Dose-response relationship between physical activity and the morbidity and mortality of cardiovascular disease among individuals with diabetes: A meta-analysis of prospective cohort studies

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Table of Contents

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Abstract

Background: The link between physical activity (PA) and cardiovascular disease (CVD) risk remains unclear.

Objective: This study aimed to summarize the evidence from prospective studies on the association between PA and CVD morbidity and mortality.

Methods: We systematically reviewed prospective cohort studies in PubMed, EMBASE, and Web of Science up to December 2022, with inclusion criteria specifying adult participants. To assess potential bias, we employed funnel plots and Egger's test. Our analysis utilized random-effects models for qualitative evaluation and applied linear and spline regression techniques to estimate dose-response associations.

Results: The meta-analysis of 12 prospective cohort studies, involving a total of 109,820 participants, revealed that higher levels of PA were associated with a reduced risk of CVD. The RR of CVD for the highest compared with the lowest PA category was 0.62 (95% CI, 0.51-0.73). The linear regression model revealed 10 MET-h/week of incrementally higher PA was associated with a 19.0% (95% CI, 11.6%-25.7%) and a 6.9% (95% CI, 4.5%-9.3%) reductions in CVD morbidity and mortality. Additionally, the spline regression curves showed nonlinear relationships between PA levels and the risk of CVD, with a limited reduction in CVD risk and some further reduction in CVD mortality in PA levels above 20 MET-h per week.

Conclusions: Increased PA correlated with decreased CVD morbidity and mortality in individuals with diabetes. The observed PA threshold aligns with general population recommendations. Gradual transition from inactivity to recommended PA levels could significantly alleviate CVD burden in diabetics.

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Dose-response relationship between physical activity and the morbidity and mortality of cardiovascular disease among individuals with diabetes: A meta-analysis of prospective cohort studies

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Abstracts

Background: Diabetes, a chronic condition affecting various organs, is frequently associated with abnormal lipid metabolism, notably increased cholesterol and triglyceride levels. These lipid abnormalities are closely linked to the development and advancement of cardiovascular disease (CVD). Although regular physical activity (PA) has consistently shown benefits in reducing CVD risk in the general population, its precise influence on CVD risk among diabetic patients remains uncertain, particularly regarding dose-response relationships.

Objective: This study aimed to summarize the evidence from prospective studies on the association between PA and CVD morbidity and mortality in individuals with diabetes, and to explore the optimal levels for public health recommendation.

Methods: We systematically reviewed prospective cohort studies in PubMed, EMBASE, and Web of Science up to December 2022, with inclusion criteria specifying the studies published in English and included adult participants diagnosed with diabetes. A random-effects model was used to pool the relative risk (RR) with the corresponding 95% confidence interval (CI) comparing the highest with the lowest PA categories in each study for qualitative evaluation. In addition, linear and spline regression analyses were used to estimate dose-response associations.

Results: The meta-analysis included 12 prospective cohort studies, involving a total of 109,820 participants with diabetes. The combined results revealed that higher levels of PA were associated with a reduced risk of CVD. The RR of CVD for the highest compared with the lowest PA category was 0.62 (95% CI, 0.51-0.73). In addition, there were four studies describing leisure-time physical activity (LTPA) and the pooled RR was 0.68 (95% CI, 0.52-

0.83) for the highest versus the lowest activity. The linear regression model revealed that each 10 MET-h/week of incrementally higher PA was associated with a 19.0% (95% CI, 11.6%-25.7%) and a 6.9% (95% CI, 4.5%-9.3%) reduction in CVD morbidity and mortality. Additionally, spline regression curves showed nonlinear relationships between PA levels and the risk of CVD and CVD mortality (both P-nonlinearity <0.001), with a limited reduction in CVD risk and some further reduction in CVD mortality above 20 MET-h per week of PA levels.

Conclusions: For patients with diabetes, especially type 2 diabetes, there was a dose-response relationship between increased PA and reduced risk of CVD morbidity and mortality. The observed PA threshold is consistent with the recommended level for the general population. Gradually moving from inactivity to a guideline-recommended PA level could therefore significantly reduce the burden of CVD in patients with diabetes.

KEYWORDS

cardiovascular risk; diabetics; exercise; dose-response association; meta-analysis

Introduction

Diabetes, as a chronic disease, poses a significant risk to the functionality of multiple organs. Alongside the impairment of nerves and blood vessels, diabetes can lead to various severe complications, including retinopathy, nephropathy, and diabetic foot ulcers [1-3]. Data from the International Diabetes Federation showed that 6.7 million people died from diabetes in 2019, and 1 in 10 adults aged 20-79 had diabetes, totaling 537 million people [4]. Medical spending on diabetes accounts for 9% of the global health spending, totaling $966 million. By 2045, there will be an increase of 3.6 million people with diabetes worldwide, and the increase in diabetes-related health expenditures will exceed 206 billion, and the number of people who will die from diabetes will increase by 2.5 million [5, 6]. Diabetic patients often exhibit abnormal lipid metabolism, including elevated levels of cholesterol and triglycerides [7]. These abnormal lipid levels are closely associated with the occurrence and progression of CVD [8]. CVD is a group of diseases caused by atherosclerosis, characterized by lipid deposition and plaque formation on the arterial walls, ultimately leading to vascular narrowing and obstruction [9]. In diabetic patients, abnormal lipid metabolism accelerates the progression of atherosclerosis, thereby increasing the risk of cardiovascular events such as myocardial infarction and stroke [10]. According to the latest guidelines, adults with diabetes face 2-3 times the risk of developing CVD [11]. The risk of atrial fibrillation in diabetic patients increases by 3%, leading to higher possibilities of stroke, heart failure, and mortality [11]. CVD remains a leading cause of death worldwide, resulting in approximately 20.5 million fatalities and accounting for one-third of the total global mortality [12, 13].

The beneficial role of regular physical activity (PA) in reducing the risk of CVD has been repeatedly confirmed in the general population [14-17]. Through PA, diabetic patients can gradually establish a healthy lifestyle, thereby improving overall health and reducing the risk of chronic diseases [18]. Regular PA has the potential to enhance insulin sensitivity, improve vascular responsiveness, and optimize cardiorespiratory fitness levels [19-21]. These physiological adaptations may contribute to a reduced incidence of CVD among individuals living with diabetes [22]. The health benefits of PA in individuals with diabetes are mentioned in existing guidelines and public health recommendations. For example, the European Society of Cardiology guidelines for PA in cardiac patients mentioned the benefits of aerobic exercise and strength training for patients with diabetes for blood glucose and blood pressure control, weight loss, and improved exercise capacity, as well as increased exercise capacity and reduced risk of CVD [23]. The WHO's recommend that 150-300 minutes of moderate to vigorous PA per week is also applicable to adults with chronic diseases such as diabetes [24].

However, previous prospective studies have yielded inconsistent results regarding the relationship between PA levels and CVD risk in patients with diabetes. Some literature highlights the health benefits of moderate to high PA levels in reducing CVD risk, particularly at the moderate level [5, 25]. Conversely, another study suggests that the association between changes in PA levels and CVD risk factors among diabetic patients is relatively weak, implying a limited direct impact on cardiovascular health [26]. Consequently, the dose-response relationship between PA and CVD risk remains unclear, requiring additional research for informed public health recommendations.

The primary objective of this meta-analysis was to synthesize evidence from prospective studies to elucidate the relationship between PA and CVD in patients with diabetes. Additionally, we aimed to quantify the weekly metabolic equivalent of task (MET) for PA exposure and clarify the dose-response relationship. Our study aimed to provide a theoretical foundation for future exercise prescriptions for individuals with diabetes, ultimately improving health outcomes in this patient population.

Methods

Search strategy

Electronic literature searches were conducted for cohort studies investigating the association between PA and CVD risk among individuals with diabetes. The searches were performed from inception to December 2022 for relevant studies published in MEDLINE, EMBASE, and the Web of Science. The study keywords used in the searches were thesaurus terms registered in MEDLINE (MeSH) or EMBASE (EMTREE), as well as entry words related to diabetes, physical activity, cardiovascular diseases, and cohort study.

Inclusion criteria

The inclusion and exclusion criteria for the study are as shown in the Table 1.

Table 1. The inclusion and exclusion criteria for the study.

Article type	
Inclusion: prospective cohort study	Exclusion: presence of additional non-pharmacological interventions
Population	
Inclusion: adult patients with diabetes	

Disease	
Inclusion: outcomes are cardiovascular diseases, including fatal and non-fatal CVD events	
Methods	
Inclusion: studies that provide or allow for the calculation of effect sizes ((i.e., relative risk [RR], hazard ratio [HR], or odds ratio [OR])); and corresponding standard error (SE) for high PA categories compared with the lowest PA category.	Exclusion: studies lacking effect sizes or where calculation is not feasible. No stratified comparison of physical activity.
Language	
Inclusion: studies in the English language	Exclusion: languages other than English

Selection process

The titles and abstracts of a large number of publications were obtained using the aforementioned search strategy. These articles were divided equally between two authors and initially screened based on the titles. Subsequently, the third author cross-checked 15% of the documents to ensure accuracy for initial inclusion. The abstracts of the initially included studies were then read independently by both authors for inclusion. Any disagreements were referred to the third author and resolved through discussion. Finally, one author reviewed the full articles, and the second author cross-checked the included literature to determine the final inclusion criteria.

Data extraction

Two authors independently extracted the key characteristics of the included studies, and discrepancies were resolved through discussion. When multiple effect measures, such as unadjusted and adjusted measures, were present in the included studies, the most fully

adjusted measures were selected. The key characteristics of the research included, but were not limited to, the author, year of publication, study population, person-years, follow-up time, cohort status, disease diagnosis methods, and methods of measuring PA.

Assessment of study quality

A quality criteria scale was developed at the study level using applicable elements from the Newcastle-Ottawa scale for cohort studies. This scale has been widely used in meta-analyses of exercises and health risks. The study-level quality assessment was conducted by two authors.

Data analysis

To assess the qualitative association between PA and CVD risk, we pooled the log RR of the highest versus the lowest PA categories from each study using the inverse variance method. Heterogeneity among the studies was evaluated using Q statistics and I^2, both overall and within each stratum after stratification [27]. If significant between-study heterogeneity was observed, a random effects model was used to calculate the pooled estimate [28].

We also conducted subgroup analyses to explore differences between subgroups to search for possible effect modifiers or sources of heterogeneity. To verify possible sources of heterogeneity, stratified analyses were conducted on the following study characteristics that we identified based on previously extracted data from the included studies: mean follow-up duration (≤10 years/>10 years), type of diabetes (1/2), diabetes duration (not available/≤10 years/>10 years), mean age (<60 years/≥60 years), PA type (total PA/ LTPA), the proportion of men (≤50%/ □ 50%), validation of PA questionnaire (no/yes), area (Asia/Europe/North America/Mixtures), and mean BMI (≤25 kg/m^2, 25 kg/m^2, ≤30 kg/m^2) [29]. Meta-regression

analysis was used to test differences between these strata.

Publication bias was primarily detected by visual assessment using funnel plots in which SE (Standard Error) was plotted against log RR for the highest and lowest PA categories in each study. Symmetry in the plot was assumed to indicate no publication bias. In addition, a statistical assessment using the Egger regression asymmetry test confirmed the symmetry [30]. To assess the robustness of our findings, we performed a sensitivity analysis by systematically omitting one study at a time to evaluate its impact on the overall pooled results.

We extracted detailed information from the literature that quantified PA in subsequent dose-response analysis studies. If the graded quantification of PA in an article was not a point estimate, we assumed a consistent width for each category of PA and considered the middle value of its upper and lower limits as the point estimate of PA for this category [31]. The same standard unit (MET-h) was used to standardize the PA doses reported in the literature.

PA is represented by different forms of exercise, such as walking, running, moderate-to-vigorous exercise, and sedentary activities. For some studies which did not directly give the corresponding quantitative data, we defined the data according to the compendium, such as for different exercise intensities, using 1.0-1.5, 1.6-2.9, 3-5.9, and ≥6 MET [32]. Following the above expression, we translate it into the corresponding point estimates: 1.5, 4.5, and 7.5 MET. If the literature only stated the average duration of a given exercise, we assumed that the individuals performed it at an intensity of 4.5 MET [33, 34].

First, we assumed a log-linear relationship between PA and CVD morbidity and mortality. To investigate this relationship, we used a weighted least squares regression model. In addition,

we employed restricted cubic spline regression models to further explore the shape of the relationship between PA and CVD outcomes. In both models, we regressed of the log RR for each non-referent group against a higher dose of PA compared to the lowest PA category. Data analysis was conducted using STATA software version 17. We considered a two-sided P-value of less than 0.05 to be statistically significant [35].

Results

Literature search

The complete search process is presented in Figure 1. Table S1 presents details of the literature search of 8,327 articles retrieved from MEDLINE, EMBASE, and Web of Science electronic literature searches. After a full-text review, seven of these articles were excluded, with specific details provided in Table S2. Twelve studies met the prespecified inclusion criteria [5, 36-46]. Table 2 presents the characteristics of the 12 included studies. Five studies validated the PA questionnaire [37, 40, 42, 43, 45]. Most of the included studies were conducted in Europe, with a total of six studies [38, 41-43, 45, 46]. Of the 12 included studies, only two focused on type 1 diabetes patients [41, 42] while the rest exclusively studied type 2 diabetes patients; four studies limited the scope of PA to LTPA [36, 40, 42, 44].

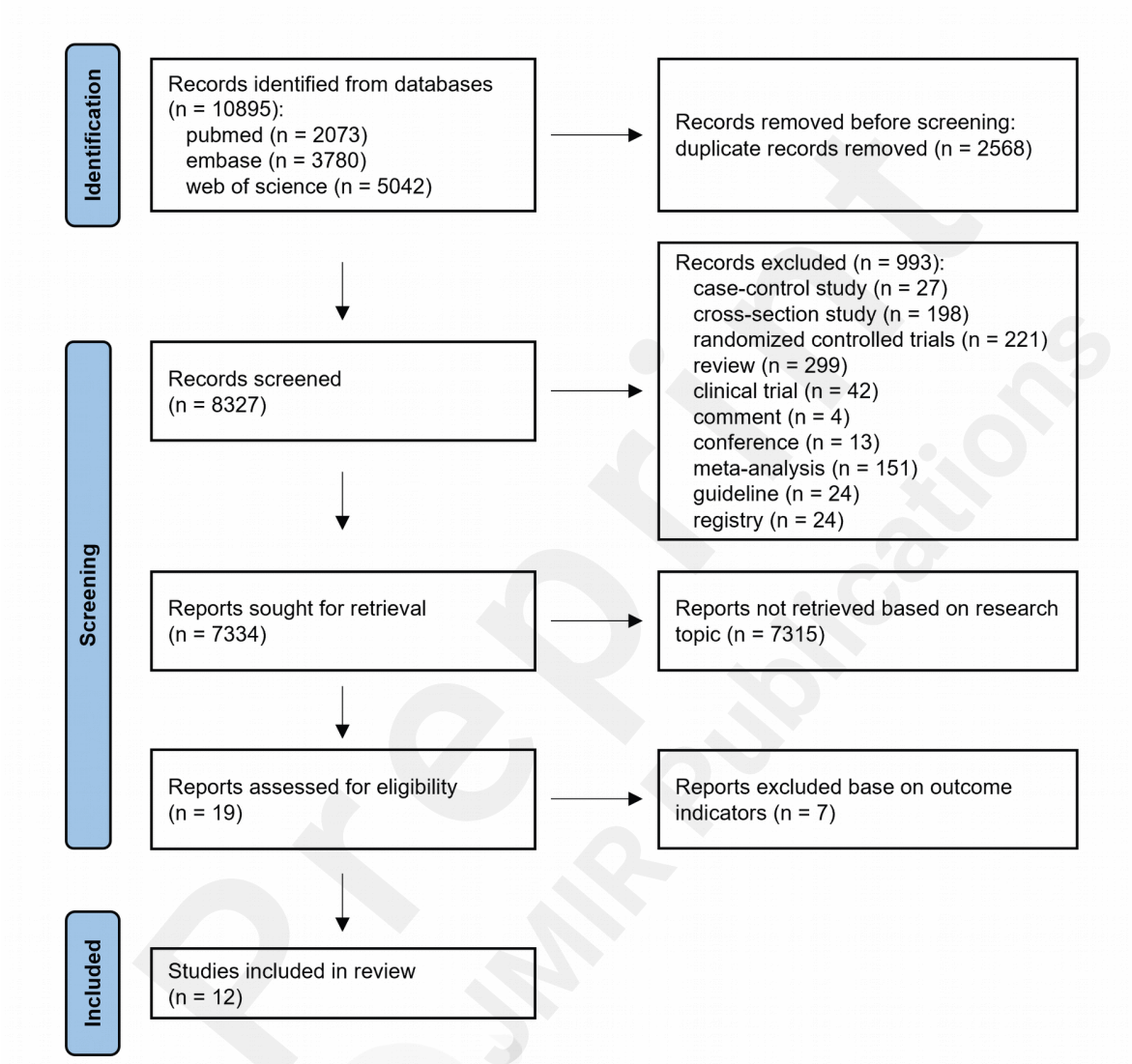


Figure 1. Study selection flowchart according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Author (year; [a]area)	[b]f/u	[c]d_duration	Age	PA type([d]d_type)	[e]PA_verified	BMI	Outcome

^Blomster JI (2013, 20+) [2]	5	7.9□6.4□	65.8 (6.4)	total PA (2)	yes	28.3 (5.2)	CVD events
Ruth E. Brown (2014, USA) [26]	9.2 ± 4.9	10.9 ± 8.8	65.5	total PA (2)	no	29.51	CVD mortality
^Yijia Chen (2022, CHM) [27]	4.5	5	62.9	total PA (2)	no	25.29	CVD mortality/heart disease mortality/sroke mortality
Enguita-Germán M (2021, ESP) [28]	5	7.3	70.5	total PA (2)	no	30.6	CVD events
^Kosuke Inoue (2020, MX) [29]	8	-	70.3	total PA (2)	no	29.17	nonfatal CVD events/Fatal CVD event
^Sone H (2013, JPN) [30]	8.05	11.0±7.1	58.5	[f]LTPA (2)	no	23.0±3.0	CHD/CHD or stroke/stroke
^Tielemans AJ (2013, EUR) [31]	7	13.6	32.7 ± 10.2	total PA (1)	no	23.59	total CVD events (men/women)
^Tikkanen-Dolenc H (2017, FI) [32]	10.3 ±3.4	21.7±12.4	38.8±12.4	LTPA (1)	yes	25.2±3.6	CVD events
Vepsäläinen T (2010, FI) [33]	18	7.8	□60	total PA (2)	yes	29.2	CVD mortality /CHD mortality

Table 2. Details of characteristics of the included studies, including study region, follow-up duration, duration of diabetes, type of diabetes, and some basic information about patients.

Author (year; [a]area)	[b]f/u	[c]d_duration	Age	PA type([d]d_type)	[e]PA_verified	BMI	Outcome
^Yung-	17	-	60±13	LTPA	yes	24.7	CVD mortality

Feng Yen (2022, TWN) [34]				(2)			
^Yerramalla MS (2020, UK) [35]	8.8 (6.1)	-	44.9□6.0□	total PA (2)	yes	-	CVD mortality
^Zethelius B (2014, CHE) [36]	4.8	5.7	59.9	total PA (2)	no	30.04	Fatal/nonfatal CVD /Fatal/nonfatal CHD/Fatal CVD

^This study was used for the dose-response analysis between PA and outcomes.

[a]area: FI, Finland; UK, United Kingdom; EUR, Europe; CHE, Switzerland; ESP, The Kingdom of Spain; JPN, Japan; TWN, Taiwan (China); USA, The United States of America; CHN, China; MX United Mexican States.

[b]f/u: follow-up years.

[c]d_duration, duration of diabetes mellitus.

[d]d_type: types of diabetes mellitus.

[e]PA_verified, validation of PA questionnaire.

[f]LTPA, leisure time physical activity.

Table S3 shows details of the confounding factors considered in each included study. Four studies detailed the patients' CVD history [5, 36, 38, 45]; seven studies considered social factors [5, 36-39, 44, 45]; and four studies took dietary factors into account [37, 40, 44, 45]. The consideration of confounders varied among the studies and more than half of the included studies adjusted the effect measure for all of the five following classic CVD risk factors: age, gender, smoking, dyslipidemia, and hypertension. A complete assessment of the quality of the literature is shown in Table S4.

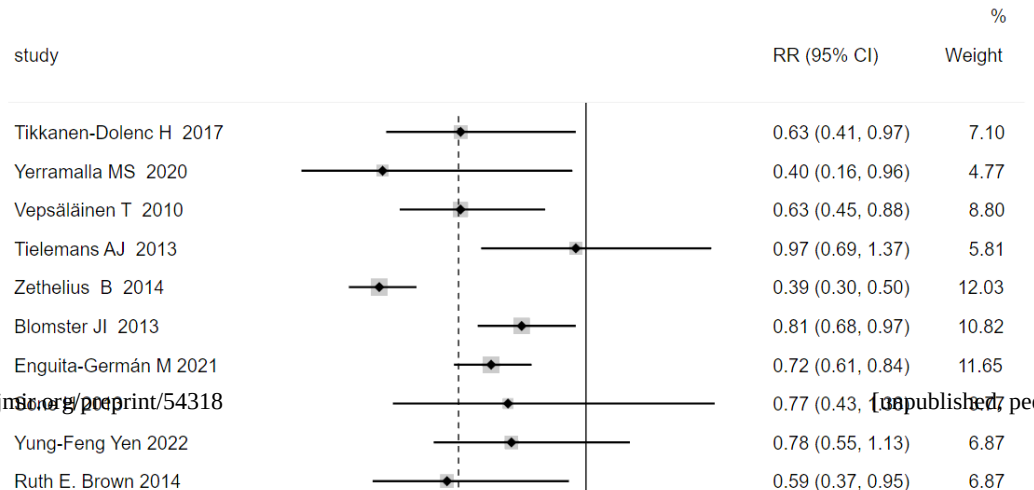
Qualitative assessment of the association of high PA with CVD risk

Of the 12 included studies, five studies included multiple outcomes, such as CHD, stroke, and heart disease [37, 39-41, 43, 46]. The outcomes of one study were fatal/non-fatal CVD, fatal/ non-fatal CHD, and fatal CVD; we chose fatal/non-fatal CVD for qualitative analysis because

it had greater representation [46]. Where the outcomes of the study were CHD or stroke and CHD and stroke; we chose CHD for qualitative analysis [40]. Where the outcomes of the study were fatal CVD, heart disease mortality, and stroke mortality; we chose fatal CVD for qualitative analysis [37]. One study included two separate outcomes, fatal and non-fatal CVD events, and we combined the estimates using a fixed-effects model [39]. Specific information regarding the studies included in the qualitative analysis is provided in Table S5.

Figure 2 shows the forest plot for the risk estimate of CVD events in relation to PA in patients with diabetes. As heterogeneity was revealed by the I^2 statistic (I^2=70.8%, p <0.001), a random-effects model was employed. The pooled RR (95% CI) of the CVD event was 0.62 (95% CI, 0.51–0.73).

Figure 2. Forest plot illustrating the summary estimate of cardiovascular disease (CVD) risk for individuals with diabetes in the highest versus lowest physical activity (PA) group, along with the 95% confidence interval. Study-specific estimates and the overall pooled estimate are depicted by circles and diamonds, respectively. Horizontal lines indicate the range of the 95% confidence interval. The size of the squares represents the weight of each study, with larger squares indicating studies with greater weight.



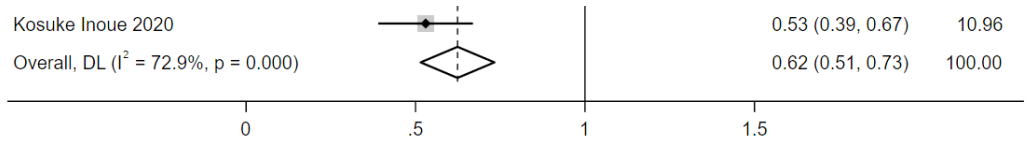
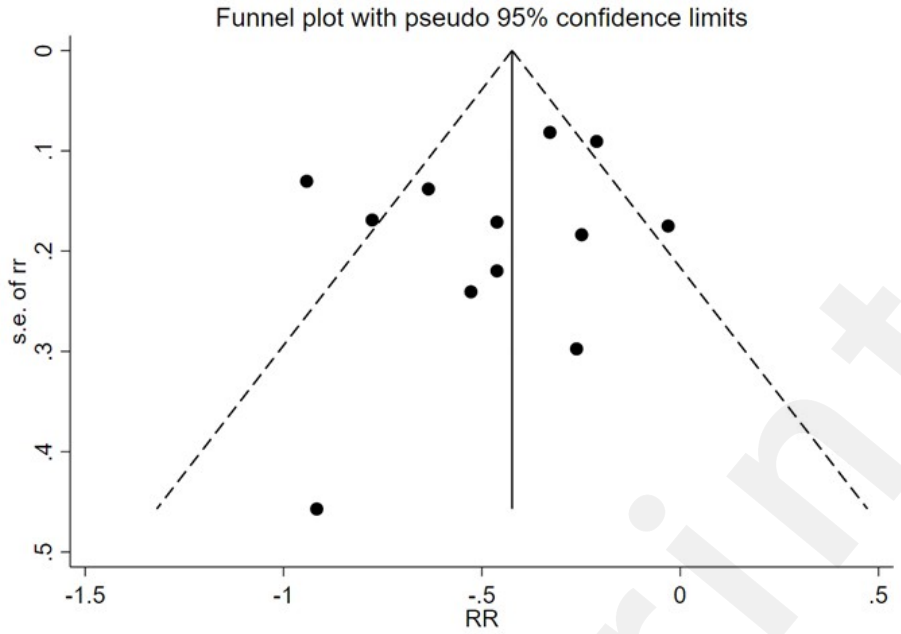


Table 3 shows the results of the stratified analyses for the key study characteristics in addition to the results of meta-regression analyses testing strata difference. The predefined characteristics did not significantly alter the combined relationship between PAD and the risk of CVD. A consistently lower risk of CVD events was observed across all strata.

To assess publication bias, we visually inspected the funnel plots presented in Figure 3. Both sides of the funnel plot were essentially symmetrical, and Egger's test was used and there was limited evidence for small-study effects (t=1.13, p=0.286), as shown in Figure S1. The results of the subgroup analyses did not identify sources of heterogeneity, but were consistent for the health benefits of PA, as shown in Figure S2-10. The results of the sensitivity analysis consistently supported our main findings, demonstrating the stability and reliability of the results, as shown in Figure S11.

Figure 3. Funnel plots assessing publication bias for the meta-analysis of prospective studies on the relationship between physical activity categories (the highest vs. the lowest) and cardiovascular disease (CVD) risk in individuals with diabetes.



	Numbers of studies	RR (95%CI)	Q statistics	I^2 (%)	P value of heterogeneity	[a]Meta-regression
Total	12	0.62(0.51-0.73)	40.58	72.90	□0.001	-
Mean follow-up duration (years)						
≤10	9	0.61(0.48-0.74)	38.43	79.20	□0.001	Referent
□10	3	0.67(0.52-0.82)	0.76	0.00	□0.001	0.64
Type of diabetes						
Type 1	2	0.79(0.45-1.12)	2.29	56.30	□0.001	Referent
Type 2	10	0.60(0.48-0.72)	35.42	74.60	□0.001	0.25
Duration of diabetes (years)						
not to mention	3	0.57(0.40-0.75)	3.00	33.40	□0.001	Referent
≤10	5	0.60(0.43-0.77)	31.71	87.40	□0.001	0.34
□10	4	0.71(0.54-0.89)	3.28	8.50	□0.001	0.98
Mean age (years)						
□60	6	0.60(0.42-0.79)	15.61	68.00	□0.001	Referent
≥60	6	0.64(0.52-0.77)	16.63	68.00	□0.001	0.77
PA type						
LTPA	4	0.68(0.52-0.83)	1.09	0.00	□0.001	Referent
Total PA	8	0.61(0.47-0.74)	38.03	81.60	□0.001	0.55
%men						
≤50	6	0.61(0.48-0.74)	9.77	48.80	□0.001	Referent
□50	6	0.62(0.44-0.80)	30.66	83.70	□0.001	0.88
Validation of PA questionnaire						

yes	5	0.54(0.43-0.65)	3.46	0.00	<0.001	Referent
no	7	0.66(0.51-0.82)	36.17	83.40	<0.001	0.48
Area						
Asia	3	0.62(0.38-0.87)	4.54	55.90	<0.001	Referent
Europe	6	0.61(0.44-0.79)	25.39	80.30	<0.001	0.63
North America	2	0.54(0.42-0.67)	0.13	0.00	<0.001	0.49
Mixtures	1	0.81(0.67-0.95)	0.00	-	<0.001	0.68
[b]BMI						
<25 kg/m^2	2	0.90(0.63-1.18)	0.45	0.00	0.502	Referent
≥25 kg/m^2	8	0.61(0.50-0.72)	14.61	52.10	0.041	0.31
≥30 kg/m^2	2	0.55(0.23-0.88)	18.01	94.40	<0.001	0.35

Table 3. Stratified analyses of pooled relative risk (RR) of cardiovascular disease (CVD) morbidity comparing high versus low levels of physical activity (PA).

[a] Meta-regression: Represents test for significance of the study modification across strata.

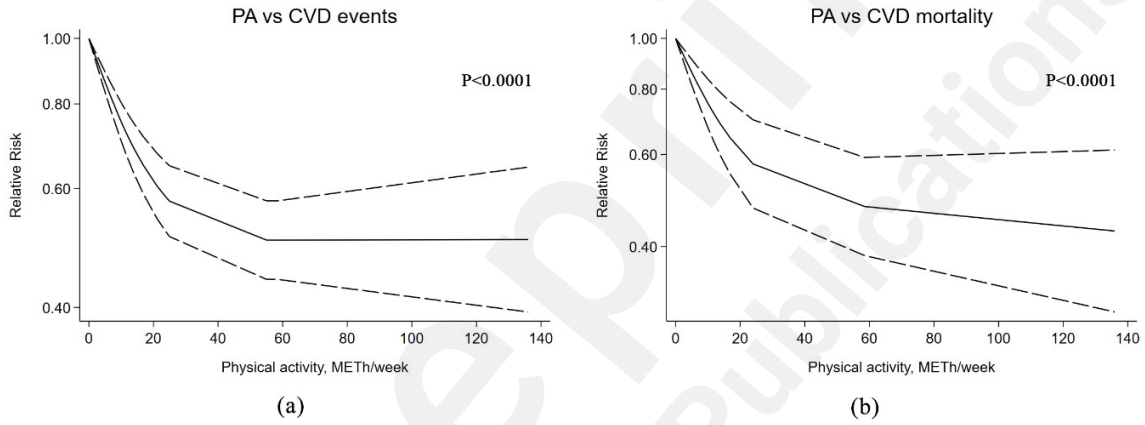
[b] BMI: Overweight is defined as BMI ≥25 kg/m^2 and obese is defined as BMI ≥30 kg/m^2.

Dose-response relationship between PA and CVD events and mortality

Specific information regarding the studies included in the quantitative analysis is provided in Table S6-S8. The log RR of CVD events and mortality against weekly PA in terms of MET-h in patients with diabetes are described in the linear and spline regression curves (showed in Figure 4). The linear regression model results indicate that a 10 MET-h/week incrementally higher PA was associated with a 19.0 (95% CI, 11.6-25.7) and a 6.9 (95% CI, 4.5-9.3) reduction in total CVD risk and risk of CVD mortality, respectively. The results of the spline regression analysis demonstrated that the relationship between PA and CVD morbidity and mortality was nonlinear (both P-nonlinearity <0.001). While there was a limited reduction in the risk of total CVD as PA levels increased, there were additional reductions in the risk of CVD mortality beyond PA levels of 20 MET-h per week.

Figure 4. Relationship between weekly physical activity (PA) and relative risk (RR) of cardiovascular

disease (CVD) events (a) and CVD mortality (b) in individuals with diabetes. Spline regression curves depicting the relationship between PA and CVD risk are presented. The solid line represents a log-linear relationship, while the dashed lines indicate the upper and lower limits of the 95% confidence interval. A distinct inflection point is observed at 20 MET hours of movement per week. The graph exhibits an overall downward trend.



Discussion

The global incidence of diabetes, particularly type 2 diabetes, is increasing annually. Patients with diabetes often experience multiple complications, and in severe cases, these complications can cause premature death [47]. Therefore, it is essential to activity guide patients with diabetes toward a healthy lifestyle, which includes regular PA, to prevent cardiovascular complications and other adverse outcomes [48, 49]. A healthy lifestyle is inseparable from active exercise, essential for health promotion and well-being enhancement. Exercise plays an important role as a preventive strategy against various chronic diseases, including CVD, stroke, diabetes, osteoporosis, and obesity, and improves the quality of life in terms of mental health [50, 51]. It is recommended that individuals with type 2 diabetes engage in regular PA and reduce their sedentary time by taking breaks between sedentary activities.

Our study aimed to synthesize evidence from prospective studies to elucidate the relationship between PA and CVD risk in patients with diabetes. The main finding of our study revealed a significant inverse correlation between regular PA and the risk of CVD in individuals with diabetes. These results align with previous studies that have shown the positive impact of exercise on glucose levels, β cell function, insulin sensitivity, vascular function, and gut microbiota, contributing to the healthy management of diabetes and reducing the risk of CVD [25].

The results of this study revealed that the trend of decreasing CVD morbidity and mortality slowed after the inflection point and leveled off with increasing PA. It is noteworthy that this

slowing trend did not affect the positive effect of PA on CVD risk. Previous studies have suggested that the health effects of high doses of PA are not yet clear, and may even be harmful to the cardiovascular system [52]. However, in this study, no negative effects were observed, and any amount of exercise was beneficial in reducing CVD risk for individuals with diabetes.

This study has some limitations. Firstly, in most of the included cohort studies, PA information was mainly obtained using questionnaires, which were differentially applied in different studies, and the findings may have been affected by the potential recall bias.

Secondly, some studies included different endpoint outcomes, such as CHD, CHD mortality, and stroke, however we did not analyze them separately either qualitatively or quantitatively, due to the relatively small number of studies on these CVD subtypes.

Thirdly, only a few of the studies included in this review addressed LTPA, and future studies may be needed to further elucidate the effects of specific types of PA on cardiovascular risk in patients with diabetes.

Finally, the inclusion of different subtypes of diabetes among the study subjects. Type 1 diabetes is typically characterized by autoimmune destruction of pancreatic β-cells, resulting from the immune system attacking insulin-producing cells, and is associated with both genetic and environmental factors [53]. In contrast, type 2 diabetes is attributed to insulin resistance and inadequate insulin secretion, closely linked to obesity, unhealthy lifestyles, and genetic factors [54]. Therefore, variations in physiological and pathological profiles between the two types may lead to disparate cardiovascular responses to PA. However, according to previous studies, both type 1 and type 2 diabetes patients benefit from engaging in

appropriate exercise routines [51, 55-59]. Consequently, we aim to analyze the overall health benefits of PA for all diabetic patients. Although the FS3 results indicate that different types of diabetes are potential factors causing heterogeneity, they indeed demonstrate health benefits for both types of patients. Given this limitation, we intend to conduct future studies that are more tailored to different subtypes of diabetic patients as much as possible.

It's worth noting that while previous studies have explored the link between PA and CVD, our study takes a more focused approach to cardiovascular health [60-62]. We conducted thorough analyses, separately examining the risks of CVD and CVD mortality. Additionally, we included relevant research conducted from 2010 to the present, enhancing the timeliness of our findings. Therefore, our research retains significant clinical value.

Conclusion

In conclusion, our study demonstrated a dose-response relationship between increased PA and decreased risk of CVD morbidity and mortality in patients with diabetes, particularly type 2 diabetes. The observed PA threshold was consistent with the recommended level for the general population, indicating that gradually increasing PA levels from a sedentary state to the recommended guidelines can significantly reduce the burden of CVD in patients with diabetes. These findings support the development and implementation of policies to promote PA among patients with diabetes, particularly those with type 2 diabetes.

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Data Availability

All data generated or analyzed in this study are publicly available and are included in this published article.

Authors' contributions

All the authors involved in drafting or revising the article and approved of the submitted version. YC drafted the manuscript. HL, GC, and RW helped conceive the design and made edits and comments to the manuscript. YC, XS, and GC carried out the literature search and helped in drafting the manuscript. All authors have read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Supplementary Tables and Figures.

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Abbreviations

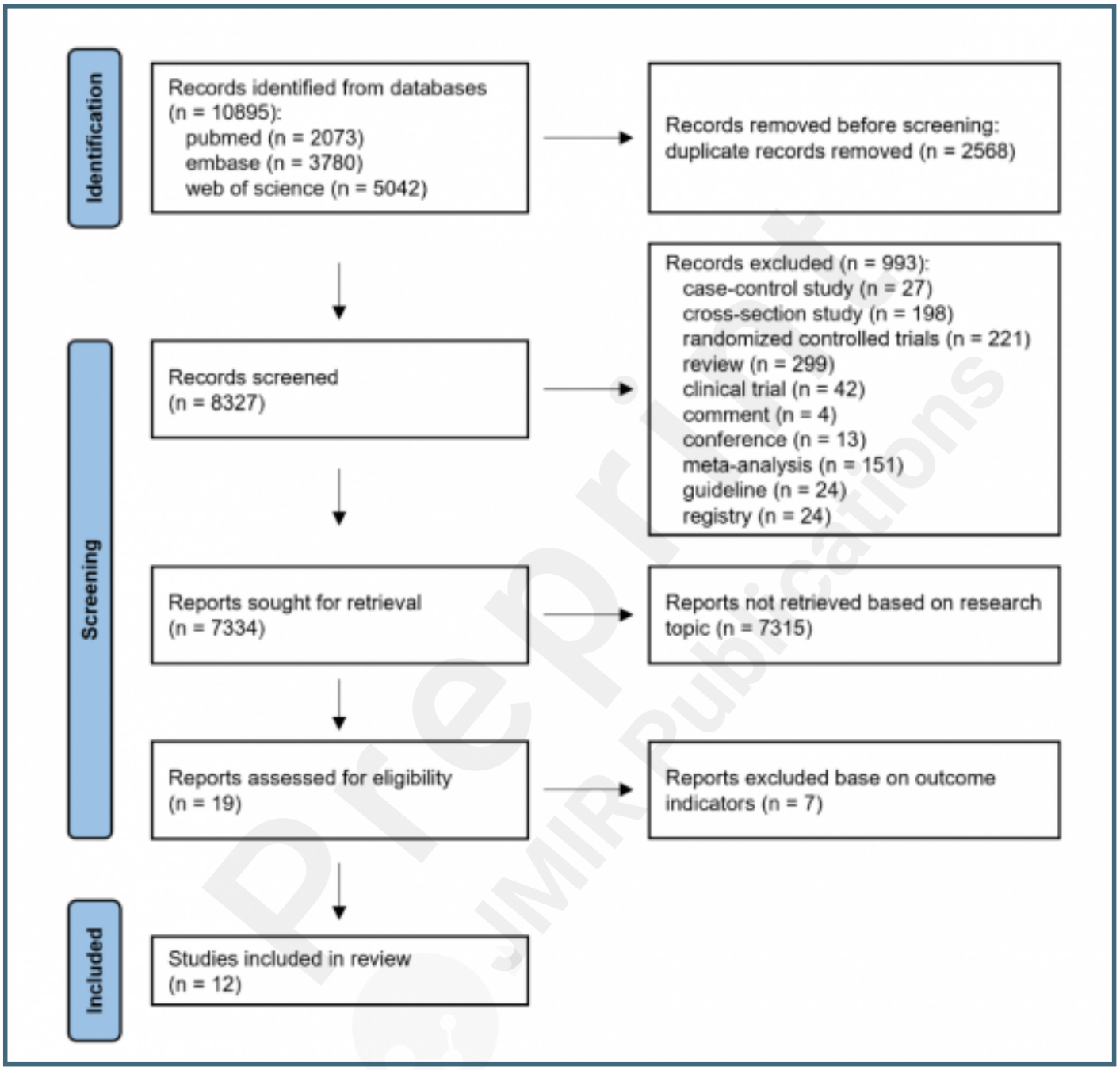
PA: Physical activity
CVD: Cardiovascular disease
RR: Relative risk
SE: Standard Error
CI: Confidence interval
LTPA: Leisure-time physical disease

CHD: Coronary artery heart disease
MET: Metabolic equivalent of task

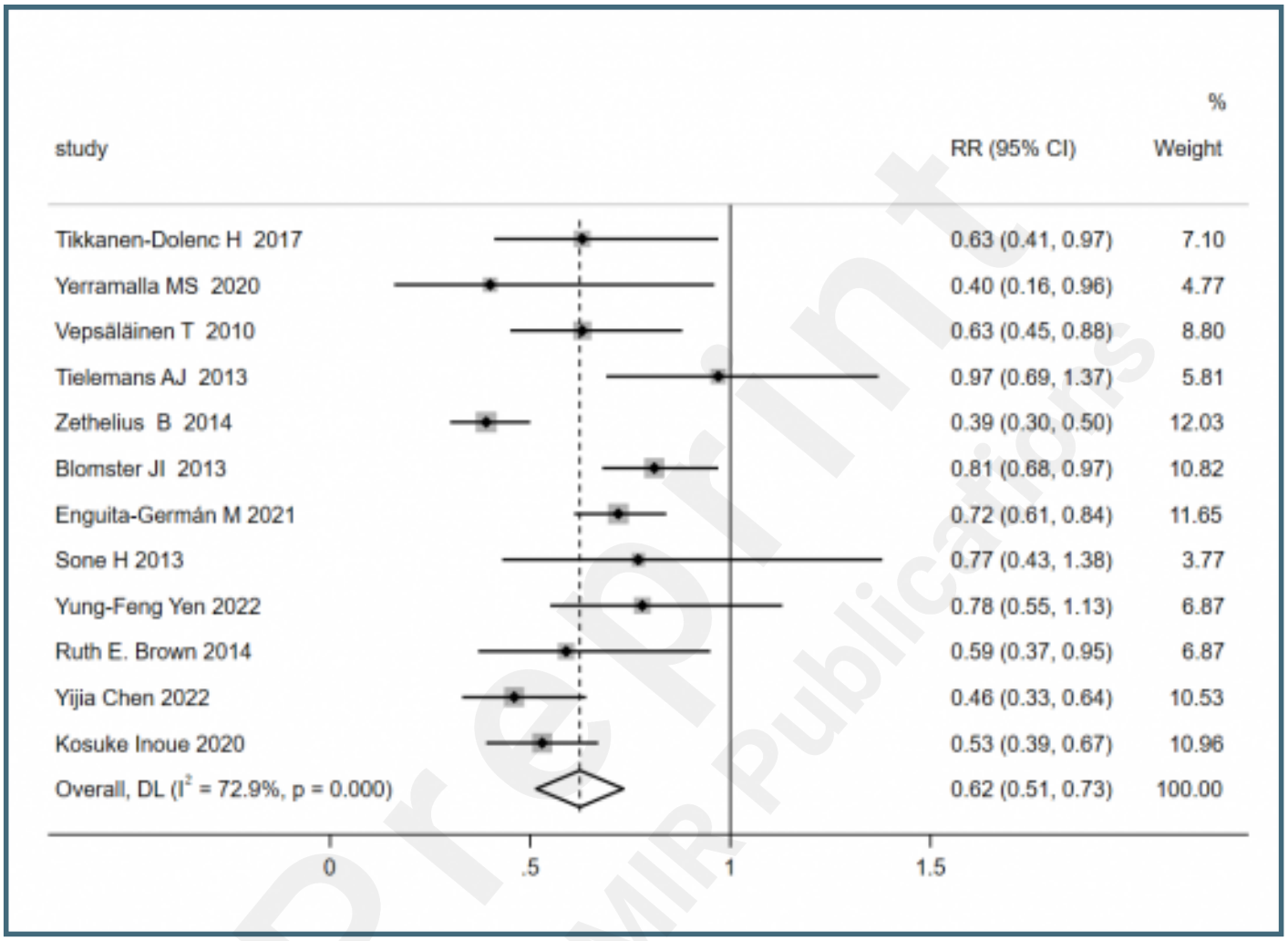
Supplementary Files

Figures

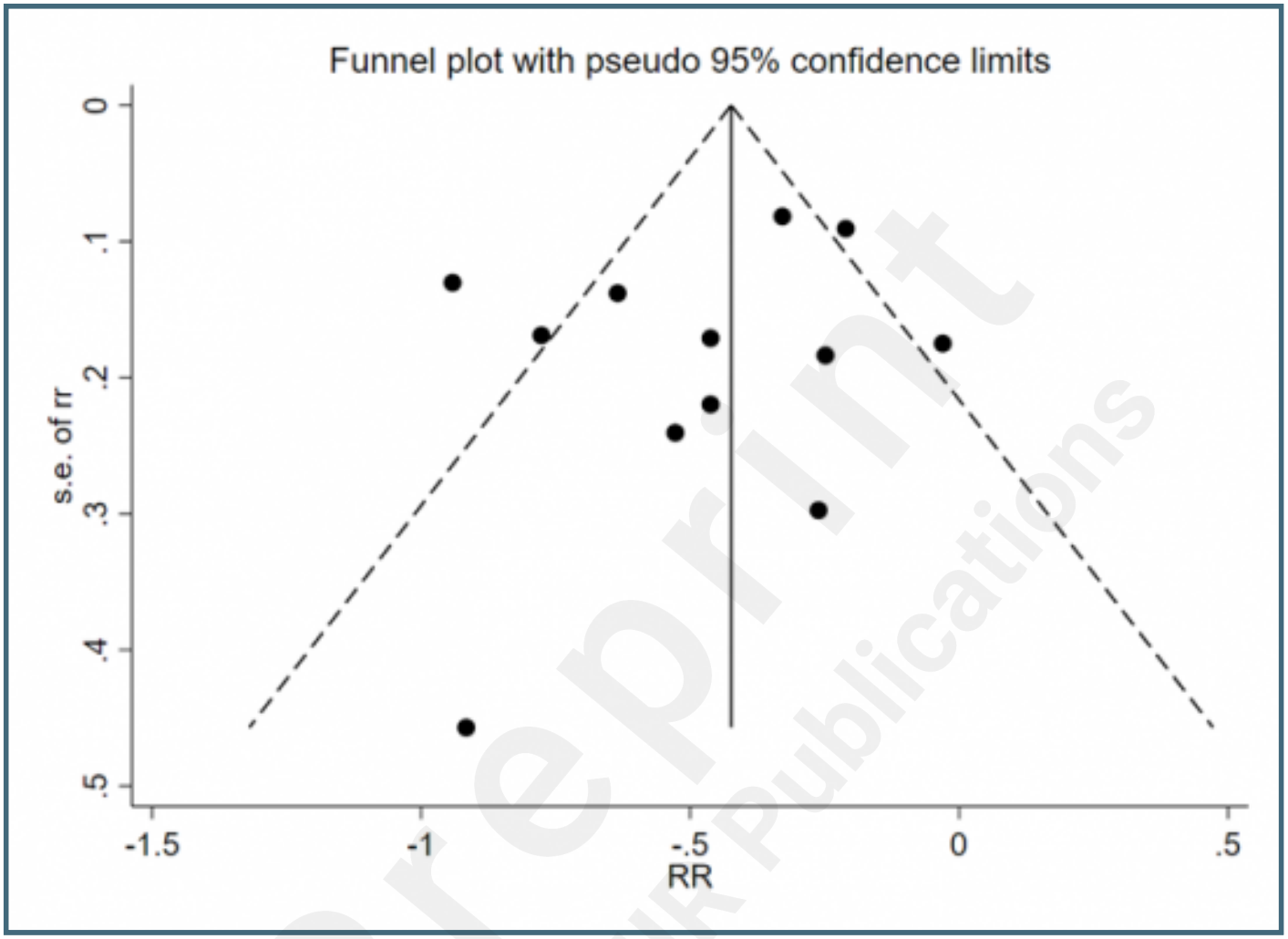
Study selection flowchart according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.



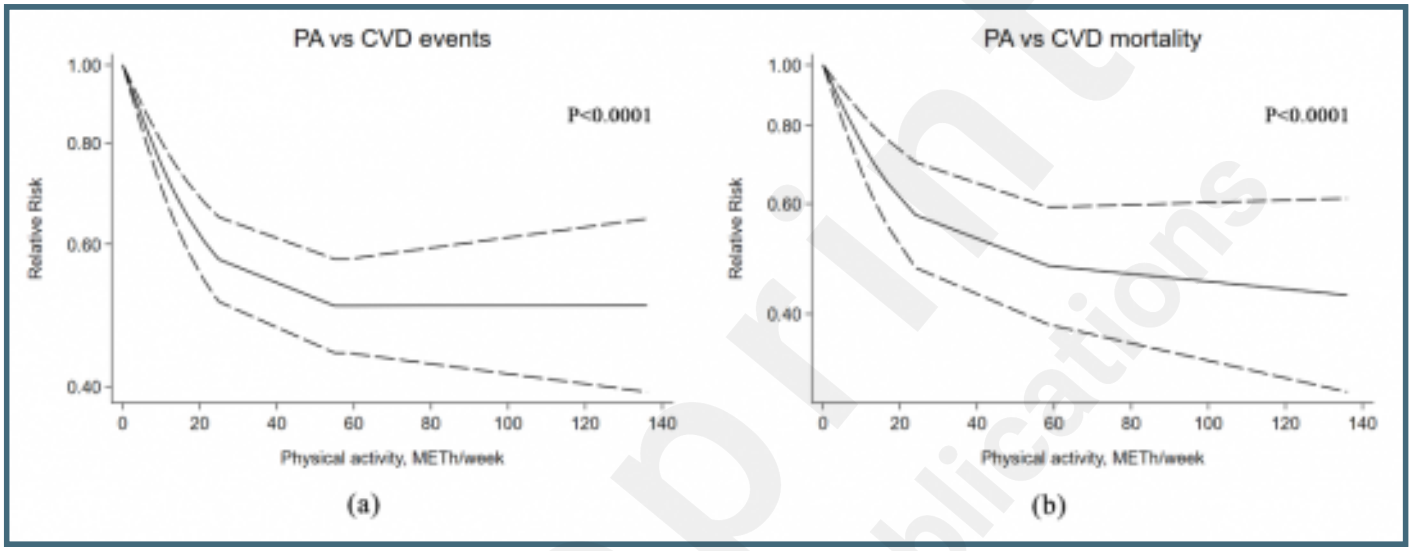
Forest plot illustrating the summary estimate of cardiovascular disease (CVD) risk for individuals with diabetes in the highest versus lowest physical activity (PA) group, along with the 95% confidence interval. Study-specific estimates and the overall pooled estimate are depicted by circles and diamonds, respectively. Horizontal lines indicate the range of the 95% confidence interval. The size of the squares represents the weight of each study, with larger squares indicating studies with greater weight.



Funnel plots assessing publication bias for the meta-analysis of prospective studies on the relationship between physical activity categories (the highest vs. the lowest) and cardiovascular disease (CVD) risk in individuals with diabetes.



Relationship between weekly PA and RR of CVD events(a) and CVD mortality (b) in diabetics. The spline regression curves of the relation between PA and risk of CVD are shown. The solid line indicates a log-linear relationship and the dashed line indicates the upper and lower limits of the 95% confidence interval. A clear inflection point can be seen at 20 MET-h of movement per week. The graph has an overall downward trend. Relationship between weekly physical activity (PA) and relative risk (RR) of cardiovascular disease (CVD) events (a) and CVD mortality (b) in individuals with diabetes. Spline regression curves depicting the relationship between PA and CVD risk are presented. The solid line represents a log-linear relationship, while the dashed lines indicate the upper and lower limits of the 95% confidence interval. A distinct inflection point is observed at 20 MET hours of movement per week. The graph exhibits an overall downward trend.



Multimedia Appendixes

Supplementary Tables and Figures.
URL: http://asset.jmir.pub/assets/0b54702e2d6a52d0f346cc99a06fdf71.docx

CONSORT (or other) checklists

PRISMA checklist.
URL: http://asset.jmir.pub/assets/4fce5e4424d7878fe8cc55038c5f62c8.pdf

TOC/Feature image for homepages

to be used for our homepage and the table-of-contents (we call this a "TOC image").