DS group, the disproportionate increase in ventilation may be because the peripheral receptors of the carotid body may detect a slight decrease in O_2 levels, leading to greater ventilation to provide O_2. By trying to deliver more O_2 to a more significant number of working muscles during the exercise, the ventilation-perfusion ratio in the DS group would favor ventilation, increasing the $P_{ET}O_2$ (Figure 1A) in the alveolus and fostering CO_2 elimination. As shown in Figure 1A, this would also produce an increase in RER, which may not be related to the different metabolic substrates used during the treadmill test but rather a consequence of ventilatory adaptations during submaximal efforts.

As well as during the peak exercise, lower values of SBP, DBP, and MAP were observed in the DS group during submaximal exercise. This could be explained by the autonomic dysfunction affecting persons with DS, which would cause a lower inotropic and chronotropic response. As suggested by previous studies, individuals with DS show signs of reduced peripheral blood flow regulation and vasoconstrictive control during sympathoexcitatory stimulus (Hilgenkamp et al., 2018; Hilgenkamp et al., 2019).

Our study results also show that DS participants, even though they had slightly lower SV values and higher HR, had similar values of Q than the non-DS individuals at submaximal workloads. On the contrary, Vis et al. (2012a) found a reduced SV and Q in adults with DS when performing exercise at submaximal intensity. On the other hand, Pitetti et al. (1992) found that the DS individuals had significantly higher mean Q and similar SV than participants with intellectual disabilities without DS. Such disparity in findings may be due to the different exercise protocols and methodologies implemented to assess hemodynamics parameters.

4.3 Limitations

This study presents some limitations. Firstly, we obtained hemodynamic information using a non-invasive finger cuff, which could have been affected by some movement in the left hand in response to changes in the speed or grade of the treadmill. However, we took all necessary precautions to ensure that this did not happen during the tests. Second, we did not assess sedentary or physical activity levels of the participants. These variables could have some effects on the cardiorespiratory and hemodynamic parameters. Thirdly, in our study we included 12 men and three women in each group, which could be considered a limitation due to the effects that sex could have on the parameters studied. Therefore, to prevent that sex may influence the results of the comparisons between groups; we matched the groups by sex. Finally, our findings should be treated with caution due to the sample size and specific age of the participants included in this study, thus having limited generalizability to other age groups. Further research is necessary to corroborate our results in younger and older adults with DS.

5 Conclusion

During submaximal exercise, we were able to verify a greater response of HR, VE and VO_2 for the same absolute workload in the participants with DS. Interestingly, the DS group showed lower, but not significant, SV and similar Q than non-DS participants at submaximal workloads. Moreover, we observed that individuals with DS persons had a reduced blood pressure response to submaximal exercise. On the other hand, the peak values of the parameters analysed in our study reinforce the results obtained in previous studies, demonstrating that people with DS have lower peak values of cardiorespiratory fitness, HR, a lower response of hemodynamic parameters (MAP; SV; Q), and a lower cardiac reserve.

Further research is needed to determine whether different types of training (i.e., strength training, concurrent training, high-intensity interval training, etc.) may elicit modifications and adaptations in submaximal and maximal cardiorespiratory and haemodynamic responses in people with DS.

Data availability statement

The raw data supporting the conclusion 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 Comité de Ética e Investigación de la Universidad Ramon Llull. The patients/participants provided their written informed consent to participate in this study.

Author contributions

GO participated in the study design, the data collection and processing, statistical analyses, conceived the paper and drafted the content; MC-C participated in the conception and study design, edited and revised the manuscript; MG-B edited and revised the manuscript; NT edited and revised the manuscript; LE edited and revised the manuscript; JG-O participated in the conception and the study design, edited and revised the manuscript; CJ participated in the study design, carried out the study, interpreting the results, helped to draft the manuscript and revised the final version of the manuscript. All authors have read and approved the final version of the manuscript and agree to be accountable for all aspect of the work.

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Conflict of interest

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

Publisher's note

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Combined resistance training with aerobic training improves physical performance in patients with coronary artery disease: A secondary analysis of a randomized controlled clinical trial

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Background: The efficacy of combined resistance training (RT) and aerobic training (AT) compared with AT alone is well established in cardiac rehabilitation (CR); however, it remains to be elucidated whether RT load (high load [HL] vs. low load [LL]) modifies the outcomes. The aim of our study was to investigate the effects of HL-RT and LL-RT combined with AT in comparison to AT alone on body composition and physical performance in patients with coronary artery disease (CAD) enrolled in phase II CR.

Methods: We randomized 79 patients with a stable CAD to 12 weeks of lower limb LL-RT + AT (35–40% of one repetition maximum [1-RM]; n = 28), HL-RT + AT (70–80% of 1-RM; n = 26), or AT (n = 25). Fifty-nine patients (75% men) with mean (standard deviation) age 61 (8) years and left ventricular ejection fraction 53 (9)% completed LL-RT (n = 19), HL-RT (n = 21) and AT (n = 19). Body composition and physical performance (upper and lower submaximal muscle strength, flexibility, balance, and mobility) were measured at baseline and post-training.

Results: Training intervention had no significant impact on time × group interaction in the body composition measures. There was a significant time × group interaction for the gait speed test, chair sit-and-reach test, arm curl test, Stork balance test, up and go test, STS-5, and 6-min walk distance (p-values $\leq$ 0.001–0.04) following the training intervention. After the training

intervention, HL-RT improved gait speed (+12%, p = 0.044), arm curl (+13%, p = 0.037), and time of Up and Go test (+9%, $p < 0.001$) to a greater extent compared with AT group, while there was a greater improvement in time of Up and Go test (+18%, $p < 0.001$) and time of five sit-to-stand tests (+14%, p = 0.016) following LL-RT when compared with AT. There were no differences between HL-RT and LL-RT in post-training improvement in any of the physical performance measures.

Conclusion: The combination of AT with HL-RT or LL-RT promoted similar improvements in physical performance, which were superior to AT. Therefore, both types of combined AT and RT can be applied to patients with CAD.

Clinical trial registration: [https://clinicaltrials.gov/ct2/show/NCT04638764] Identifier [NCT04638764].

KEYWORDS

strength training, cardiac rehabilitation, myocardial infarction, muscle strength, mobility, balance

Introduction

Cardiac rehabilitation (CR) is recognized as a multidisciplinary intervention for secondary prevention and treatment of patients with coronary artery disease (CAD) (1–3), wherein exercise training presents a core component. Over the years, exercise training in CR has evolved from the single exercise modality intervention predominately based on aerobic training (AT) (4) to a multicomponent intervention consisting of AT and resistance training (RT), with flexibility, coordination, and balance training advised as adjunct training modalities (1).

In the past two decades, meta-analyses have shown the superior effects of combined AT with RT on maximal aerobic capacity (5, 6) and muscle strength (5–7) when compared with AT in patients with CAD. Despite being understudied in CR, high load (HL) RT has shown similar superiority as progressive low load (LL) to moderate load RT over AT alone (6). While the efficacy of combined RT and AT has been established, the dose-dependent relationship between RT load and improvement in physical performance remains to be established in patients with CAD. In healthy young and older adults, HL-RT (e.g., >70% of one repetition maximum [1-RM]) induced greater gains in maximal muscle strength (8, 9) and physical performance (8) compared with LL-RT (<40% of 1-RM) and had a similar effect on muscle hypertrophy (9). Therefore, we expect similar findings to be established also in patients with CAD.

To date, previous studies have reported changes in body composition (10–13) and physical performance (14) following combined AT and RT when compared with AT in patients with CAD. Despite conflicting results, some studies have shown an improvement in hip and waist circumference (14, 15), and body fat (10, 11) following both training modalities, while lean body mass increased only following combined AT and RT (11, 12). When comparing both training interventions, there were no differences in the waist and hip circumference (14, 15) and body fat mass (10), whereas only one study showed a greater increase in lean body mass following AT and RT in relation to AT (13). In addition, this study also showed a dose-dependent relationship between the weekly volume of RT (two vs. three weekly sessions) and improvement of lean leg mass following AT and RT compared with AT.

Furthermore, screening of physical performance following multicomponent exercise training has been limited in patients with CAD, despite a high prevalence of frailty and sarcopenia, especially among older patients (16). All available studies have shown improvement in flexibility (11, 15) in all training groups, while submaximal muscle strength improved only following combined AT and RT (7, 14). In addition, studies showed no between-group difference in flexibility (11, 15), and greater improvement in upper and lower limb submaximal muscle strength following combined AT and RT (13, 14). Moreover, it still must be established whether the combination of RT and AT provides additional benefits on submaximal endurance (e.g., 6-min walk test [6MWT]) compared with AT alone, which was previously associated with improved distance of 6MWT (17).

The aim of the study was to establish whether the dose-dependent relationship between RT load (HL- and LL-RT) and improvement in body composition and physical performance existed. Therefore, we hypothesized that HL-RT and LL-RT would elicit greater improvement of submaximal muscle strength and endurance, and greater decrease in body fat mass and an increase in lean body mass when compared with AT. In addition, we also hypothesized that HL-RT would

provide greater gains in lower limb submaximal strength compared with LL-RT.

Materials and methods

Study design

In this randomized controlled clinical trial, patients with CAD were randomly assigned to three intervention groups using cluster randomization: HL-RT combined with interval AT; LL-RT combined with interval AT; and interval AT alone as standard care. The study was designed in accordance with Consolidated Standards of Reporting Trials (18) and the rationale and design of the study are available elsewhere (19). In line with standard procedures in CR, we used cluster randomization (sealed envelope for each randomized cluster) to allocate patients to each training group. We randomized between 3 and 5 patients to each cluster, depending on the Coronavirus-2019 hospital restrictions.

This study presents prespecified secondary outcomes of a randomized controlled clinical trial (19), while the primary outcomes were reported elsewhere (20). The outcomes of the study were: changes in physical performance (submaximal muscle strength, mobility, endurance, balance, and flexibility) and body composition (body mass, waist and hip circumference, lean and fat mass, and phase angle). The outcomes of the study were assessed by an experienced kinesiologist, which was not blinded to group allocation due to the protocols of routine CR during the Coronavirus-19 pandemic.

The measurements were conducted at baseline and after 36 training sessions. In addition to extensive baseline medical examination by a cardiologist and cardiopulmonary exercise test (CPET) performed on a separate day, all other outcomes of the study were assessed during a single visit to the out-patient CR center. On the measurement day, we first measured patients' body composition, followed by flexibility tests, mobility test, upper and lower limb muscle strength test, familiarization of patients with RT on the leg press machine, and finished with a submaximal endurance test in a fatigue minimized order.

Participants

We recruited patients with a stable CAD (after acute coronary syndrome and/or percutaneous coronary intervention) from the Division of Cardiology, General Hospital Murska Sobota, Slovenia. Only patients 18–85 years old, with left ventricular ejection fraction $\geq$ 40%, documented CAD (acute coronary syndrome and/or percutaneous coronary intervention about 1 month after event or procedure), referred to phase II CR and with the completed baseline cardiopulmonary exercise test were included in the study (1). Exclusion criteria were in accordance with the previous recommendation and are available elsewhere (17, 19). Recruitment of patients started in July 2020 and was completed in June 2021.

Training protocol

Patients performed three exercise sessions per week for 12 weeks or until the completion of 36 sessions), with at least 48 h rest between sessions. Each training session consisted of three periods: general warm-up (10 min dynamic flexibility exercises followed by calisthenics using elastic bands and/or LL dumbbells and balance exercises), main period (45 min of AT and 10 min of RT), and cool-down period (5 min static stretching and breathing exercises). After a general warm-up, patients in all three groups performed aerobic interval cycling (3–5 min of workload cycling separated by 2 min of rest) progressing from 50% of maximal peak power achieved at baseline CPET to 80% of peak power (19).

In addition, patients in both RT groups performed a total of 36 sessions on a leg press machine (three measurements of 1-RM and 33 RT sessions). Both RT groups differed in training load, whereas the training volume was matched by the number of repetitions. The range of repetitions and progression of RT followed previously published recommendations (1, 17, 21, 22). The workload in the HL-RT group progressed from the initial three sets at an intensity of 70% of 1-RM (6–11 repetitions per set) to 80% of 1-RM (6–8 repetitions per set). The workload in the LL-RT group progressed from the initial three sets at an intensity of 35% of 1-RM (12–22 repetitions per set) to 40% of 1-RM (12–16 repetitions per set). During the eighth week of training (on 22nd training session), patients' 1-RM was re-evaluated in all three groups and the new 1-RM was used to prescribe RT for the final part of the intervention. During the final 4 weeks of training, the load in the HL-RT group was progressed from 70% 1-RM (11 repetitions per set) to 80% 1-RM (6–8 repetitions per set), and the load the in LL-RT group progressed from 35% 1-RM (22 repetitions per set) to 40% 1-RM (12–16 repetitions per set). A lifting cadence of 1 s: 1 s (concentric and eccentric contraction) was used, with 90 s rest between sets (23). Patients were familiarized with proper lifting techniques and were instructed to inhale during the eccentric contraction and exhale during the concentric contraction to avoid the Valsalva maneuver (17, 21).

Patients' safety was ensured with continuous monitoring of heart rate and blood pressure before, during, and after each training modality. The intervention was guided by a kinesiologist, while safety was ensured by a medical nurse and physiotherapist, with a cardiologist available for consultations on-site. Additional safety procedures are in detail described elsewhere (19).

Measurements

Cardiopulmonary exercise test

Maximal aerobic capacity was assessed using an adjusted ramp protocol (24) on a Schiller ERR 911 ergometer and a Cardiovit CS-200 excellence ergo-spirometer (Schiller, Baar, Switzerland) to determine workload for AT. After short instruction, patients completed a spirometry test. Afterward, we determined patients' baseline heart rate, blood pressure, and gas exchange in a seated position. The test was initiated with patients who started cycling without workload for 3 min at 50–60 rpm, followed by increasing workload every minute for an additional 10–25 W until exhaustion and/or exercise-limiting contraindications. The test was conducted by a kinesiologist and supervised by a medical nurse.

Measurements of body composition

Body height and mass were measured on Marsden DP3810 weighing scale and stadiometer (Marsden Weighing Group, Rotherham, United Kingdom); and waist and hip circumference were measured with a standard measuring tape. Waist circumference was measured midpoint between lowest rib and the iliac crest, and the hip circumference was measured in the widest part of the gluteal region. The average circumference out of two measurements was used in the final analysis (14).

Body composition was assessed in the morning (before 10 a.m.) using bioimpedance measurement with a Bodystat Quadscan 4000 Touch (Bodystat, Douglas, Isle of Man, United Kingdom) with patients lying in a supine position after 10 min rest. Electrodes were connected to the hands (wrist and middle finger) and feet (ankle and above the knuckle of the toe) after those areas were cleaned with alcohol. Patients were asked to be fasted and to report their fluid intake prior to measurement. Post-training assessment of body composition was performed during the same time of the day as during the baseline assessment (±2 h). Outcome measures were body fat, lean body mass, and phase angle (ratio between cellular [intracellular and extracellular] resistance and membrane-specific reactance) as a marker of cellular health (25). All body composition variables were calculated according to the manufacturer's guidelines using height, mass, waist and hip circumference, age, and sex data.

Measurement of maximal leg strength

Patients underwent leg-press familiarization and performed submaximal strength tests using a Life Fitness Leg Press Pro 2 (Life Fitness Inc., Rosemont, IL, United States). Following standard warm-up (see section "Training protocol"), patients were familiarized with proper lifting techniques and leg press testing. During the measurement, patients performed a specific warm-up comprising of eight and six repetitions at 50 and 70% of their perceived 1-RM, respectively. After short rest, the weight was progressively increased until reaching the workload that can be lifted three to five times (3–5 RM). There was a 2–3 min rest between the trials (22). The 1-RM was calculated using the established 1-RM prediction equation (predicted 1-RM = maximal load lifted/1.0278–0.0278 × number of repetitions) (26).

Measurement of physical performance

Patients underwent extensive evaluation of physical performance to evaluate mobility, submaximal muscle strength, upper and lower limb flexibility, postural balance, and submaximal endurance, using a 4 m spontaneous gait speed test, hand grip test, arm curl test, five repetition sit-to-stand test (STS-5), back scratch test, chair sit-and-reach test, up and go test, Stork balance test, and 6MWT distance (27, 28).

Mobility, flexibility, gait speed, and balance

The usual-pace gait speed test was conducted on a 4 m track, and the best time of two measurements was used for further calculation of speed (28).

The Up and Go test was performed two times with 60 s of break between trials on 8 feet track (2.44 m), and the time required to get up from a seated position, walking, and turning at 2.44 m, and returning to a seated position was used in the final analysis (27).

The back scratch test and the chair sit-and-reach test assessed the flexibility of upper limb and lower limbs, respectively (27). In the back scratch test, the distance between fingers was measured two times, and the nearest distance was used as an outcome (negative value was marked when middle fingers could not touch each other, otherwise the result presented a positive value).

In the chair sit-and-reach test, the distance between the extended tip of middle finger and the tip of toe in the forward bend sitting position was measured two times on each leg, and the nearest distance was used in the final analysis (positive value = middle finger reached over the tip of toe, otherwise the result presented a negative value) (27).

The Stork balance test was measured while patients maintained the position on one leg with their hips on the hips and the other foot against the medial side of the knee of the stance leg. The best time (in seconds) out of three trials was used in the final analysis (29).

Submaximal muscle strength and endurance

The hand grip strength test was assessed using the Jamar Smart Hand dynamometer (Patterson Medical Ltd., Warrenville, IL, United States). Patients performed three repetitions, with 60 s of rest in a sitting position with an elbow flexed at a 90° angle. The highest value expressed in kg was included as an outcome (30).

The upper limb strength-endurance was assessed using the arm curl test, and patients were instructed to perform a maximal

number of elbow flexions in 30 s. A dumbbell weight of 2.27 and 3.63 kg was used for women for men, respectively (27).

STS-5 estimated lower limb muscle strength and was performed two times, with a 60 s of rest. The fastest time of the fifth stand was used as an outcome (28).

The one-leg heel raise test was performed until exhaustion on a step wearing sports shoes (without heel), with fingertip touching the wall at shoulder height, knee fully extended, and the non-dominant leg held above the floor. A cadence of 60 heel raise cycles/min was used and the maximal number of correctly repeated heel raises was used as an outcome (31).

The 6-min walk test (6MWT) was performed on a 30 m track, and the total distance measured to the nearest meter was included as an outcome. Before and after the test, we measured heart rate, blood oxygen saturation, and blood pressure, and patients reported Borg dyspnea score on a 0–10 points scale (32, 33).

Statistical analysis

The initial sample size calculations were based on mean changes (post-training – baseline values) in aerobic capacity or isometric maximal knee-extensor torque (primary outcomes) when comparing the effects of combined AT with either HL-RT or LL-RT with standard care (AT), and the exact calculations are available elsewhere (19, 20). Since we prespecified the analysis of the secondary outcomes in our study protocol (19), we also performed sample size calculations for the present sub-analysis. The calculations were based on previously reported mean changes in the Up and Go test when comparing the effect of HL-RT with LL-RT in older healthy adults. Calculations showed that at least 15 patients with CAD (5 patients per group) needed to be enrolled to detect a mean change of 0.6 s in the up and go test, assuming a statistical power of 0.90 ($\beta = 0.10$) and $\alpha = 0.05$ (34).

Categorical variables are presented as numbers and percentages, and numerical variables are presented as means and standard deviations or median and interquartile (asymmetrically distributed variables). We screened all numeric variables for the normality of distribution (Shapiro–Wilk test), and homogeneity of variances (Levene's test). The final analysis was performed according to per-protocol analysis, including all patients with completed 24–36 sessions (19). We assessed between-group differences in baseline and post-training change (% change = post-training value - baseline value/baseline value × 100%) using the one-way analysis of variance (ANOVA) or Kruskal–Wallis test (for asymmetrically distributed variables). In addition to both tests, we performed *post hoc* analysis using the Tukey or Bonferroni test. The effect of training intervention was calculated using unbalanced group two-way repeated measures ANOVA or analysis of covariance (ANCOVA), when analysis of baseline measures indicated a significant between-group difference. We used Bonferroni adjustment within two-way ANOVA to calculate the within-group effects of training intervention. In addition to ANCOVA, we assessed the within-group improvement following training intervention using the paired sample *t*-test or the Wilcoxon test, where necessary. Partial eta squared was used to calculate the effect size of each variable. The analysis was conducted using IBM SPSS 25 software (SPSS Inc., Armonk, NY, United States) at the level of statistical significance set at alpha < 0.05.

Results

We screened 154 patients with CAD and included 79 patients in the study (**Figure 1**). Fifty-nine patients were included in the final analysis, age = 61 (8) years, height = 172.1 (8.4) cm, weight = 85.47 (15.43) kg, and left ventricular ejection fraction = 53 (9)%. Patients were enrolled 2 (1.5–3.0) months post-acute coronary syndrome or percutaneous coronary intervention in the study. At baseline, there were no between-group differences in baseline body height and weight, clinical characteristics, smoking status, and pharmacological therapy (**Table 1**). Atrial fibrillation was more prevalent in the AT group than in HL-RT and LL-RT groups ($p = 0.038$).

All measurements and the training intervention were performed without major cardiovascular events or complications (e.g., angina pectoris, blood pressure > 220/110 mmHg, palpitation, atrial fibrillation, arrhythmias, etc.). With the exception of some reports of the delay onset of muscle soreness following the baseline heel raises test and the 1-RM test, no exercise-limiting musculoskeletal problems were noted.

All patients completed all 36 sessions to out-patient CR apart from two patients in the HL-RT group with 24 completed sessions. Adherence to AT (one patient completed 35 sessions in AT group; one patient completed 34 sessions; and four patients completed 35 sessions in the LL-RE group; two patients completed 35 sessions in the HL-RT group) and RT (one patient completed 35 sessions) was high, with no between-group difference in adherence to AT ($p = 0.240$) and RT ($p = 0.475$).

Table 2 presents the change in body composition following training intervention in all groups. At baseline, there was a significant difference between groups in hip circumference (LL-RT vs. AT = −7.7 cm, $p = 0.017$) and fat mass (LL-RT vs. AT = −8.20 kg, $p = 0.035$). When adjusted for baseline difference, there were no significant differences between groups in post-training hip circumference and fat mass. Two-way repeated measures ANOVA has demonstrated a significant time effect for waist circumference, hip circumference, waist to hip ratio, fat mass, and lean mass (p-values = < 0.001–0.002, $\eta^2 = 0.166$–0.896), and no significant time × group interaction for none of the body composition variables. There was a decrease in waist circumference in the LL-RT group (−2.5 cm,

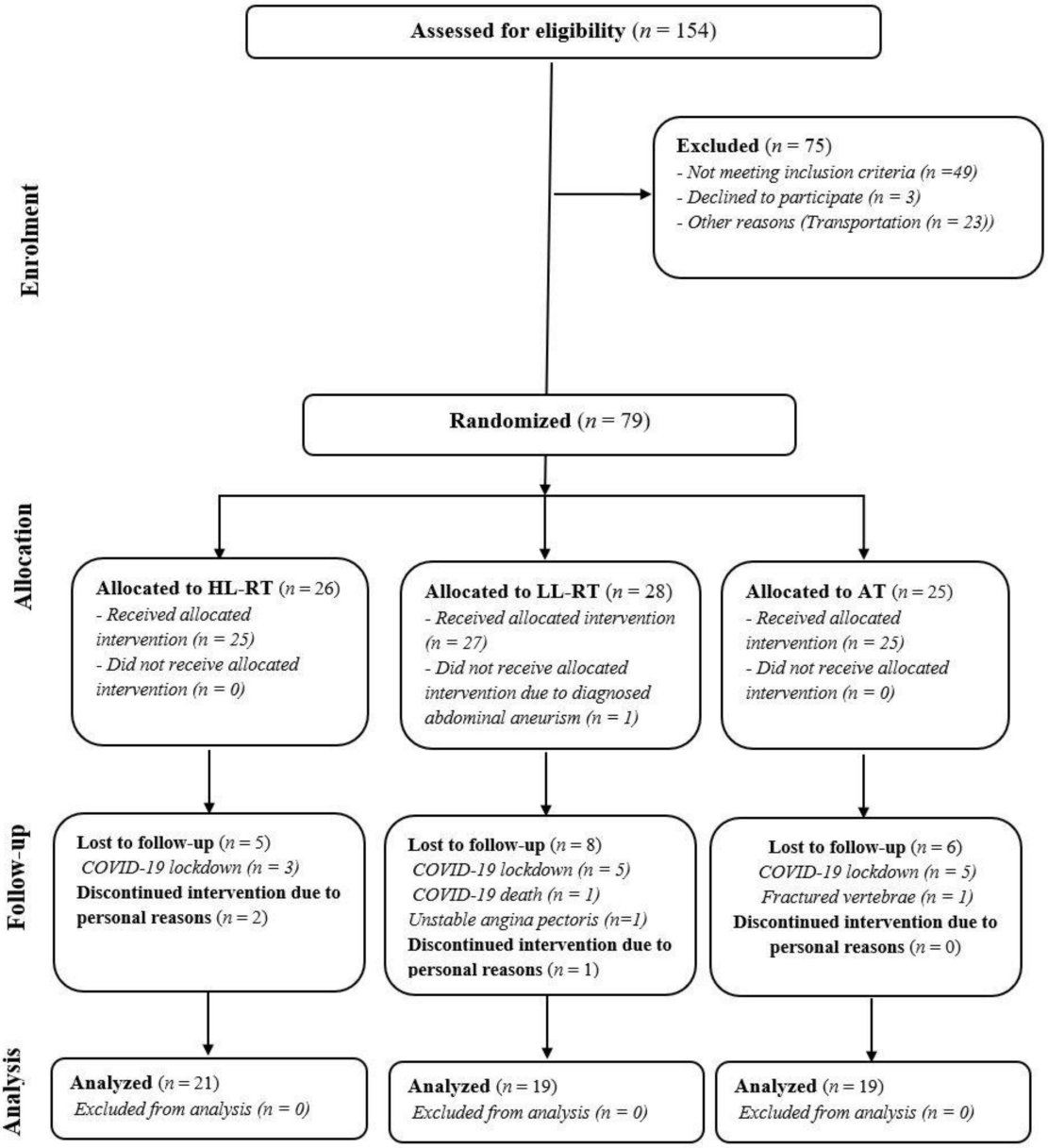

FIGURE 1
CONSORT flowchart of the study. HL-RT, high load-resistance training; LL-RT, low load-resistance training; CON, aerobic training; COVID-19, Coronavirus-19.

p = 0.001) and borderline decrease in HL-RT (−1.4 cm, p = 0.056) following the training intervention. AT group significantly increased fat% (+1%, p = 0.048), decreased lean mass% (−1%, p = 0.048), and lean mass (−1.05 kg, p = 0.016) following the training intervention. When comparing the groups in post-training improvement (% change), there was no significant difference in any of the body composition variables.

All training groups had a similar level of baseline physical performance (Table 3), with the exception of the heel raise test (LL-RT vs. AT = + 8 repetitions, p = 0.012). When adjusted for baseline difference, AT group performed significantly less heel raises compared with the LL-RT group (adjusted mean difference = 6 repetitions, p = 0.022) and HL-RT group (adjusted mean difference = 7 repetitions, p = 0.002) following the training intervention. Two-way repeated measures ANOVA has demonstrated a significant time effect for all physical performance tests (all $p < 0.001$, η^2 = 0.235–0.708), and a significant time × group interaction for the gait speed test, chair sit-and-reach test, arm curl test, Stork balance test, up and go test, STS-5

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TABLE 1 Baseline anthropometry, clinical characteristics, and cardiovascular risk factors.

	Sample (n = 59)	AT group (n = 19)	LL-RT group (n = 19)	HL-RT group (n = 21)	P (ANOVA)
Age (years)	61 (8)	61 (9)	61 (7)	62 (8)	0.910
Gender [males, (%)]	44 (75)	14 (74)	15 (79)	15 (71)	0.931
Anthropometry					
Height (cm)	172.1 (8.4)	170.4 (8.8)	172.8 (8.6)	172.9 (7.9)	0.582
Weight (kg)	85.47 (15.43)	90.94 (19.04)	81.46 (13.37)	84.15 (12.56)	0.148
Clinical data					
LVEF (%)	53 (9)	50 (45, 60)	55 (50, 60)	50 (45, 58)	0.454
Time from clinical event to inclusion to CR (months)	2.0 (1.5, 3.0)	2.0 (2.0, 2.5)	2.5 (1.5, 3.0)	2.0 (1.5, 2.8)	0.832
Myocardial infarction, f (%)					
NSTEMI	25 (42)	9 (47)	8 (42)	8 (38)	
STEMI	24 (41)	7 (37)	7 (37)	10 (48)	0.947
Unstable AP/PCI	10 (17)	3 (16)	4 (21)	3 (14)	
Comorbidities and risk factors					
Arterial hypertension	41 (70)	15 (79)	11 (58)	15 (71)	0.383
Hyperlipidaemia	49 (83)	16 (84)	14 (74)	19 (91)	0.384
Diabetes	9 (15)	4 (21)	3 (16)	2 (10)	0.602
Atrial fibrillation	5 (9)	4 (21)	1 (5)	0 (0)	0.038
Thyroid disease	5 (9)	2 (11)	2 (11)	1 (5)	0.727
Renal disease	4 (7)	0 (0)	2 (11)	2 (10)	0.534
Smoking, f (%)					
non-smoker	14 (24)	3 (16)	3 (16)	8 (38)	
ex-smoker	35 (59)	13 (68)	11 (58)	11 (52)	0.346
smoker	10 (17)	3 (16)	5 (26)	2 (10)	
Pharmacological therapy, f (%)					
Aspirin	57 (97)	17 (90)	19 (100)	21 (100)	0.200
Beta blocker	59 (100)	19 (100)	19 (100)	21 (100)	1.000
ACE inhibitor/ARB	58 (98)	19 (100)	18 (95)	21 (100)	0.644
Statin	59 (100)	19 (100)	19 (100)	21 (100)	1.000
Antiplatelet drug	58 (98)	18 (95)	19 (100)	21 (100)	0.644
Anticoagulation drug	5 (9)	3 (16)	1 (5)	1 (5)	0.509
Diuretic	5 (9)	4 (21)	0 (0)	1 (5)	0.071

Data are presented as mean (standard deviation) or as median (first quartile, third quartile), AT, aerobic training; LL-RT, low load resistance training; HL-RT, high load resistance training; LVEF, left ventricular ejection fraction; (N)STEMI, (non-) ST segment-elevated myocardial infarction; AP, angina pectoris; PCI, percutaneous coronary intervention; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blockers.

and 6MWT distance (p-values = < 0.001–0.04, η^2 = 0.108–0.350).

HL-RT and LL-RT significantly improved gait speed (both $p < 0.001$), upper limb flexibility (LL-RT, $p = 0.003$; HL-RT, $p = 0.030$), hand grip strength (LL-RT, $p = 0.003$; HL-RT, $p < 0.001$), and time of Up and Go test (both $p < 0.001$) following training intervention. All training groups significantly improved lower limb flexibility (AT, $p = 0.023$; LL-RT, $p < 0.001$; HL-RT, $p < 0.001$), upper limb strength (AT, $p = 0.007$; LL-RT, $p < 0.001$; HL-RT, $p < 0.001$), postural balance (AT, $p = 0.009$; LL-RT and HL-RT, both $p < 0.001$), time of STS-5 (AT, $p = 0.026$; LL-RT and HL-RT, both $p < 0.001$), heel raises (AT, $p = 0.002$; LL-RT and HL-RT, both $p < 0.001$), and 6MWT distance (all groups, $p < 0.001$). There was significantly greater improvement in gait speed (+12%, $p = 0.044$), upper limb strength (+13%, $p = 0.037$), Up and Go test time (+9%, $p < 0.001$), and borderline improvement STS-5 time (+9%, $p = 0.056$) in HL-RT group compared with AT group. In addition, Up and Go test time (+18%, $p < 0.001$) and STS-5 time (+14%, $p = 0.016$) were improved significantly more in LL-RT group compared with AT group.

Discussion

To our knowledge, this is the first study to compare the effects of HL-RT and LL-RT in a combination with AT on body composition and physical performance in

TABLE 2 Body composition at baseline and post-training.

		N	Baseline	Post-training	% change	P (% change)	2-way ANOVA/ANCOVA	
							Time effect/Effect of baseline	Interaction/Post-training difference
Weight (kg)	AT	19	90.94 (19.04)	90.49 (17.87)	0 (4)		$p = 0.187$	$p = 0.974$
	LL-RT	19	81.46 (13.37)	80.91 (13.90)	−1 (4)	0.775	$\eta^2 = 0.031$	$\eta^2 = 0.001$
	HL-RT	21	84.15 (12.56)	83.47 (13.48)	−1 (3)			
Waist (cm)	AT	19	108.9 (14.5)	107.7 (13.6)	−0 (−3, 1)		$p < 0.001$	$p = 0.381$
	LL-RT	19	99.9 (10.2)	97.3 (10.4)	−3 (−5, 0)	0.140	$\eta^2 = 0.216$	$\eta^2 = 0.034$
	HL-RT	21	101.7 (10.1)	100.3 (10.5)	−2 (−2, −0)			
Hip (cm)	AT	19	109.6 (10.1)	109.4 (8.6)	−1 (−2, 1)		**$p < 0.001$**	**$p = 0.370$**
	LL-RT	19	101.9 (5.1)	101.5 (5.5)	−2 (−4, 0)	0.611	**$\eta^2 = 0.896$**	**$\eta^2 = 0.036$**
	HL-RT	21	104.8 (6.5)	104.4 (6.5)	−2 (−2, 0)			
WHR	AT	19	0.99 (0.07)	0.98 (0.08)	0 (−2, 2)		$p < 0.001$	$p = 0.155$
	LL-RT	19	0.98 (0.07)	0.96 (0.07)	0 (−2, 0)	0.079	$\eta^2 = 0.254$	$\eta^2 = 0.064$
	HL-RT	21	0.97 (0.06)	0.96 (0.06)	−1 (−1, 1)			
Fat (%)	AT	19	28.2 (9.2)	29.2 (8.7)	5 (8)		$p = 0.500$	$p = 0.138$
	LL-RT	19	22.3 (4.7)	22.0 (5.2)	−2 (11)	0.104	$\eta^2 = 0.008$	$\eta^2 = 0.070$
	HL-RT	20	24.9 (8.4)	24.7 (7.6)	1 (9)			
Fat (kg)	AT	19	26.0 (11.0)	26.7 (10.3)	5 (12)		**$p < 0.001$**	**$p = 0.095$**
	LL-RT	19	17.8 (3.3)	17.6 (4.5)	−2 (14)	0.157	**$\eta^2 = 0.900$**	**$\eta^2 = 0.083$**
	HL-RT	20	21.0 (8.3)	20.5 (7.5)	−1 (11)			
Lean (%)	AT	19	71.8 (9.2)	70.8 (8.7)	−2 (−3, 1)		$p = 0.497$	$p = 0.139$
	LL-RT	19	77.7 (4.7)	78.0 (5.2)	1 (−2, 3)	0.086	$\eta^2 = 0.008$	$\eta^2 = 0.069$
	HL-RT	20	75.1 (8.4)	75.3 (7.6)	0 (−2, 3)			
Lean (kg)	AT	19	64.9 (13.6)	63.9 (13.1)	−2 (3)		$p = 0.002$	$p = 0.354$
	LL-RT	19	63.6 (12.5)	63.3 (12.4)	0 (2)	0.372	$\eta^2 = 0.166$	$\eta^2 = 0.037$
	HL-RT	20	63.4 (11.7)	62.4 (11.5)	−2 (3)			
Dry lean (kg)	AT	19	14.3 (4.1)	14.3 (4.0)	1 (3)		$p = 0.168$	$p = 0.322$
	LL-RT	19	14.2 (3.9)	14.0 (3.9)	−1 (4)	0.181	$\eta^2 = 0.034$	$\eta^2 = 0.040$
	HL-RT	20	14.3 (4.2)	14.1 (4.3)	−2 (5)			
Phase angle (°)	AT	19	6.5 (1.0)	6.5 (0.7)	2 (8)		$p = 0.138$	$p = 0.755$
	LL-RT	19	6.8 (0.9)	6.8 (1.0)	1 (5)	0.663	$\eta^2 = 0.040$	$\eta^2 = 0.010$
	HL-RT	20	6.4 (0.8)	6.5 (0.9)	2 (7)			

Data are presented as mean (standard deviation) or as median (first quartile, third quartile). WHR, waist to hip ratio, LL-RT, low load resistance training, HL-RT, high load resistance training, AT, aerobic training, ANOVA, analysis of variance, ANCOVA, analysis of covariance, and η^2, partial eta squared (effect size). Text in bold presents ANCOVA results.

patients with CAD. HL-RT and LL-RT decreased only waist circumference and waist-to-hip circumference ratio following training; however, this was not significantly different compared with AT. All training modalities induced favorable effects on flexibility, upper and lower body submaximal muscle strength, and balance. HL-RT improved gait speed and upper body muscle strength to a greater extent compared with AT alone, whereas both HL-RT and LL-RT were associated with greater improvement of STS-5 time.

Previous studies have shown conflicting results of combined AT and RT on anthropometry. One study has shown a similar decrease in waist-to-hip circumference ratio following HL-RT (−0.01) (14) as was observed in our study following HL-RT (−0.01) and LL-RT (−0.02), with no differences when compared with AT. In contrast, the addition of LL-RT to AT failed to induce any changes in waist circumference (13). Similar to our study, previous studies failed to establish the effect of combined AT with RT on body mass (13, 35). Furthermore, combined AT and RT were associated with a decrease in fat mass or fat%(11–13, 35), which was in most studies greater compared with AT (11, 13, 35). On the contrary, we have observed an increase in fat mass% following AT, whereas fat mass% remained unchanged following HL-RT and LL-RT. This discrepancy can be explained by a greater energy requirement needed to maintain body mass while performing RT. In healthy older adults, the energy requirements for engagement in HL-RT increased by nearly 15% (36).

TABLE 3 Physical performance at baseline and post-training.

		N	Baseline	Post-training	% change	P (%change)	2-way ANOVA/ANCOVA	
							Time effect/Effect of baseline	Interaction/ Post-training difference
Up and Go test	AT	19	4.90 (0.79)	4.74 (0.76)	−7 (−10, 7)		$p < 0.001$	$p < 0.001$
	LL-RT	19	5.43 (1.36)	4.08 (0.81)	−25 (−33, −20)	0.000	$\eta^2 = 0.634$	$\eta^2 = 0.350$
	HL-RT	21	5.18 (0.95)	4.27 (0.70)	−16 (−25, −9)			
Gait speed (m/s)	AT	19	1.32 (0.26)	1.37 (0.26)	2 (−6, 14)		$p < 0.001$	$p = 0.035$
	LL-RT	19	1.34 (0.19)	1.53 (0.21)	9 (1, 32)	0.041	$\eta^2 = 0.397$	$\eta^2 = 0.113$
	HL-RT	21	1.31 (0.17)	1.50 (0.20)	14 (3, 23)			
Stork balance test (s)	AT	19	59.25 (49.44)	81.46 (62.34)	32 (7, 138)		$p < 0.001$	$p = 0.018$
	LL-RT	19	67.79 (47.24)	116.56 (69.69)	62 (34, 119)	0.213	$\eta^2 = 0.588$	$\eta^2 = 0.134$
	HL-RT	21	59.93 (44.74)	113.19 (75.34)	77 (42, 164)			
Back scratch test (cm)	AT	19	−13 (15)	−11 (12)	Na		$p < 0.001$	$p = 0.668$
	LL-RT	19	−10 (10)	−6 (11)	Na	Na	$\eta^2 = 0.235$	$\eta^2 = 0.014$
	HL-RT	21	−10 (12)	−7 (13)	Na			
Chair Sit-and-reach test (cm)	AT	19	2 (11)	5 (9)	Na		$p < 0.001$	$p = 0.020$
	LL-RT	19	0 (13)	7 (12)	Na	Na	$\eta^2 = 0.545$	$\eta^2 = 0.130$
	HL-RT	21	−3 (12)	4 (11)	Na			
Sit-and-Reach test (cm)	AT	19	14 (11)	16 (11)	Na		$p < 0.001$	$p = 0.083$
	LL-RT	19	15 (11)	19 (11)	Na	Na	$\eta^2 = 0.475$	$\eta^2 = 0.085$
	HL-RT	21	10 (13)	15 (10)	Na			
Hand grip strength (kg)	AT	19	42.2 (9.7)	44.3 (10.2)	6 (2, 13)		$p < 0.001$	$p = 0.397$
	LL-RT	19	43.4 (12.0)	47.2 (10.2)	7 (−1, 24)	0.886	$\eta^2 = 0.311$	$\eta^2 = 0.034$
	HL-RT	21	42.5 (11.8)	46.8 (11.5)	8 (−1, 12)			
Arm curl test (reps)	AT	19	22 (6)	24 (6)	10 (15)		$p < 0.001$	$p = 0.009$
	LL-RT	19	25 (6)	29 (4)	18 (18)	0.039	$\eta^2 = 0.605$	$\eta^2 = 0.154$
	HL-RT	21	22 (6)	27 (6)	23 (13)			
STS-5 test (s)	AT	19	8.55 (1.30)	7.77 (1.04)	−9 (10)		$p < 0.001$	$p = 0.020$
	LL-RT	19	8.73 (2.25)	6.54 (1.10)	−20 (16)	0.012	$\eta^2 = 0.517$	$\eta^2 = 0.130$
	HL-RT	21	8.35 (2.13)	6.79 (1.45)	−16 (13)			
Heel raise test (reps)	AT	19	16 (7)	20 (8)	25 (6, 36)		**$p < 0.001$**	**$p = 0.002$**
	LL-RT	19	24 (10)	32 (8)	26 (16, 45)	0.056	**$\eta^2 = 0.598$**	**$\eta^2 = 0.209$**
	HL-RT	21	19 (7)	29 (10)	36 (25, 72)			
6-MWT (m)	AT	19	508 (89)	554 (84)	10 (1, 15)		$p < 0.001$	$p = 0.041$
	LL-RT	19	531 (90)	613 (79)	15 (8, 22)	0.158	$\eta^2 = 0.708$	$\eta^2 = 0.108$
	HL-RT	21	523 (83)	592 (86)	12 (7, 19)			

Data are presented as mean (standard deviation) or as median (first quartile, third quartile). STS, sit-to-stand test five times; 6MWT, 6-min walk test; LL-RT, low load resistance training; HL-RT, high load resistance training; AT, aerobic training; Na, not applicable; ANOVA, analysis of variance; ANCOVA, analysis of covariance, and η^2-partial eta squared (effect size). Text in bold presents ANCOVA results.

Oppositely to our expectations, HL-RT and LL-RT failed to induce changes in lean body mass and lean body mass%, as reported in the previous studies (11–13, 35). The majority of the available studies on patients with CAD have demonstrated a greater increase in lean body mass following combined RT and AT when compared with AT (11–13, 35). The improvement in lean body mass compared with AT was greater following progressive moderate- to HL-RT (13) or HL-RT (11). In addition, one of the previous studies also showed that a higher weekly frequency of RT (three times vs. once a week) evoked greater gains in lean body mass (13), indicating a potential dose-dependent response of combined RT and AT. In light of previous findings, our results suggest that applying only one resistance exercise (e.g., leg press) in the RT regime failed to provide adequate stimulus for muscle hypertrophy, as was demonstrated in previous studies, which used whole-body resistance exercises (11, 13, 35) and longer RT interventions (24 weeks–1 year) (13, 35). Furthermore, the phase angle was established to be positively associated with physical activity following exercise interventions, while it is still unknown which exercise modality or intensity may provide the greatest benefit (37). Our study showed that neither HL-RT nor LL-RT

when combined with AT did not induce favorable changes. At baseline, the phase angle was high; thus, none of the patients were classified as sarcopenic (cut-off: < 4.25° for men and < 4.55° for women) (25). This likely reduced its sensitivity to post-training change in already well-conditioned patients with CAD. Therefore, it seems that this measure is more suitable for frail patients with cardiovascular disease.

The use of physical performance measures remains limited in an age and cardiovascular diagnosis diverse population of patients enrolled in CR (38). Physical performance assessments were mostly used in older patients enrolled in CR (39, 40) and were shown to be safe and feasible (40), with no differences in physical performance levels between minimal (e.g., percutaneous coronary intervention) and more invasive cardiovascular intervention (e.g., coronary artery bypass grafting, aortic valve replacement) (40). In addition to the assessment of maximal aerobic capacity and maximal muscle strength (20), our study was the first to implement an extensive assessment of different physical abilities in middle-aged patients with CAD. Baseline physical performance in our sample of patients was comparable to reference values of similarly aged healthy older adults. For example, the hand grip strength of our patients was between 42 and 43 kg which is in line with reference values of German community-dwelling older adults aged 65 years (men: 42 kg and women: 25 kg) (41). The same observation was found for up and go test, in which our patients even outperformed a healthy population between 60 and 69 years (4.9 s–5.43 s vs. 7.91 s) (42). The distance of 6MWT was above 500 meters which is the general cut-off for a healthy population (43). Our findings, therefore, highlight the importance of the actual physical performance of patients with CAD, which is contrary to the perceptions of most health professionals. Such clinical presumptions may underestimate actual patient performance that reflects in suboptimal exercise loading (during AT and especially RT) resulting in incomplete exploitation of the therapeutic potential of exercise intervention in patients with CAD.

Even though greater gains in physical performance were observed in physically frail patients with cardiovascular disease (39), our well-conditioned patients with CAD improved physical abilities in most of the measured tests, with the exception of gait speed, upper limb flexibility, and Up and Go test time in AT group. We observed a similar increase in gait speed as it was reported following combined AT and very LL-RT in older patients enrolled in CR (39). In addition, our study has also demonstrated that only HL-RT elicited a greater increase in gait speed compared with AT, indicating the importance of RT at higher intensities in previously well-conditioned patients with CAD. Furthermore, our study has shown an improvement in arm curl, STS-5, and heel raises following all three training interventions, which is partially in contrast to other studies (13, 14). Previous two studies in patients with CAD have demonstrated a greater improvement of upper and lower limb muscle endurance and submaximal strength following combined AT and RT when compared to AT, with no post-training changes following AT (13, 14). In our study, the additional improvement in upper and lower muscle strength in AT was potentially modified by our extensive warm-up comprised of dynamic flexibility exercises accompanied by calisthenics using low resistance elastic bands or LL dumbbells. Nevertheless, the improvement in lower limb submaximal muscle strength and mobility (e.g., time of the up and go test, time of STS-5, and heel raises) was greater following HL-RT and LL-RT compared with AT, similarly as reported previously (13, 14). Despite significant improvement in heel raises in all three training groups, only the improvement in LL-RT (+8 reps) and HL-RT (+10 reps) groups were clinically significant, as more than six heel raises were previously established to detect a true change in patients with CAD (44). In addition, the absence of difference between RT groups in outcomes of submaximal muscle strength additionally supports the importance of maximal muscle strength assessment, whereas we showed superior effects of HL-RT over LL-RT (20).

To date, studies that compared the effects of HL-RT and LL-RT on body composition and various physical abilities are limited only to healthy young and older adults (8, 9). While the effects of HL-RT and LL-RT on body composition remain unknown in (un)healthy older adults, a meta-analysis has demonstrated similar effects of both RT modalities on muscle hypertrophy in healthy young adults (9). Such findings were also established in our study; however, the improvement in muscle hypertrophy was lower and non-significant, most likely due to the implementation of only a single lower limb resistance exercise compared with multiple upper and lower limb resistance exercises used in most of the previous interventions (9). Furthermore, another systematic review with meta-analysis comparing HL-RT and LL-RT has shown similar effects of HL-RT and LL-RT on submaximal muscle strength and endurance in healthy older adults (8), as demonstrated in our study. The review also showed no differences in flexibility between intensities, despite improvement in flexibility following both training modalities (8). Moreover, studies in patients with CAD have shown that RT combined with AT did not provide additional improvements in flexibility (11, 15). These findings derived from elderly with and without CAD are in line with our results, and collectively suggest that the flexibility exercises performed usually during warm-up and post-exercise sessions may present an adequate stimulus for flexibility gains, regardless of addition and intensity of RT.

Despite being advised as an adjunct exercise modality (1), the implementation of balance assessments and exercises remains underused in CR, with a scarce body of evidence on the exact characteristics of balance training (39, 45). It seems that the impact of the training intervention is solely related to the

duration and complexity of balance training within the CR. In older adults with CAD, the inclusion of few balance exercises failed to promote post-training changes (39), while better structured and progressive balance training implemented in multimodal exercise intervention induced greater improvement in balance test and time of Up and Go test compared with usual care (45). In our study, the addition of complex balance exercises in the warm-up phase of each exercise session enhanced the effects of AT on the Stork balance test in all training groups and has also enhanced greater benefits on time of Up and Go test following HL-RT (+9%) and LL-RT (+18%) compared with AT alone. Furthermore, RT is expected to improve submaximal endurance time or distance in cardiovascular disease patients (17), and most studies implementing RT in their exercise-based CR measured 6MWT distance in elderly patients with CAD (39) or patients with HF (46). Similar to our findings, studies have shown an increase of 6MWT distance following the training intervention, without differences between training modalities (39, 46). Since all three training groups underwent the same progressive AT, our results along with previous studies suggest that AT alone promotes sufficient stimulus for post-training changes in submaximal endurance and that the inclusion of single lower limb RT exercise provides no additional benefits.

Our study has some limitations. To date, no study has compared the differences between HL-RT and LL-RT when combined with AT in patients with CAD; thus, our study was likely underpowered to detect post-training differences between HL-RT and LL-RT in body composition and physical performance. Nevertheless, our study presents one of the largest interventions to compare the effects of combined RT and AT in patients with CAD (5, 6). The assessments of body composition in our study may be limited by the use of bioimpedance, as it is well established that method compared with dual-energy X-ray absorptiometry overestimates lean mass and underestimates fat mass in middle aged to older healthy adults (47). Moreover, the results of our study may also be influenced by the selection of physical performance tests. Despite choosing well-established physical performance tests that were supposed to be most suitable to the age range of patients enrolled in CR (≥65 years) (38), most patients displayed excellent physical performance levels at baseline, which minimized test sensitivity to post-training change. Therefore, future studies should apply maximal assessments of aerobic capacity and muscle strength, regardless of age and conditioning levels of the patients to differentiate the effects of HL-RT and LL-RT. Lastly, the addition of RT was limited only to a single exercise (e.g., leg press machine); thus, the inclusion of upper body, trunk, and calf resistance exercises could yield additional beneficial changes in body composition and whole-body submaximal muscle strength. However, this was not possible due to Coronavirus-19 restriction and absence of medical staff.

Conclusion

Our study has shown similar beneficial effects of HL-RT and LL-RT when combined with AT on submaximal physical performance during early CR for patients with CAD. Therefore, LL-RT can be used as an alternative to HL-RT for exercise intolerable patients with cardiovascular disease (patients with frailty, sarcopenia, and/or co-existing chronic musculoskeletal syndromes). Still, however, more research is needed to further investigate the feasibility and efficacy of HL-RT over LL-RT using multiple resistance exercises for upper and lower limbs and trunk muscles with balance exercises as an adjunct component. In addition, further research should target to study such effects on older, frail, and/or sarcopenic patients with CAD and heart failure, which would benefit the most from these multimodal interventions in CR.

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 National Medical Ethics Committee of Slovenia (registration number: 0120-573/2019/15). The patients/participants provided their written informed consent to participate in this study.

Author contributions

TK conceived the study design, recruited and consented the participants to the study, conducted the research, analyzed the data, performed the statistical analysis, interpreted the data, drafted the manuscript, and is responsible for the final content. NŠ conceived the study design and revised the manuscript. ML and VH conceived the study design, supervised the study, revised the manuscript, and are responsible for the final content. All authors approved the final version of the manuscript.

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Conflict of interest

NŠ was employed by Science to Practice Ltd. ML received grants from Roche Diagnostics and personal fees from Vifor Pharma and AstraZeneca outside submitted work.

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

Publisher's note

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The mediation function of resting heart rate in how physical activity improves all-cause mortality: Continuous and automatic measurement *via* cardiac implantable electronic devices

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Background: Physical activity (PA) and resting heart rate (RHR) are connected with all-cause mortality. Moreover, there was an inverse correlation between PA and RHR. However, the causal relationship between PA, RHR, and long-term mortality has been rarely evaluated and quantified, particularly the mediation effect of RHR in the association between PA and all-cause mortality.

Objective: To describe the relationship between PA and RHR when consistently measured *via* cardiac implantable electronic devices (CIED) and further explore the mediation effect of PA on all-cause mortality through RHR.

Materials and methods: Patients who underwent CIED implantation and received remote home monitoring services were included. During the first 30–60 days after CIED implantation, daily PA and RHR were continuously measured and automatically transmitted by CIED. The primary endpoint was all-cause mortality. The multiple linear regression model was used to confirm the relationship between PA and RHR. The predictive values of both PA and RHR for all-cause mortality were assessed by multivariable Cox proportional hazards models. The causal mediation model was further established to verify and quantify the mediation effect of RHR in the association between PA and all-cause mortality.

Results: A total of 730 patients with CIED were included. The mean daily PA and RHR were 10.7 ± 5.7% and 61.3 ± 9.1 bpm, respectively. During a mean follow-up period of 55.8 months, 187 (26.5%) death was observed.

A negative linear relationship between PA and RHR was demonstrated in the multiple regression model (β = −0.260; 95% CI: −0.377 to −0.143, $p < 0.001$). Multivariable Cox proportional hazards analysis showed that both lower levels of PA (HR = 0.907; 95% CI: 0.878–0.936, $p < 0.001$) and higher RHR (HR = 1.016; 95% CI: 1.001–1.032, $P = 0.031$) were independent risk factors of all-cause mortality. Causal mediation analysis further confirmed and quantified the mediation function of RHR in the process of PA improving all-cause mortality (mediation proportion = 3.9%; 95% CI: 0.2–10.0%, $p = 0.036$).

Conclusion: The effects of the higher level of PA on improving life prognosis may be partially mediated through RHR among patients with CIED. It indicates that changes in the autonomic nervous function during postoperative rehabilitation exercises should get more attention.

KEYWORDS

physical activity, resting heart rate (RHR), all-cause mortality, remote home monitoring (RHM), mediation effect analysis

Introduction

Physical activity (PA) is defined as any bodily movement produced by the skeletal muscles that need to consume energy (1). Thus, in addition to participating in sports activities with high intensity, several daily activities with low intensity in our life such as part of work, taking a walk, housework, and recreational events can be regarded as part of PA as well. Strong evidence supports that regular PA can potentially prevent major adverse cardiovascular events and all-cause mortality in both healthy people and patients with cardiovascular diseases (CVDs) (2–5). In recent years, the possible existence of the "physical activity paradox" raises further discussion about PA (6–8). However, the high heterogeneity among different studies should also be noted, especially the differences in the measurement of PA. In previous clinical studies, the level of daily PA was assessed by using self-assessment questionnaires, which may be highly subjective and lack uniform evaluation criteria (9, 10). More importantly, the potential underlying mechanism by which PA improves outcomes needs to be further revealed. Previous studies support that regular PA could contribute to enhancing the overall autonomic nervous system (11, 12), which may be one of the reasons for the improved prognosis.

Heart rate, especially resting heart rate (RHR), is an easily accessible indicator in the assessment of sympathetic and parasympathetic activity; thus, it can reflect physical and general fitness (13, 14). Therefore, in several cohorts, RHR may be an alternative when direct measures of PA levels are lacking (15–17). Elevated RHR measured at several single points in time has been shown to be related to more cardiovascular adverse events and a higher risk of all-cause mortality (17–21). Meanwhile, an inverse correlation between PA and RHR was described in previous studies (15–17). Nevertheless, although the relationship between PA, RHR, and all-cause mortality was often mentioned and cited, the causal relationship among them was rarely evaluated and quantified in the same cohort, specifically the mediation effect of RHR in the association between PA and all-cause mortality. Therefore, the aim of this study is to describe the relationship between PA and RHR when consistently measured *via* cardiac implantable electronic devices (CIED) and further explore the mediation function of RHR in how PA improves prognosis.

Materials and methods

Study design

The Study of Home Monitoring System Safety and Efficacy in Cardiac Implantable Electronic Device-implanted Patients (SUMMIT) registry is an observational, prospective, and multi-center trial. We retrospectively analyzed archived home monitoring transmission data from the SUMMIT registry. The present study was approved by the ethics committee of Fuwai Hospital (ID: 2010-296) and all other participating organizations. All patients provided written informed consent before entering this study, which complied with the Declaration of Helsinki.

Patient selection

From May 2010 to April 2014, patients who underwent CIED implantation, including implantable cardioverter

defibrillator (ICD) and cardiac resynchronization therapy defibrillator (CRT-D), were included upon meeting two inclusion criteria: (i) CIED with a remote home monitoring system and the system is continuously working during the follow-up, and (ii) data including RHR and PA are available during the target window. The exclusion criteria were as follows: (i) during the target window for RHR measurement, the percentage of daily ventricular pacing in a single-chamber device was more than 10%, or the percentage of average daily atrial and ventricular pacing percentage in a dual-chamber device was more than 10%; (ii) age at CIED implantation was younger than 18 years; (iii) the postoperative survival period was less than 3 months; or (iv) received heart transplantation. Patients were divided into four groups on average based on the baseline level of daily PA. PA group 1 (range, 0.3–6.8%; $n = 182$), PA group 2 (range, 6.9–10.1%; $n = 182$), PA group 3 (range, 10.2–14.5%; $n = 183$), and PA group 4 (range, 14.5–33.3%; $n = 183$).

Data measurement and collection

Data on the patients' demographic variables (e.g., gender, age at device implantation), clinical complications (e.g., hypertension, diabetes mellitus), and medication intake (e.g., diuretics, beta-blockers) were collected before discharge from medical history.

Both PA and RHR were continuously measured and automatically transmitted every day by the remote monitoring system of CIED (Biotronik, Berlin, Germany). PA was measured using the acceleration sensors of CIED, and any acceleration above 0.473 m/s^2 was recognized as activity. The value of daily PA was shown as the percentage in the remote monitoring system. For example, 1% means 0.24 h of daily PA and 10% means 2.4 h. Previous studies have proved that the acceleration sensors were highly sensitive in detecting PA (22–24). In order to better reflect the automatic nervous function, RHR was defined as the average value of heart rate from 2 o' clock to 6 o' clock at night, considering the influence of daily activities and daytime mood. Meanwhile, the target window for collecting PA and RHR was 30 to 60 days postoperatively in order to avoid the potential influence of operation on PA.

Follow-up and outcome ascertainment

Daily PA and RHR were measured and automatically transmitted to the service center after CIED implantation. If data transmission is interrupted during the follow-up, clinical specialists will contact the patient and family members to confirm the monitoring function of the device and the condition of the patient. Also, routine telephone and outpatient follow-ups were conducted to collect clinical information about outcomes. The primary endpoint was all-cause mortality and the date of death was confirmed by medical records or death certificate.

Statistical analysis

Categorical variables, which were presented as numbers with relative percentages, were compared using the chi-square test, whereas continuous variables, which were expressed as mean standard deviation, were compared between the groups using one-way analyses of variance. Box plots and Scatter plots were used to describe the distribution of RHR among different PA groups and assess the relationship between PA and RHR, respectively. Then, simple and multiple linear regression models were used to further confirm the trend. The independent predictive values of both PA and RHR for long-term all-cause mortality were assessed by univariable and multivariable Cox proportional hazards models. Variables with a P value of < 0.05 in the univariable models and other potential confounders were entered into the multivariable analysis [age at CIED implantation, gender, diabetes mellitus, stroke, ischemic cardiomyopathy (ICM), left ventricular ejection fraction (LVEF), left ventricular end-diastolic dimension (LVEDD), CRT-D implantation, diuretics usage, and aldosterone antagonist usage].

According to Baron and Kenny's (25) procedure, the causal mediation model was built to assess the possible mediation effect of RHR on the association between PA and all-cause mortality. As shown in **Figure 1**, there are three variables in the causal chains, including the independent variable (e.g., PA), mediator (e.g., RHR), and outcome variable (e.g., all-cause mortality). Causal mediation analysis allowed us to further explore the role of RHR in the impact of PA on all-cause mortality if the following three principles are met. Firstly, there is a linear relationship between the independent variable and the mediator in the multiple regression model (i.e., in Path A, changes of the independent variable account for the changes of the possible mediator). Secondly, the independent variable (e.g., PA) can predict the risk of the outcome variables (e.g., all-cause mortality) in the multivariable Cox regression model 1 without the mediator (e.g., RHR) (i.e., in Path B, changes of the outcome variables depend on the changes of the independent variable). Thirdly, the possible mediator (e.g., RHR) can also be an independent predictor for outcome variables (e.g., all-cause mortality) in the multivariable Cox regression model 2 where confounders are included in model 1 and additional mediators (e.g., PA) were included (i.e., in Path C, changes of the possible mediator significantly can be responsible for the outcome variables). In addition, the average causal mediation effect (ACME) and mediation proportion were further quantified by the R mediation package.

All statistical analyses were performed using IBM SPSS Statistics for Windows, version 23 (IBM Corp., Armonk, NY,

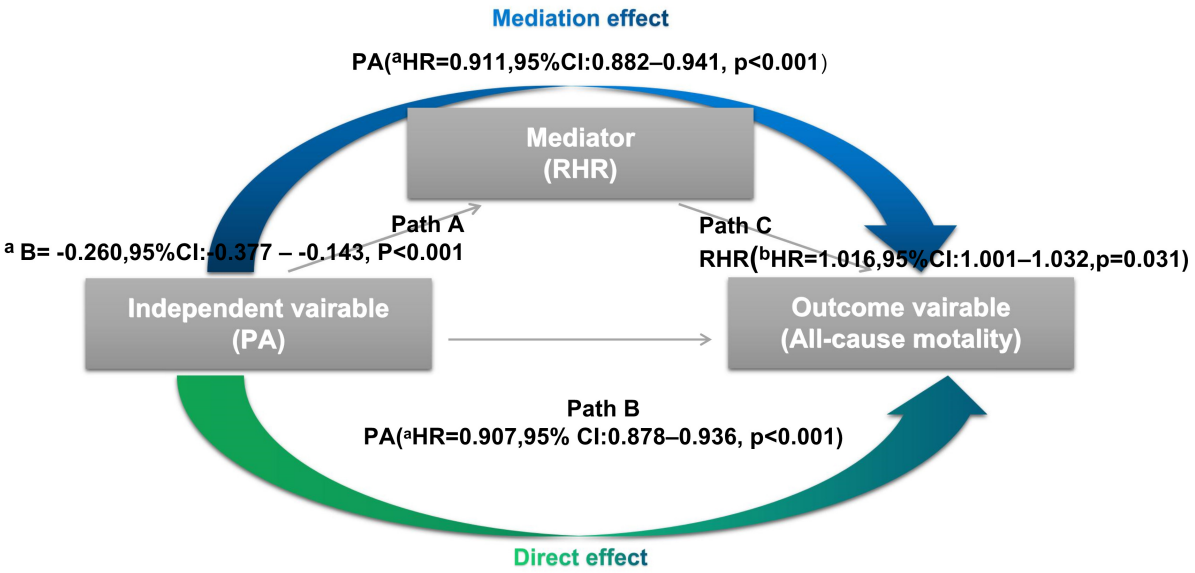

FIGURE 1
Processes of the causal mediation analysis In Path A, there is a significant linear relationship between physical activity (PA) (independent variable) and resting heart rate (RHR) (mediator) by the multiple regression model. In Path B, PA (independent variable) is shown as an independent predictor for all-cause mortality (outcome variables) in the multivariable Cox regression model without RHR. In Path C, RHR (mediator) can also be an independent predictor for all-cause mortality in the multivariable Cox regression model 2 where the mediator (e.g., PA) were included. CI, confidence interval; HR, hazard ratio; PA, physical activity; RHR, resting heart rate. [a]Each additional 1% increase in PA. [b]Each additional 1 beats increase in RHR.

USA) and R version 4.0.3 (Bunny-Wunnies Freak Out, The R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was set at a P value < 0.05, and all tests were two-sided.

Results

Baseline characteristics and clinical outcome

Of the 1,015 patients who underwent CIED implantation with home-monitor function, 285 patients were excluded because of the following reasons: home monitoring data including PA or RHR were unavailable ($n = 229$); the average atrial pacing percentage $> 10\%$ or average ventricular pacing percentage in a dual-chamber device $> 10\%$ ($n = 50$), age at CIED implantation is younger than 18 years old ($n = 3$), and the postoperative survival is less than 3°months ($n = 3$). The flow chart is shown in **Figure 2**.

A total of 730 patients were included in the analyses and Baseline characteristics are shown in **Table 1**. The mean PA and RHR were 10.7 ± 5.7% and 61.3 ± 9.1 bpm, respectively. Based on the level of daily PA, patients were evenly divided into four groups: PA group 1 (range, 0.3–6.8%; $n = 182$), PA group 2 (range, 6.9–10.1%; $n = 182$), PA group 3 (range, 10.2–14.5%; $n = 183$), and PA group 4 (range, 14.5–33.3%; $n = 183$). The mean age of the participants at CIED implantation was 60.4 ± 13.9 years, 74.8% were men, 26.4% of patients received CRT-D implantation, 31.2% had hypertension, and 33.8% were ICM. The means of body mass index (BMI) and LVEF were 23.6 ± 3.0 kg/m^2, and 42.8 ± 14.9%, respectively. Significant differences in the RHR ($p < 0.001$), age at CIED implantation ($p < 0.001$), LVEF ($p = 0.03$), history of diabetes ($p = 0.002$), stroke ($p < 0.001$), ICM ($p < 0.001$), diuretics usage ($p = 0.008$), and aldosterone antagonist usage ($p = 0.005$) were observed among different groups. During a mean follow-up period of 55.8 ± 22.7 months, 187 (26.5%) death was observed in the total cohort. With the daily PA increased, the rate of all-cause mortality in each group was gradually decreased (44.0% vs. 30.2% vs. 16.4% vs. 12.0%, $p < 0.001$).

The relationship between physical activity and resting heart rate measured by cardiac implantable electronic devices

Figure 3A shows the distribution of RHR among different daily PA groups. The daily PA gradually increased from group 1 to 4 (4.2 ± 1.7% vs. 8.5 ± 1.0% vs. 12.3 ± 1.2% vs. 18.4 ± 3.9%), and the corresponding RHR decreased continuously (64.6 ± 10.0 bpm vs. 61.4 ± 9.0 bpm vs. 59.9 ± 8.0 bpm vs. 59.3 ± 8.4 bpm). As shown in the scatter

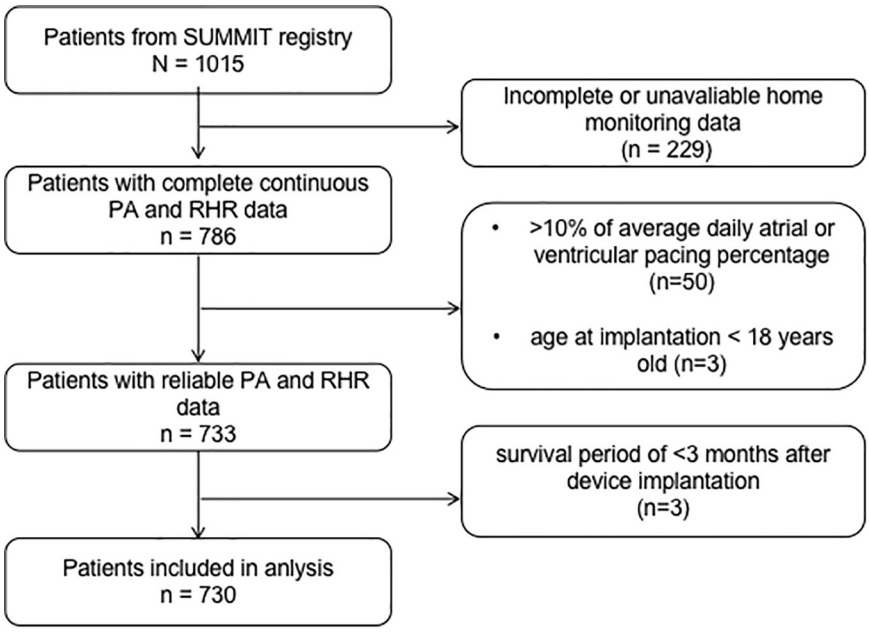

FIGURE 2
Flow chart for patient selection. PA, physical activity; RHR, resting heart rate.

TABLE 1 Baseline characteristics.

Parameters	Total (N = 730)	Group 1 (n = 182)	Group 2 (n = 182)	Group 3 (n = 183)	Group 4 (n = 183)	P-value
Home monitoring data						
PA, %	10.9 ± 5.7	4.2 ± 1.7	8.5 ± 1.0	12.3 ± 1.2	18.4 ± 3.9	-
RHR, bpm	61.3 ± 9.1	64.6 ± 10.0	61.4 ± 9.0	59.9 ± 8.0	59.3 ± 8.4	< 0.001
Demographics						
Gender, male	546 (74.8)	120 (65.9)	131 (72.0)	145 (79.2)	150 (82.0)	0.002
Age*, years	60.4 ± 13.9	66.3 ± 13.2	61.2 ± 14.1	58.9 ± 13.5	55.2 ± 12.6	< 0.001
BMI, Kg/m^2	23.6 ± 3.0	23.4 ± 3.0	23.6 ± 3.4	23.5 ± 2.9	23.7 ± 2.8	0.817
CRT-D, %	193 (26.4)	52 (26.9)	47 (24.3)	46 (23.8)	48 (24.9)	0.904
Echocardiography						
LVEF, %	42.8 ± 14.9	40.3 ± 14.8	42.3 ± 14.8	44.5 ± 15.1	44.1 ± 14.8	0.03
LVEDD, mm	58.7 ± 13.2	58.8 ± 12.0	59.1 ± 13.5	58.6 ± 13.5	58.4 ± 13.8	0.97
Comorbidities						
Hypertension	228 (31.2)	63 (27.6)	61 (26.8)	58 (25.4)	46 (20.2)	0.204
Diabetes mellitus	76 (10.4)	31 (40.8)	21 (27.6)	15 (19.7)	10 (13.2)	0.002
Stroke	16 (2.2)	11 (68.8)	2 (12.5)	2 (12.5)	1 (6.2)	< 0.001
ICM	247 (33.8)	79 (35.3)	65 (26.3)	61 (24.7)	42 (16.0)	< 0.001
Paroxysmal AF	82 (11.2)	26 (31.7)	21 (25.6)	19 (23.2)	17 (20.7)	0.475
Medication						
ACEIs/ARBs	257 (35.2)	71 (27.6)	61 (23.7)	69 (26.8)	56 (21.8)	0.310
Diuretics	189 (25.9)	63 (33.3)	48 (25.4)	42 (22.2)	36 (19.0)	0.008
Aldosterone antagonists	260 (35.6)	83 (31.9)	63 (24.2)	63 (24.2)	51 (19.6)	0.005
Beta-blockers	413 (56.6)	100 (54.9)	94 (51.6)	113 (62.1)	106 (57.9)	0.248
Amiodarone	212 (29.0)	51 (24.1)	56 (26.4)	49 (23.1)	56 (26.4)	0.795

ACEIs, angiotensin-converting enzyme inhibitors; AF, atrial fibrillation; ARBs, angiotensin receptor blockers; BMI, body mass index; CRT-D, cardiac resynchronization therapy with defibrillation; ICM, ischemic cardiomyopathy; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic dimension; PA, physical activity; RHR, resting heart rate.
*Age at the device implantation.

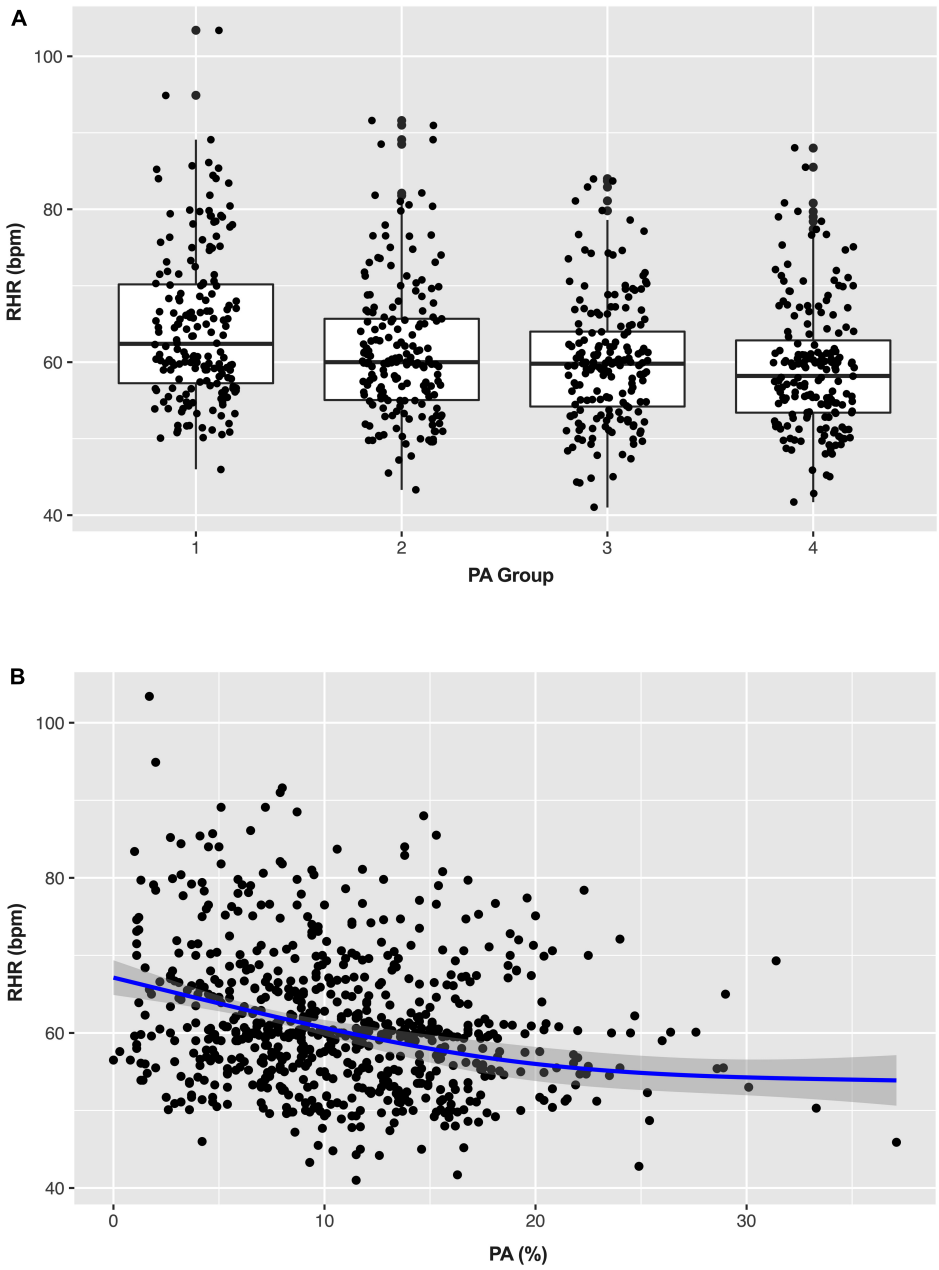

FIGURE 3
Box **(A)** and scatter plots **(B)** show the distribution of physical activity (PA) and resting heart rate (RHR). PA, physical activity; RHR, rest heart rate.

plot (Figure 3B), there is an inverse linear relationship between PA and RHR. A simple linear regression model was further established to assess, and the β of RHR was −0.338 (95% CI: −0.452 to −0.225, $p < 0.001$). After adjustment for potential confounders (age, gender, LVEF, stroke, ICM, and β-blocker) in the multiple linear regression analysis, the β of RHR was −0.260 (95% CI: −0.377 to −0.143, $p < 0.001$) which means that RHR was decreased by 0.26 bpm for each additional 1% increase of daily PA.

Predictive values of physical activity and resting heart rate for all-cause mortality

Estimated survival by the Kaplan-Meier method for the entire cohort stratified by quartile of daily PA (Figure 4A) and RHR (Figure 4B), respectively. In univariable Cox regression analyses, both daily PA and RHR by quartile were significantly associated with survival (Table 2). In univariable Cox regression

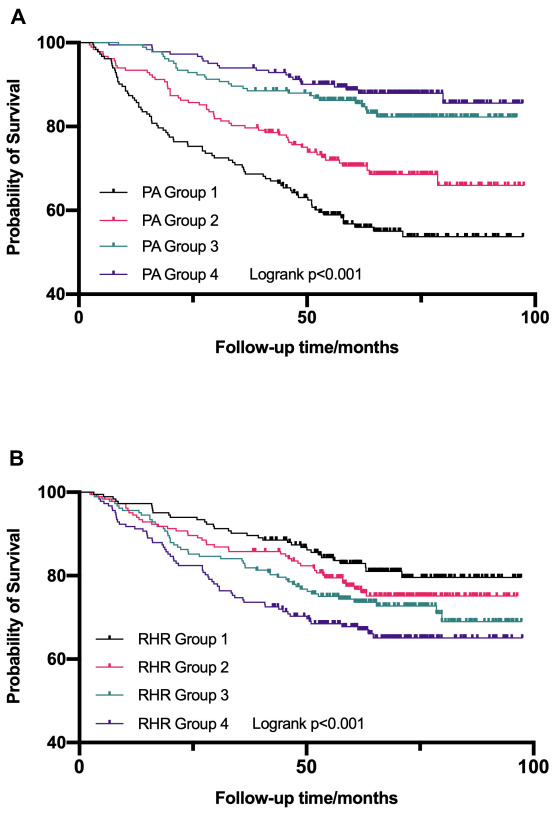

FIGURE 4
Kaplan–Meier survival curves were established to assess the predictive ability for all-cause mortality in the different quartile of daily physical activity (PA) **(A)** and resting heart rate (RHR) **(B)**. PA, physical activity; RHR, rest heart rate.

model 1, a higher level of PA was related to reduced risks of all-cause mortality (HR = 0.907; 95% CI: 0.878–0.936, $p < 0.001$) after adjustment of possible variables (age at CIED implantation, gender, diabetes mellitus, stroke, ICM, LVEF, LVEDD, CRT-D implantation, diuretics usage, and aldosterone antagonist usage). In multivariable Cox regression model 2, adjusting for all confounders included in model 1 and additional RHR, daily PA was still a protective factor of all-cause mortality (HR = 0.911; 95% CI: 0.882–0.941, $p < 0.001$), illustrates that each additional 1% increase of daily PA can reduce the risk of all-cause mortality by 8.9%.

Also, the univariable multivariable Cox regression analyses were established to further assess the predictive value of RHR on the risk of all-cause mortality (**Table 2**). Elevated RHR was related to higher risks of all-cause mortality (HR = 1.024; 95% CI: 1.008–1.041, $P = 0.003$) after adjustment for the confounders in model 1 (age at CIED implantation, gender, diabetes mellitus, stroke, ICM, LVEF, LVEDD, CRT-D implantation, diuretics usage, and aldosterone antagonist usage). After adjustment for the confounders mentioned in model 1 and additional PA (multivariable model 2), RHR as a continuous variable remained an independent predictor of all-cause mortality (HR = 1.016; 95% CI: 1.001–1.032, $P = 0.031$), indicating that each 1 bpm increase in RHR can account for a 1.6% increase in the risks of all-cause mortality. However, the association was weak in different RHR quantile groups.

Mediation analysis

As mentioned above, all three principles for causal mediation analysis have been met (**Figure 1**). In Path A, there is a significant linear relationship between PA (independent variable) and RHR (mediator) in the multiple linear regression model. Path B illustrated that PA (independent variable) was an independent predictor for all-cause mortality (outcome variables) using the multivariable Cox regression analysis without RHR involved. In Path C, RHR (mediator) remained significant in predicting all-cause mortality when PA (independent variable) was also included. As **Figure 5** shown, mediation effect of RHR was statistically significant in the association of improved PA on reduced all-cause mortality (ACME = 0.49; 95% CI: 0.025–1.13, $P = 0.036$; total effect = 11.25; 95% CI: 8.05–15.09, $P < 0.001$), and the mediation proportion was 3.9% (prop. mediated = 3.9%; 95% CI: 0.2–10.0%, $P = 0.036$), indicating 3.9% effect of PA on the risks of all-cause mortality was mediated through RHR.

Discussion

This retrospective analysis aimed to explore the relationship between RHR and PA which are continuously measured by CIED, and their value in predicting long-term all-cause mortality. The causal mediation analysis was established to verify the possible mediation effect of RHR on how PA improves all-cause mortality. The main findings were: (1) RHR was negatively related to PA, and both PA and RHR were independent predictors for long-term all-cause mortality; and (2) the mediation function of RHR was firstly confirmed and quantified in the process of PA improving all-cause mortality using causal mediation analysis for the first time, which may be critical to elucidate the potential mechanisms of the association between PA and all-cause mortality.

Clear evidence for the health benefits of PA began to emerge in the 1950s (5). Thereafter, the importance of regular PA to reduce mortality risks was gradually established (2–4). Although the possible reasons for the "PA paradox" were well-discussed recently (6–8), the heterogeneity among studies and the limitation of PA evaluation should not be ignored. PA was mostly assessed by using self-reported structured questionnaires in earlier research (6–12). The structure of each questionnaire with the evaluation latitude varies in different studies, which might contribute to the deviation of PA measurement.

TABLE 2 Predictive values of physical activity (PA) and resting heart rate (RHR) for all-cause mortality outcomes.

All-cause mortality	Univariate		Multivariate (model 1)		Multivariate (model 2)	
	HR 95% CI	*P*-value	HR 95% CI	*P*-value	HR 95% CI	*P*-value
PA (1% increase)[a]	0.889 (0.862–0.916)	< 0.001	0.907 (0.878–0.936)	< 0.001	0.911 (0.882–0.941)	< 0.001
PA quantile 1 (ref.)	P-trend < 0.001		P-trend < 0.001		P-trend < 0.001	
PA quantile 2	0.614 (0.436–0.866)	0.005	0.716 (0.505–1.014)	0.060	0.753 (0.529–1.070)	0.114
PA quantile 3	0.305 (0.202–0.463)	< 0.001	0.376 (0.246–0.575)	< 0.001	0.400 (0.260–0.614)	< 0.001
PA quantile 4	0.202 (0.125–0.327)	< 0.001	0.271 (0.164–0.448)	< 0.001	0.288 (0.174–0.477)	< 0.001
RHR (1 bpm increase)[b]	1.037 (1.022–1.052)	< 0.001	1.024 (1.008–1.041)	0.003	1.016 (1.001–1.032)	0.031
RHR quantile 1 (ref.)	P-trend = 0.002		P-trend = 0.204		P-trend = 0.439	
RHR quantile 2	1.261 (0.797–1.994)	0.322	0.983 (0.617–1.567)	0.942	0.977 (0.614–1.553)	0.920
RHR quantile 3	1.621 (1.046–2.512)	0.031	1.206 (0.771–1.886)	0.412	1.180 (0.756–1.844)	0.466
RHR quantile 4	2.129 (1.396–3.249)	< 0.001	1.451 (0.932–2.258)	0.099	1.315 (0.849–2.037)	0.120

Multivariable Cox regression model 1 was adjusted for age at implantation, sex, LVEF, LVEDD, ICD, or CRT-D implantation, LVEF, DM, stroke, ICM, use of diuretics, and use of aldosterone antagonists. Multivariate Cox regression model 2 was adjusted for the above-mentioned confounders, as well as PA or HRV. CI, confidence interval; CRT-D, cardiac resynchronization therapy defibrillator; DM, diabetic mellitus; HR, hazard ratio; ICD, implantable cardioverter defibrillator; ICM, ischemic cardiomyopathy; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic dimension; PA, physical activity; RHR, resting heart rate. [a]Each additional 1% increase in PA; [b]Each additional 1 bpm increase in RHR.

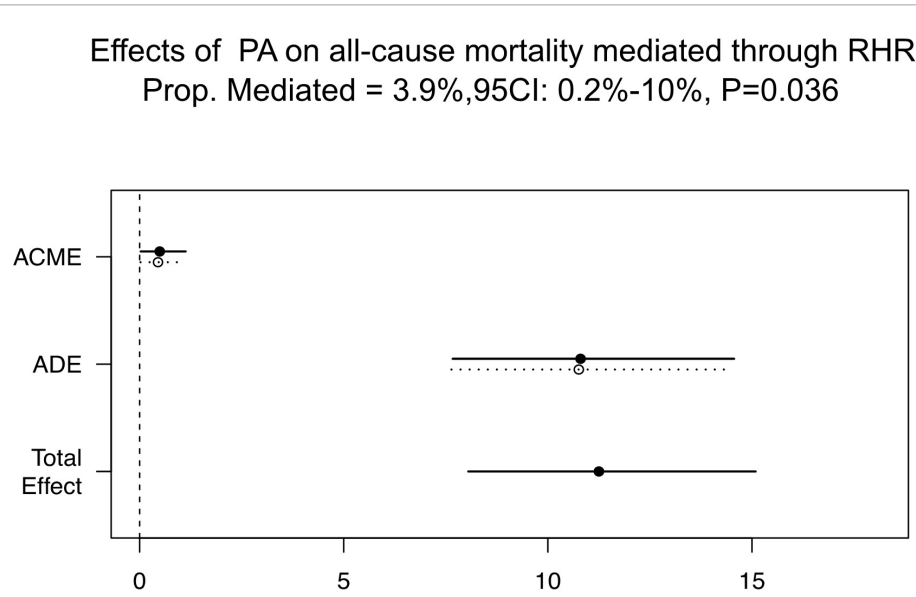

FIGURE 5
Causal mediation analysis results. ACME, average causal mediation effect; ADE, average direct effect; CI, confidence interval; PA, physical activity; RHR, rest heart rate; Prop. Mediated, mediation proportion.

Recently, CIED was reported that could automatically collect information about PA through data analysis from equipped sensor accelerometers (22–24). Although the PA intensity measured by this method was limited by the preset threshold, it provided a quantitative, objective, easily accessible measure that may reflect individual functional status. The inverse relationship between device-measured PA and mortality was also identified among patients with heart failure (22). In accordance with previous studies, this study showed that every additional 1% increase in PA could result in an 8.9% reduction in risks of all-cause mortality.

Also, our findings support that elevated RHR is independently associated with increased all-cause mortality, since every additional 1 bpm increase in RHR could lead to a 1.6% increase in the risks of all-cause mortality. Previous research has focused on the relationship between RHR and prognosis, RHR was measured by palpating the radial pulse or during blood pressure monitoring and assessed at a single point after several minutes of rest (11, 12, 19, 20, 24). This may not accurately reflect the autonomic nervous function and physiological state, which may partly account for differences in the cut-off value of RHR among published studies (19, 20,

24). In this study, RHR was automatically and continuously collected by CIED sensors from 2:00 am to 6:00 am when patients are already asleep to avoid the influence of daily activities, work, and emotions on autonomic nervous function. Although the prognostic effect of RHR was not significant in subgroups, it did not affect the main result.

Given the methodological limitations of self-reported PA, as an indicator of physical fitness and general health, RHR might be an alternative measure of the level of daily PA (11, 12, 15). Emaus et al. (11) reported the association of RHR with PA measured by different methods. RHR was negatively associated with the increasing level of self-reported PA. This pattern was demonstrated in this study as well. As daily PA gradually increased, the corresponding RHR decreased continuously. After adjusting for potential confounding factors, significant negative and linear correlations between PA and RHR existed among patients with CIED. RHR was decreased by 0.26 bpm for each additional 1% increase in daily PA.

As discussed above, both PA and RHR have independent predictive values for all-cause mortality among patients with CIED, and they also have a linear relationship. Thus, causal mediation analysis was performed following Baron and Kenny's (25) procedure. It showed that 3.9% (95% CI: 0.2–10.0%, $P = 0.036$) of the mediation effect of PA on the risks of all-cause mortality was mediated through RHR. This is the first study that verified and quantified the mediating effect of RHR on the progress of high PA improving long-term prognosis. The mechanism by which a high level of PA improves prognosis may partly be because of the low RHR induced by high PA. Specifically, the improvement in the autonomic nervous functions may be one of the reasons why regular PA decreased all-cause mortality. Therefore, RHR may be essential in providing insights into understanding the benefits of high levels of PA. Furthermore, changes in the autonomic nervous function during postoperative rehabilitation exercise should be considered among patients with CIED. Finally, when direct measures of PA levels are lacking, RHR may be used as an alternative to assess the relationship between PA and prognosis.

Limitations

This study has some potential limitations that should be recognized. First, The mediation effect in this analysis is significant but relative low. It may indicate that the mechanism by which enhanced exercise improves prognosis is very complex, and the improvement of autonomic nervous function is only part of it. Data like PA and RHR were retrospectively collected and analyzed in this study. Prospective studies are needed to further quantify the mediation function of RHR. Second, the relationship between RHR and outcomes was weak in different RHR quartile groups. Although it does not affect the main results, a large sample and more detailed grouping methods were also needed to further explore differences in RHR subgroups. Third, although the accelerometer was highly sensitive in detecting whether a person is active or not, the intensity of PA measured was limited by the preset threshold. More accurate algorithms are needed to further distinguish the levels of PA. In addition, all selected patients were those with ICD or CRT-D and underwent a high risk of sudden cardiac death, which may cause potential effects on daily PA and RHR. Thus, generalizing the findings to other populations requires more caution.

Conclusion

The findings of this study show that both PA and RHR, continuously measured by CIEDs, were independent predictors for long-term all-cause mortality. Moreover, causal mediation analysis further verified that the partial mediation effects of PA on improving life prognosis were mediated through RHR. It indicates that the changes in autonomic nervous function may be an important step in the process of improving the prognosis by regular PA. Changes in the autonomic nervous function during postoperative rehabilitation exercise should get more attention among patients with ICD/CRT-D.

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 National Center for Cardiovascular Diseases, Fuwai Hospital, Chinese Academy of Medical Sciences, Peking Union Medical College, Beijing, China. The patients/participants provided their written informed consent to participate in this study.

Author contributions

CC and XS had the idea for the study. CC wrote the draft report. SZ and XS revised the manuscript. All authors contributed to the study design, data interpretation, read, and approved the final manuscript.

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Conflict of interest

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

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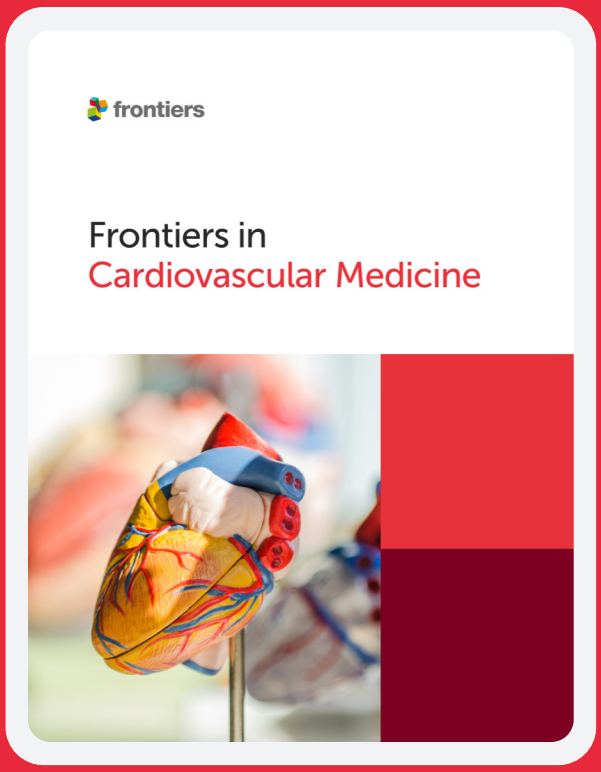

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