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Associations of leisure-time physical activity with cardiovascular mortality: A systematic review and meta-analysis of 44 prospective cohort studies

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Abstract

Background: Many cohort studies within the past few decades have shown the protective effect of leisure-time physical activity on cardiovascular mortality. To summarise the evidence from prospective cohort studies on the relationship between the amount of leisure-time physical activity and the risk of cardiovascular mortality, a dose–response meta-analysis was conducted in this study.

Methods and results: Electronic databases, including PubMed and Embase databases, Scopus and Cochrane Library, were systemically retrieved by two investigators from inception to 14 June 2018 for related studies. The maximum adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) were extracted, and a dose–response analysis was conducted using the restricted cubic splines. Finally, a total of 44 studies comprising 1,584,181 participants was enrolled into this meta-analysis. The HRs of cardiovascular mortality for moderate and high leisure-time physical activity were 0.77 (95% CI 0.74–0.81) and 0.73 (95% CI 0.69–0.77), respectively. Among these 44 studies, 19 were eligible for the dose–response meta-analysis, which suggested a linear negative correlation of leisure-time physical activity with cardiovascular mortality, regardless of age, gender and the presence of underlying cardiovascular disease or not.

Conclusions: Leisure-time physical activity shows a linear negative correlation with the risk of cardiovascular mortality regardless of age, gender and the presence of cardiovascular disease or not. However, the cardiovascular benefits of leisure-time physical activity is decreased for those aged over 65 years or those with a history of cardiovascular disease. Moreover, leisure-time physical activity displays more cardiovascular benefits to people followed up for over 10 years than to those followed up for less than 10 years. Besides, high-intensity leisure-time physical activity has more obvious cardiovascular benefits than those of moderate-intensity leisure-time physical activity.

Keywords
Leisure-time physical activity, cardiovascular mortality, meta-analysis

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Introduction

An increasing number of epidemiological studies have shown that low physical activity (PA) is a strong independent risk factor for cardiovascular mortality (CVM).[1–3] In addition, quantitative estimates also convince us that a sedentary lifestyle will lead to about 30% of deaths from coronary heart disease[4] and an increased risk of premature cardiovascular death.[5,6] As is well known, PA exerts a protective effect on the incidence and mortality of cardiovascular disease (CVD), which may mainly be achieved through its

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positive influence on the risk factors, such as weight gain, hypertension, glucose tolerance and dyslipidemia.[7,8] Therefore, the American College of Sports Medicine has currently recommended at least 30 minutes of moderate-intensity cardiorespiratory exercise training for at least 5 days a week, or at least 20 minutes of high-intensity cardiorespiratory exercise training for at least 3 days a week, or a combination of these two activities, to counter the growing physically inactive lifestyle.[9] The health promotion effects of PA have been learned, especially in many industrialised countries; nonetheless, the participation in PA remains poor.[10]

PA can be divided into four most common domains, including household, transportation, work and leisure time. Of these, leisure-time physical activity (LTPA) is generally regarded as a kind of PA for leisure, which is also one of the essential PAs for relaxation. In the modern society characterised by the fast-paced work and living environment, people can actively take full advantage of their leisure time to experience all kinds of PAs, based on the process of entertainment fitness. Typically, the status of LTPA is becoming increasingly important in this high-intensity working environment. A previous meta-analysis has illustrated the relationship between PA and CVM;[11] however, it gives no specific distinction between the PA types, and the generally called PA refers to all PA types. More importantly, several studies have shown that there may be an independent dose–response between PA and CVM.[9,12] However, it remains unclear about the appropriate amount of LTPA for cardiovascular health at the population level, and whether more LTPA will be better. Therefore, the current meta-analysis aimed systematically to assess the association of LTPA with CVM, and to evaluate the quantifiable dose–response relationship between LTPA and CVM.

Methods

Literature retrieval and study selection

The protocol and report of this meta-analysis were based on the meta-analysis of observational studies in epidemiology guidelines.[13] No ethical approval was provided, because only data from the published studies were used in this meta-analysis.

Electronic databases, such as PubMed and Embase database, the Cochrane Library and Scopus, were systemically retrieved by two investigators from inception to 14 June 2018, for published studies reporting the relations of LTPA with CVM, regardless of language. Meanwhile, the references of the retrieved articles were also consulted for further study. Typically, the key words, including 'physical activity', 'cardiovascular mortality' and 'prospective', were adopted for literature retrieval. Meanwhile, the Boolean operator 'AND' was used among these three groups of keywords, while 'OR' was used within each group. The detailed retrieval process is shown in Supplementary Appendix 1. Moreover, the study inclusion criteria were as follows: (a) prospective studies recruiting people aged over 18 years; (b) studies treating LTPA as the exposure of interests, which included at least two categories (such as low and high); (c) studies treating CVM as the outcome; (d) studies with available data on relative risk (RR) or hazard ratio (HR) and corresponding 95% confidence intervals (CIs); and (e) information from detailed conference abstracts was also included. The study exclusion criteria were as follows: (a) studies enrolling the study population of less than 18 years and non-prospective studies; (b) studies on non-LTPA and non-CVM; (c) studies with no available data on RR or HR and corresponding 95% CIs; (d) studies with the longest follow-up data or the largest number of population would be included for duplicated publications; and (e) case reports and letters were excluded.

Data extraction and quality assessment

The following data, including first author, publication year, geographical location, study design, number of participants, follow-up duration, age, percentage of women, assessment of LTPA and CVM and main findings, were extracted by two investigators (WKC and ZL) independently using a unified data list. Any disagreement was settled by mutual consultation or by the opinion of a third researcher (WJL). Besides, the HRs or RRs (moderate vs. low, high vs. low) of the maximum covariate adjustment were extracted, among which, HR was used as a common indicator of the study, while its RR was considered to be equivalent to HR. All results were expressed as HRs. Typically, the original authors would be contacted to find out ambiguous or missing information. Furthermore, the Newcastle–Ottawa scale (NOS) items[14] were used for study quality assessment, with a total score of 9 stars. A study with an NOS score of 6 or more stars was deemed as high quality, while that with an NOS score of less than 6 stars was considered to be of low quality.

Statistical analyses

Stata 12.0 was used in all statistical analyses. Meanwhile, statistical heterogeneity was evaluated using the I^2 statistic; I^2 values of 25%, 50% and 75% represented low, moderate and high inconsistency, respectively.[15] Moreover, the potential sources of heterogeneity were evaluated through meta-regression and subgroup analysis. In addition, the P value of meta-regression was calculated through a permutation

test of 10,000,[16] so as to control the spurious findings. Meanwhile, sensitivity analysis was conducted to test the impact of each individual study on the pooled results, and the potential publication bias was assessed using Begg's test.[17] Notably, a random effect model, rather than a fixed effect model, was used to estimate more conservatively the pooled HRs, because the former could better explain the heterogeneity between studies.

In addition, the random effect model was utilised to evaluate the linear and non-linear dose–response relationships between LTPA and CVM in two stages. To be specific, the generalised least squares regression was used in the first stage to estimate the restrictive three spline models with three knots at the 25th, 50th and 75th percentiles of the LTPA level,[18] and the correlations within the published HRs of each group were also estimated.[19] Subsequently, the pooled results according to the restricted maximum likelihood method were integrated into the multivariate random-effect meta-analysis. In the meantime, the non-linear P value was calculated through testing the values of the second spline coefficient equivalent to zero. Typically, the number of cases in each LTPA category (at least three categories) and the number of participants (person-years), as well as the corresponding HRs (95% CI) should be available in the dose–response analysis. Any missing data regarding the number of cases in each category were deduced from the total number of cases and the reported risk estimates.[20] Besides, the intensity of LTPA (such as swimming, running, aerobics, football, tennis and other sports) was expressed by metabolic equivalents (METs), which was greater than 6 METs. Typically, walking is a moderate intensity activity (3–6 m), while LTPAs of less than 3 METs corresponded to mild intensity activities (such as heavy housework, family improvement activities, manual and horticultural work).[21] Besides, METs·hours a week was also calculated by multiplying the intensity of LTPA with the number of hours of LTPA per week, which could be used as a measure of the amount of LTPA.[22] According to previous reports, mild, moderate and high intensity activities were assigned as 2, 4 and 8, respectively, to estimate the METs·hours a week.[23] Notably, the amplitude of the upper limit of the highest LTPA was assumed to be the same as that of the adjacent category, if it was not provided in the study. A difference of $P \leq 0.05$ was considered as statistically significant.

Results

As shown in Supplementary Figure 1, a total of 8953 studies (including 3746 from PubMed, 600 from Embase database, 4517 from Scopus and 87 from Cochrane) were originally identified, and three additional studies were found through hand-searching. Sixty-eight of these 8953 studies were selected after eliminating the duplicated studies, reading titles or abstracts, and consulting the full-text studies. In addition, eight out of these 68 remaining studies were excluded after detailed review as a result of: (a) reviews ($n = 3$); (b) cross-sectional studies ($n = 2$); (c) not using LTPA as the exposure of interests ($n = 11$); (d) not treating CVM as the outcome ($n = 6$); (e) study with the missed follow-up rate of over 50% ($n = 1$); and (f) study using duplicated data ($n = 1$). Finally, 44 studies comprising 1,584,181 participants were included in this meta-analysis.

The detailed characteristics of the enrolled studies in this meta-analysis are shown in Supplementary Table 1.[24–67] Most studies have categorised LTPA into low, moderate and high LTPA groups. A few studies have homogenised LTPA, such as the study of Shiroma et al.,[61] which divided LTPA into five groups on average. We consider that the first group is low, the third is moderate and the fifth is high. At the same time, any article carried out according to a specific gender analysis (such as male and female) was regarded as two studies. According to Supplementary Table 2, the quality of these included studies was acceptable worldwide, as all of them had a NOS score of 6 or more stars.

Meta-analysis

Moderate versus low group. As shown in Supplementary Figure 2, compared with low-intensity LTPA, the moderate-intensity LTPA could outstandingly reduce CVM (HR 0.77, 95% CI 0.74–0.81) ($N = 40$). The funnel plot of the moderate-intensity LTPA versus low-intensity LTPA is presented in Supplementary Figure 3. Besides, the Begg's test revealed no obvious evidence of a publication bias ($P = 0.119$). In sensitivity analysis, the results were only slightly changed after each individual study was eliminated.

High versus low group. It could be observed from Supplementary Figure 4 that, compared with low-intensity LTPA, high-intensity LTPA could remarkably decrease CVM (HR 0.73, 95% CI 0.69–0.77) ($N = 44$). Meanwhile, the funnel plot of the moderate-intensity LTPA versus low-intensity LTPA is displayed in Supplementary Figure 5. Moreover, the Begg's test revealed no obvious evidence of a publication bias ($P = 0.106$). In sensitivity analysis, only a slight change was observed in the results after removing each individual study.

Quantitative synthesis. According to Figure 1, 19 studies were eligible to participate in the dose–response meta-analysis of LTPA and CVM. The results demonstrated a continuous and dose–response relationship between

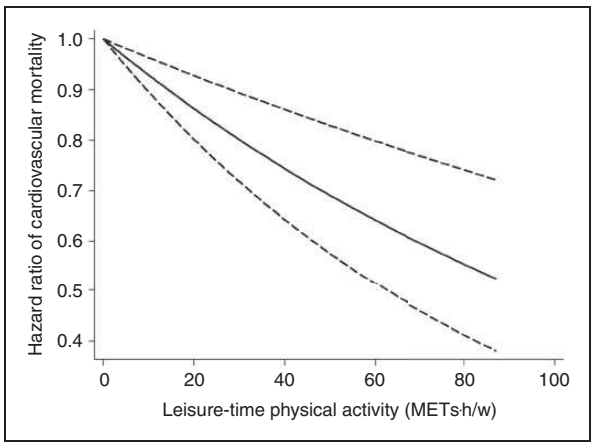

Figure 1. Dose–response of leisure-time physical activity (LTPA) and cardiovascular mortality (CVM) (total population). The bold and the dashed lines represent the estimated risk ratio (hazard ratio) and the 95% confidence interval, respectively.

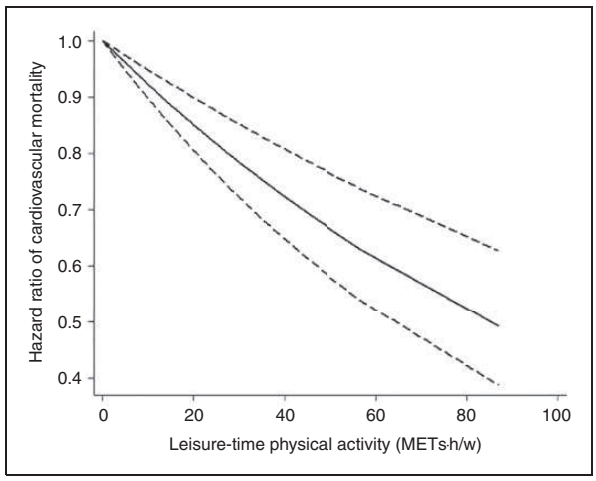

Figure 3. Dose–response of leisure-time physical activity (LTPA) and cardiovascular mortality (CVM) (without cardiovascular disease (CVD)). The bold and the dashed lines represent the estimated risk ratio (hazard ratio) and the 95% confidence interval, respectively.

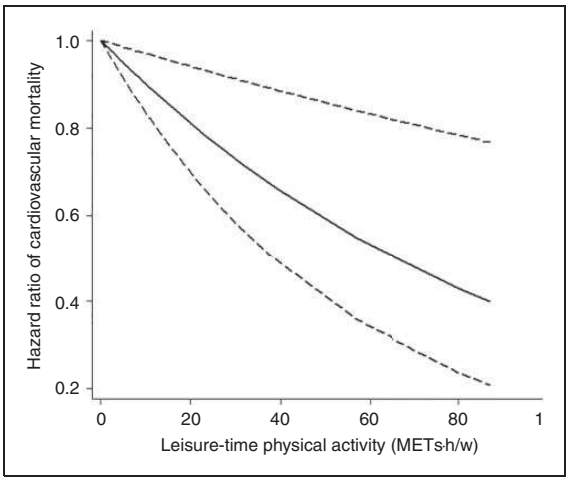

Figure 2. Dose–response of leisure-time physical activity (LTPA) and cardiovascular mortality (CVM) (with cardiovascular disease (CVD)). The bold and the dashed lines represent the estimated risk ratio (hazard ratio) and the 95% confidence interval, respectively.

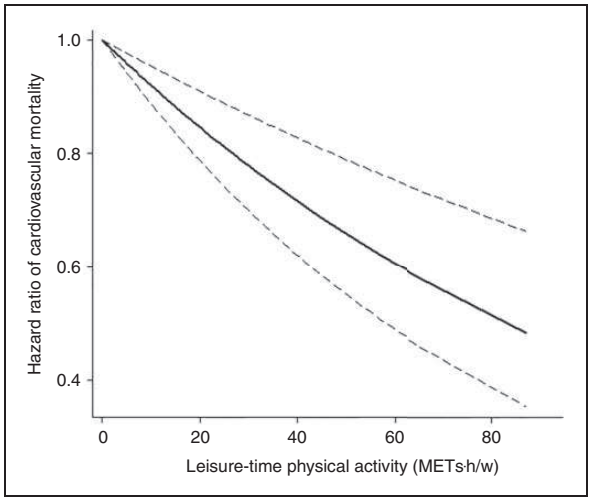

Figure 4. Dose–response of leisure-time physical activity (LTPA) and cardiovascular mortality (CVM) (<65 years). The bold and the dashed lines represent the estimated risk ratio (hazard ratio) and the 95% confidence interval, respectively.

the quantitative estimates of the amount of LTPA and the risk of CVM in the total population ($P_{\text{for non-linearity}} = 0.119$). The baseline population characteristics might markedly influence the pooled results; on this account, all studies were further divided into four subgroups, including gender (female or male), age (≥65 or <65 years), underlying CVD (with or without) and follow-up duration (≥10 or <10 years), as shown in Figures 2–9.

Supplementary Table 3 presents the relationship between the risk of CVM and the one-hour increases of moderate-intensity LTPA and high-intensity LTPA. LTPA displayed a negative linear dose–response relationship with the risk of CVM in these four subgroups. In the subgroup analysis of age (≥65 and <65 years), the risks of CVM were decreased by 1.4% and 3.3% for one1 hour of moderate-intensity LTPA, and 2.8% and 6.4% for one hour of high-intensity LTPA, respectively. In the subgroup analysis of gender (female and male), the risks of CVM were reduced by 2.5% and 1.7% for one hour of moderate-intensity LTPA, and 4.9% and 3.2% for one hour of high-intensity LTPA, respectively. Meanwhile, in the subgroup analysis of the underlying CVD (with and without), the

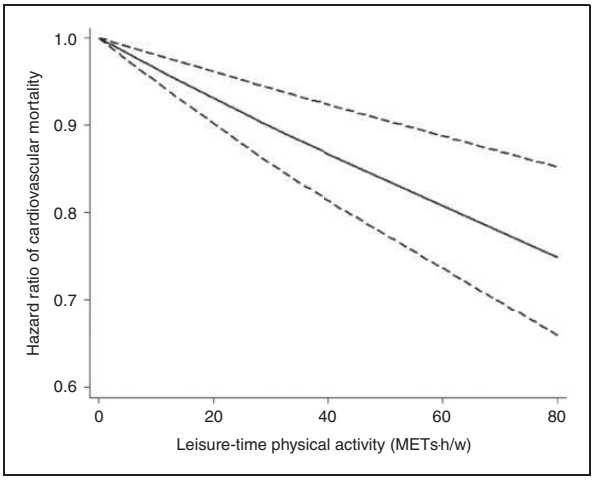

Figure 5. Dose–response of leisure-time physical activity (LTPA) and cardiovascular mortality (CVM) (≥65 years). The bold and the dashed lines represent the estimated risk ratio (hazard ratio) and the 95% confidence interval, respectively.

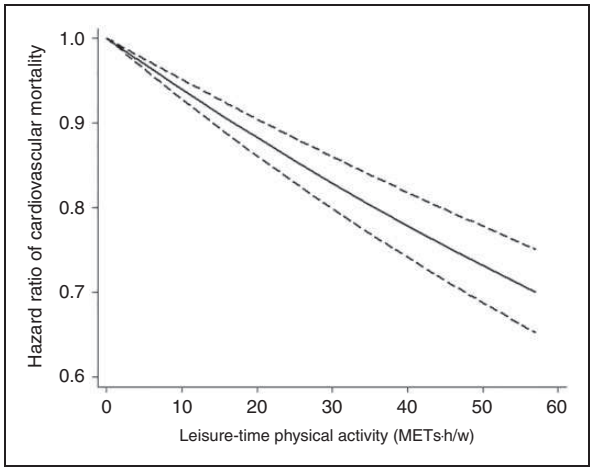

Figure 7. Dose–response of leisure-time physical activity (LTPA) and cardiovascular mortality (CVM) (female). The bold and the dashed lines represent the estimated risk ratio (hazard ratio) and the 95% confidence interval, respectively.

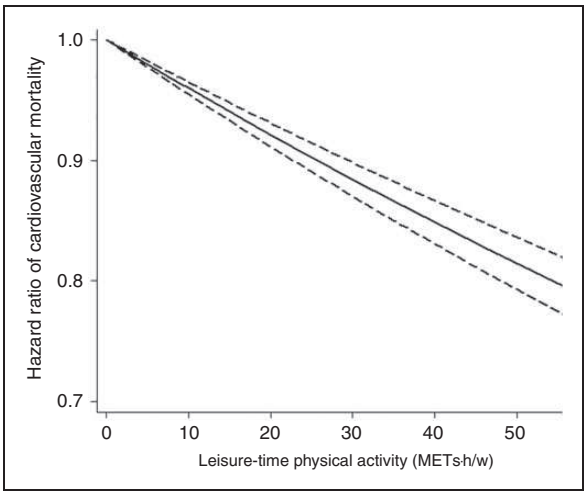

Figure 6. Dose–response of leisure-time physical activity (LTPA) and cardiovascular mortality (CVM) (male). The bold and the dashed lines represent the estimated risk ratio (hazard ratio) and the 95% confidence interval, respectively.

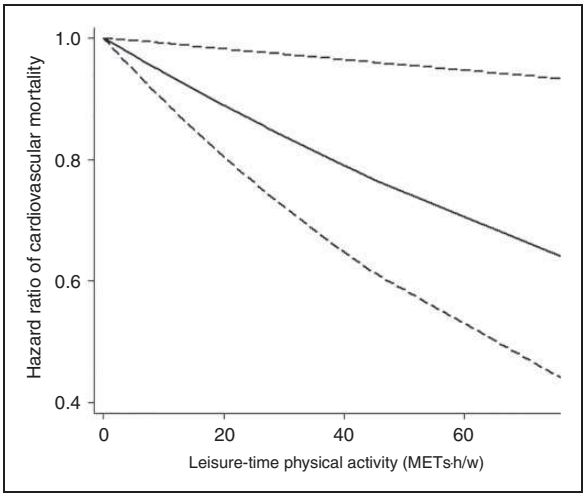

Figure 8. Dose–response of leisure-time physical activity (LTPA) and cardiovascular mortality (CVM) (follow-up <10 years). The bold and the dashed lines represent the estimated risk ratio (hazard ratio) and the 95% confidence interval, respectively.

risks of CVM were lowered by 4.2% and 3.2% for one hour of moderate-intensity LTPA, and 8.3% and 6.3% for one hour of high-intensity LTPA, respectively. Besides, in the subgroup analysis of the follow-up duration (≥10 and <10 years), the risks of CVM were reduced by 3.2% and 2.3% for one hour of moderate-intensity LTPA, and 6.2% and 4.6% for one hour of high-intensity LTPA, respectively.

Moreover, subgroup analysis and meta-regression were also performed to explain the sources of heterogeneity (moderate vs. low, and high vs. low), as shown in Supplementary Table 4. On analysis, the sources of heterogeneity might derive from the following aspects, including the follow-up duration, the mean age of participants, sex, the geographical location of the study (including Asia, Europe, America and others), the score of study quality and the presence of underlying CVD. It was found when comparing the moderate group with the low group that, follow-up duration ($P = 0.05$) and study quality ($P = 0.03$) might contribute to the study heterogeneity. Similarly, follow-up duration was also found to make a potential contribution to the study heterogeneity after comparing the high

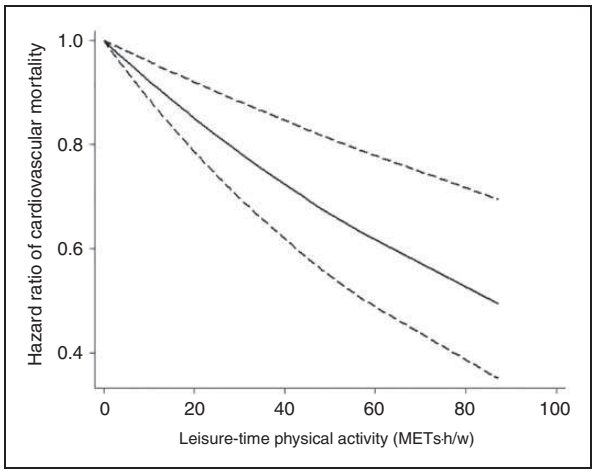

Figure 9. Dose–response of leisure-time physical activity (LTPA) and cardiovascular mortality (CVM) (follow-up $\geq$10 years). The bold and the dashed lines represent the estimated risk ratio (hazard ratio) and the 95% confidence interval, respectively.

group with the low group ($P = 0.048$). In the sensitivity analysis, the elimination of studies with the widest CIs or the narrowest CIs would only slightly affect the results.

Discussion

Findings from this meta-analysis involving 1,584,181 people suggest that any intensity of LTPA would still reduce the risk of CVM, even when it is lower than that recommended by the World Health Organization 2010 global recommendations on physical activity for health.[68]

Many previous studies have focused on the relationship between LTPA and the risk of CVM; nonetheless, the different baseline characteristics of the study population make it impossible for a complete and detailed meta-analysis. Besides, the results of quantitative analysis have suggested a negative correlation between LTPA and the risk of CVM. Importantly, the benefits of LTPA are independent of sex, age and the presence of underlying CVD. However, the cardiovascular benefits of LTPA are reduced for patients aged over 65 years or with a history of CVD, which may be attributed to the fact that the benefits of LTPA can not offset the risk of long-term chronic disease-related death. Batty et al.[58] showed that in people with symptomatic angina, the discomfort of chest pain would help to regulate their intensities of PA. However, such a regulatory mechanism does not work in asymptomatic people, leading to an increased risk of coronary heart disease mortality. In addition, Huerta et al.[59] indicated no significant association between LTPA and the risk of CVM, which might be ascribed to the lack of data regarding cardiac and respiratory health in people involved in that study. Compared with one hour of moderate-intensity LTPA, the benefits of one hour high-intensity LTPA to the risk of CVM are more obvious. Studies by Rognmo et al. showed that high-intensity PA would more efficiently increase coronary arterial oxygen.[69] Compared with patients followed up for less than 10 years, LTPA in the follow-up population for over 10 years would bring more cardiovascular benefits. On the other hand, it reflects that the longer LPTA duration will achieve greater cardiovascular benefits.

Recent studies have proposed various mechanisms to explain the health benefits of LTPA. Typically, the protective effects of PAs on the risks of CVD include adjustments to blood pressure, lipid levels, glucose tolerance or body mass index.[70] In addition, PA can directly affect the function and structure of the vascular system, which is referred to as vascular relief and regulation. It may help to reduce cardiovascular risk, which is known as the 'vascular deconditioning and conditioning' effect and may contribute to reducing cardiovascular risk.[71] Other potential benefits include improving endothelial cell function, reducing plaque progression, stabilising the induced plaques, decreasing myocardial oxygen demand and alleviating thrombosis.[72,73] Chastin et al.[74] suggested in their study that low-intensity PAs were beneficial for acute and chronic cardiometabolic responses and might also reduce the risk of mortality, which was associated with its acute positive effects on glucose and insulin. Meanwhile, studies by Schmid and Leitzmann[75] have shown that frequent LTPA among the elderly could help to maintain or reflect the overall cardiopulmonary adaptability, which could markedly affect the prevention of CVD in a positive manner. However, these mechanisms are complex and require further studies.

Of note, our meta-analysis has the following strengths. First, this is the first meta-analysis completed based on the baseline characteristics of the study population. Second, subgroup analysis and meta-regression are conducted in this meta-analysis to explain the sources of heterogeneity, the results of which suggest that study quality and follow-up duration may be one of the sources of heterogeneity. Meanwhile, the pooled HRs may be slightly affected in the sensitivity analysis. Third, the dose–response analysis is further divided into four subgroups according to the baseline characteristics of the enrolled studies, and the HRs for CVM are also calculated through the one hour increase in moderate-intensity PA and one hour increase in high-intensity PA, respectively.

Meanwhile, this meta-analysis is also inevitably associated with certain limitations. First, there is moderate–high heterogeneity in this meta-analysis.

According to the subgroup analysis and meta-regression, other covariates, except for study quality and follow-up duration, can not well explain the sources of heterogeneity. Second, subjective bias may exist in assessing the PA classification using a questionnaire or the frequency of self-reported PA. Third, the relationship between LTPA and CVM remains unknown in older adults aged over 81 years due to data limitation. Moreover, the maximum LTPA in the dose–response analysis is 100 METs·hours a week, and the relationship between over 100 METs·hours a week of LTPA and CVM remains unknown. Fourth, although most studies have been adjusted for the maximum hybrid variables, the effects of residual confounding factors still can not be excluded.

Conclusions

Our findings suggest a linear negative correlation between LTPA and the risk of CVM regardless of age, gender and the presence of CVD. However, the cardiovascular benefits of LTPA are decreased for those aged over 65 years or with a history of CVD. Moreover, LTPA shows more cardiovascular benefits to people followed up for over 10 years than to those followed up for less than 10 years. Besides, high-intensity LTPA will lead to more obvious cardiovascular benefits than those of moderate-intensity LTPA.

Author contribution

WKC, WJL and WSC contributed to the conception or design of the work. WKC, ZZ, WSC and LD contributed to the acquisition, analysis, or interpretation of data for the work. WKC, CY and WSC drafted the manuscript. WKC, ZZ, WJL and LD critically revised the manuscript. All authors gave final approval and agree to be accountable for all aspects of the work ensuring integrity and accuracy.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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