Physical Activity and Risk of Major Diabetes-Related Complications in Individuals With Diabetes: A Systematic Review and Meta-Analysis of Observational Studies

Diabetes Care 2022;45:3101–3111 | https://doi.org/10.2337/dc22-0886

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BACKGROUND

Physical activity is a cornerstone in diabetes management; however, evidence synthesis on the association between physical activity and long-term diabetes-related complications is scarce.

PURPOSE

To summarize and evaluate findings on physical activity and diabetes-related complications, we conducted a systematic review and meta-analysis.

DATA SOURCES

We searched PubMed, Web of Science, and the Cochrane Library for articles published up to 6 July 2021.

STUDY SELECTION

We included prospective studies investigating the association between physical activity and incidence of and mortality from diabetes-related complications, i.e., cardiovascular disease (CVD), coronary heart disease, cerebrovascular events, heart failure, major adverse cardiovascular events, and microvascular complications such as retinopathy and nephropathy, in individuals with diabetes.

DATA EXTRACTION

Study characteristics and risk ratios with 95% CIs were extracted. Random-effects meta-analyses were performed, and the certainty of evidence and risk of bias were evaluated with use of the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) and Risk Of Bias In Non-randomised Studies - of Interventions (ROBINS-I) tools.

DATA SYNTHESIS

Overall, 31 studies were included. There was moderate certainty of evidence that high versus low levels of physical activity were inversely associated with CVD incidence, CVD mortality (summary risk ratio 0.84 [95% CI 0.77, 0.92], *n* = 7, and 0.62 [0.55, 0.69], *n* = 11), and microvascular complications (0.76 [0.67, 0.86], *n* = 8). Dose-response meta-analyses showed that physical activity was associated with lower risk of diabetes-related complications even at lower levels. For other outcomes, similar associations were observed but certainty of evidence was low or very low.

LIMITATIONS

Limitations include residual confounding and misclassification of exposure.

CONCLUSIONS

Physical activity, even below recommended amounts, was associated with reduced incidence of diabetes-related complications.

META-ANALYSIS

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Received 6 May 2022 and accepted 19 September 2022

This article contains supplementary material online at https://doi.org/10.2337/figshare.21158605.

In 2021, 10.5% of individuals between the ages of 20 and 79 years had been diagnosed with diabetes globally and 12.2% of deaths in this age-group were caused by diabetes-related mortality (1). Individuals with diabetes are at risk for developing further health-related complications, including macrovascular diseases such as cardiovascular diseases (CVD), cerebrovascular events, and heart failure (HF), as well as microvascular disease (MVD), such as retinopathy and nephropathy, and neuropathy (2–5). Physical activity has been shown to reduce early mortality in individuals with diabetes and may be effective in preventing diabetes-related complications (6,7). Therefore, exercise recommendations are often used by physicians aiming to treat metabolic risk factors such as obesity, insulin resistance, and hyperglycemia, hypercholesterolemia, and hypertriglyceridemia (8).

The World Health Organization (WHO) recommends that adults with chronic diseases spend at least 150–300 min in moderate aerobic physical activity per week (9). This can be exchanged for at least 75–150 min of vigorous aerobic physical activity or the corresponding MET of moderate-to-vigorous physical activity (MVPA) (8.25–16.5 MET-h/week) (10). Although adherence to these guidelines may lead to a significant decrease in metabolic risk factors, even a minor increase in physical activity, below the recommended duration, has been shown to be effective in decreasing mortality in individuals with noncommunicable diseases (11).

While there is much evidence for the association between physical activity and type 2 diabetes prevention (12), evidence on the relationship of physical activity with diabetes-related complications needs to be summarized and evaluated. Findings from intervention studies on this topic are scarce. In Look AHEAD (Action for Health in Diabetes), with a focus on a combined diet and exercise intervention, it was reported that the lifestyle intervention reduced the risk of developing MVD and was beneficial for CVD prevention in a subgroup of participants with at least 10% weight loss (13,14). Furthermore, while the Diabetes Prevention Program (DPP) was effective in reducing the development of diabetes among participants with impaired glucose levels, the lifestyle intervention—a combination of diet and exercise—did not reduce long-term cardiovascular risk (15). Alternatively, there is further evidence available from epidemiological cohorts. In 2013, Kodama et al. (16) carried out a meta-analysis, and findings showed a prospective inverse association between physical activity and reduced relative risk of all-cause mortality and CVD incidence in individuals with diabetes. However, since then, several new findings from large cohort studies have been published on this topic, also investigating further relevant outcomes, such as microvascular complications, including nephropathy and retinopathy (17–22). Additionally, the certainty of evidence of these associations needs to be evaluated, and the optimal level of physical activity prospectively associated with the greatest risk reduction needs to be clarified. Therefore, we conducted a systematic review with meta-analysis to summarize and evaluate the evidence on the association between physical activity and major diabetes-related complications in individuals with diabetes. For identification of the optimal levels of physical activity for diabetes management, linear and nonlinear dose-response meta-analyses were performed.

METHODS

A protocol was prospectively preregistered at International prospective register of systematic reviews (PROSPERO) (CRD42020166772) (https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=166772). We followed the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (23).

Data Sources and Searches

A systematic literature search was conducted in PubMed, Web of Science, and the Cochrane Library from inception until 6 July 2021. We used predefined search terms (Supplementary Table 1) and did not use any filters or language restrictions. Reference lists of identified articles were screened to check for further potential studies.

Study Selection

We included observational, prospective studies that investigated the association of any type of physical activity and incidence of diabetes-related complications in individuals with diabetes age ≥18 years at baseline reporting relative risk estimates. Diabetes-related complications were defined as incidence of CVD, CVD mortality, specific CVD end points such as coronary heart disease (CHD) (including fatal or nonfatal angina pectoris or myocardial infarction, coronary revascularization [angioplasty, percutaneous coronary interventions, coronary bypass graft surgery], angiographic stenosis, and ischemia), cerebrovascular events, HF, major adverse cardiovascular events (MACE) (including cardiovascular mortality, myocardial infarction, stroke), incidence of MVD, including retinopathy and nephropathy, and incidence of neuropathy, peripheral artery disease, and foot ulcers and amputations. Studies on gestational diabetes mellitus, adolescents, or children were excluded from the review. Titles and abstracts of articles were screened, and for articles deemed appropriate, the full text was checked for eligibility. The literature screening was conducted by at least two independent investigators (A.La., A.Le., E.M., M.N., T.S., M.R.). Discrepancies were resolved through discussions within the review team. For publications reporting on the same cohort investigating the same exposure and outcome, we selected the study with the highest number of included participants/cases and/or the longest period of follow-up (6,24).

Data Extraction and Quality Assessment

Data were extracted by one investigator and double-checked for accuracy by an independent, second reviewer (A.Le., A.La., E.M., M.R., M.N., S.S.). Details extracted from the selected publications include author, year of publication, country, diabetes type, sex, mean age, study design, cohort name, follow-up years, number of participants, total cases, person-years, physical activity assessment, type of physical activity, outcome definition, outcome assessment, and effect measure with 95% CI, as well as any confounders included in the multivariable-adjusted models. We contacted authors of studies if relevant data were missing (18,25–27), and we received data from one study that were not shown in the original report (18). All exposure data were converted to MET-h per week. Thus, the Compendium of Physical Activities was used to assign MET-h to each reported exposure variable based on type, duration, and intensity of physical activity, as previously described (28,29).

The risk of bias (ROB) for each study was assessed with the Risk Of Bias In Non-randomised Studies - of Interventions (ROBINS-I) Cochrane tool (30), with consideration of the following seven domains: confounding, selection of participants, exposure assessment, misclassification during follow-up, missing data, outcome measurements, and selective reporting (Supplementary Table 2). Two investigators (M.R., E.S.) independently assessed the ROB, and discrepancies were resolved in a discussion with a third reviewer (S.S.).

Data Synthesis and Analysis

The summary risk ratio (SRR) and the corresponding 95% CIs for the association of physical activity and diabetes-related complications were calculated with the random-effects model of DerSimonian and Laird (31). Meta-analyses were conducted for each outcome separately with comparison of the highest with the lowest levels of physical activity, as reported in the underlying studies. We conducted meta-analyses on the following outcomes: incidence of CVD, including specific CVD outcomes such as CHD, cerebrovascular events, HF, and MACE, as well as CVD and CHD mortality, and incidence of MVD, such as retinopathy and nephropathy. The outcomes major microvascular events, retinopathy, and nephropathy were summarized as MVD incidence, and whenever possible, separate meta-analyses were conducted for these outcomes. No publication was identified with investigation of the prospective association between physical activity and incidence of neuropathy, peripheral artery disease, and foot ulcers and amputations in individuals with diabetes.

In addition, we conducted linear dose-response meta-analyses as suggested by Greenland and Longnecker for total physical activity (per 10 MET-h per week) and the outcomes, depending on availability of data (32). This analysis required information on cases, person-years, exposure quantities, and effect measures including 95% CIs for at least three exposure categories. Missing information on cases and person-years was estimated with use of the information on the total number of cases and participants plus the follow-up period as previously described (33). If a study reported exposure quantities as ranges, we calculated the midpoint between the upper limit and lower limit. For open categories, we assumed an equal width as the adjacent category. Nonlinear dose-response meta-analyses were conducted with use of restricted cubic spline models (34). A likelihood ratio test was applied to investigate nonlinearity.

Inconsistency and between-study heterogeneity were assessed with I^2, in conducting subgroup analyses stratified by ROB (moderate, serious), sex, type of diabetes (type 1 diabetes, type 2 diabetes, unknown, all types), geographic area (Asia, North America, Europe), and selected confounders considered in the primary studies (diabetes duration, socioeconomic status, smoking), and applying meta-regression (35). For the stratified analysis by sex, we used data from primary studies where findings were reported for men and women separately (36–39). In addition, if data were available, we conducted subgroup analyses by different type of physical activity, including total physical activity, leisure-time physical activity (LTPA), MVPA, and walking.

Publication bias and small study effects were evaluated with funnel plots and Egger test if ≥10 studies were available for an association (40). Asymmetry of the funnel plot, plus a P value <0.10 for Egger test, was considered indicative of a potential publication bias (41). All statistical analyses were carried out with Stata statistical software (version 17; StataCorp, College Station, TX).

Certainty of Evidence

Certainty of evidence was assessed for all associations with the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) tool by two investigators independently (M.R., S.S.) (42). High or moderate certainty of evidence can be interpreted as follows: it is very likely or probable that the true effect lies close to the estimated finding, and a recommendation can be made. Low or very low certainty of evidence indicates that our confidence in the result is limited or very weak, respectively (43).

Data and Resource Availability

Data were extracted from published research articles, all of which are available and accessible. All data sets generated during the current study are available on reasonable request from the corresponding author.

RESULTS

Literature Search Results

In total, 13,072 publications were identified with a systematic database search. From 108 full texts screened, 31 studies were included (6,17,18,20–22,24–27, 36–39,44–60). A detailed overview of the selection process can be found in Fig. 1. Information regarding excluded studies and the respective exclusion criteria can be found in Supplementary Table 3.

Study Characteristics

The included studies were published between 1995 and 2021, with investigation of populations in the U.S. (18,25,38, 39,45–49,54,57), Europe (6,20–22,24,27, 36,50,55,56,59,60), Asia (17,26,37,51–53), and Australia (58) and one cohort combining 20 different countries (44). Fourteen studies included individuals with type 2 diabetes (17,20,25,26,37,44,50–54, 56,59,60), six included patients with type 1 diabetes (18,21,22,36,46,55), and five included patients with type 1 and patients with type 2 diabetes (6,24,27, 39,58), and in six type of diabetes was not specified (38,45,47–49,57). Physical activity was recorded via self-reports in all studies. While some of the studies used validated questionnaires (6,18,20–22,24,26,27,37,47,50,52,54,55,58–60), no information on validation status was provided for the other studies (17,25,36, 38,39,44–46,48,49,51,53,56,57). Physical activity was recorded as follows: total physical activity (6,17,36,37,45,46,51,56,60), MVPA (18,20,47,54,59), LTPA (21,22,26,27, 39,44,48,50,52,55,58), cycling (24), walking (25,49), walking in combination with running (57), and exercise or vigorous physical activity (38,53). Detailed characteristics of each study can be found in Supplementary Table 4.

Six studies were rated to have moderate and 25 studies as serious ROB (Supplementary Fig. 1). The main sources of bias included bias due to confounding (not all relevant confounders were considered in the primary study) or misclassification of the exposure (physical activity was assessed with nonvalidated tools) (Supplementary Fig. 2).

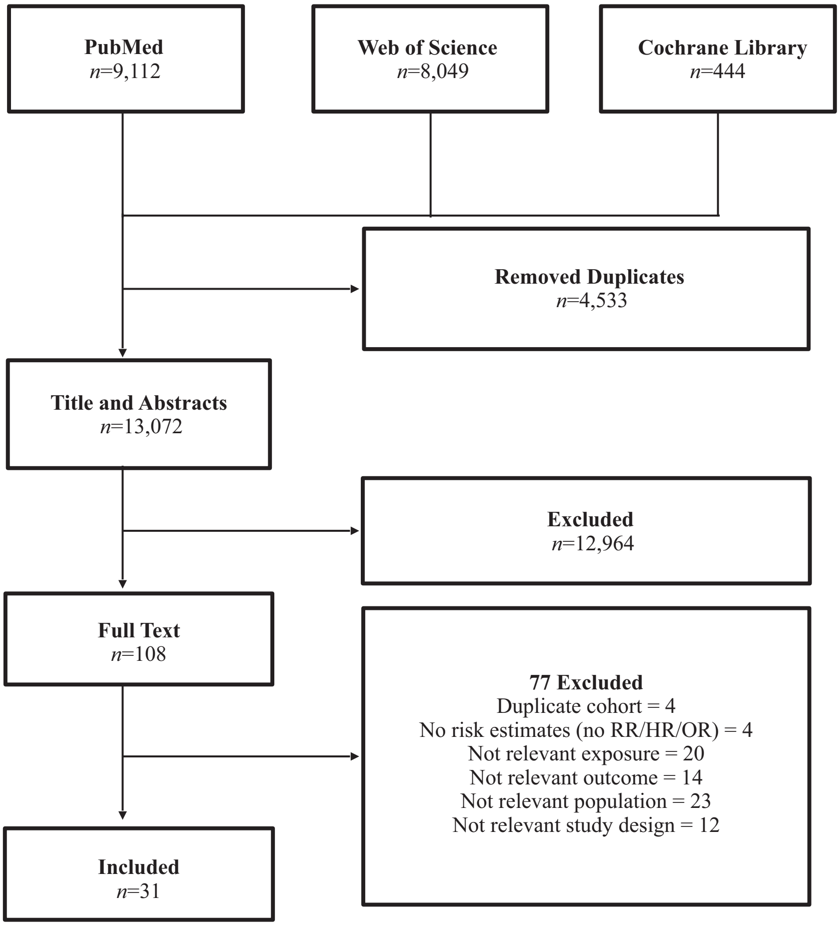

Figure 1—Flowchart describing literature search. HR, hazard ratio; *n*, number of publications; OR, odds ratio; RR, risk ratio.

CVD Incidence and Mortality

Seven studies were identified where physical activity and total CVD incidence were examined (20,26,36,37,54,55,60). A high compared with low level of physical activity was associated with a 16% decreased relative risk of CVD (SRR 0.84 [95% CI 0.77, 0.92; I^2 = 0%, *n* = 7]) (Table 1, Fig. 2*A*). The SRR per 10 MET-h/week increase in physical activity and risk of CVD was 0.97 (0.93, 1.00; I^2 = 6%, *n* = 4) (Table 1). The steepest decrease in risk was observed for total physical activity up to 20 MET-h/week; however, there was no indication for nonlinearity (*P* for nonlinearity = 0.264) (Fig. 3*A*). The certainty of evidence was moderate for this association (Supplementary Table 5).

In five studies, association of physical activity with CHD incidence was described (18,26,39,54,60). Individuals in the highest category of physical activity were 16% (SRR 0.84 [95% CI 0.76, 0.93; I^2 = 0%, *n* = 5]) less likely to experience incident CHD than the reference group (Table 1 and Fig. 2*A*). With each 10 MET-h/week increase of total physical activity, the relative risk decreased by 11% but was not precisely estimated (0.89 [0.77, 1.03; I^2 = 45%, *n* = 3]) (Table 1). There was no indication for a nonlinear dose-response relationship (*P* for nonlinearity = 0.792) (Fig. 3*B*). The certainty of evidence was determined to be low (Supplementary Table 5).

We identified six publications on physical activity and incidence of cerebrovascular events (17,26,37,45,51,54). Higher compared with lower level of physical activity was associated with a 26% decreased relative risk of cerebrovascular events (SRR 0.74 [95% CI 0.65, 0.84; I^2 = 26%, *n* = 6]) (Table 1 and Fig. 2*A*). In dose-response analysis, a 10 MET-h/week increase in total physical activity was associated with an 8% decrease in incidence of cerebrovascular events, but again, the 95% CI was wide (0.92 [0.80, 1.04; I^2 = 1%, *n* = 2]) (Table 1). Nonlinearity was not suggested (*P* for nonlinearity = 0.932) (Fig. 3*C*). Furthermore, the certainty of evidence was low (Supplementary Table 5).

In three studies the association of physical activity with HF incidence was investigated (38,45,47). In high versus low physical activity meta-analysis, SRR was reduced by 24% (0.76 [95% CI 0.65, 0.88; I^2 = 0%, *n* = 3]) (Table 1 and Fig. 2*A*). Additionally, we identified two studies on the association between physical activity and MACE (18,44). High levels of physical activity were also associated with an 18% decreased relative risk of MACE (0.82 [0.70, 0.97; I^2 = 0, *n* = 2]) (Table 1 and Fig. 2*A*). No dose-response meta-analysis could be conducted for these outcomes because of lacking information. The certainty of evidence was low for both outcomes (Supplementary Table 5).

We identified 11 publications examining association between physical activity and total CVD mortality (6,25,27,49,50,53,54,56,57,59,60). In comparisons of high versus low overall physical activity, the SRR of CVD mortality was 38% reduced (0.62 [95% CI 0.55, 0.69; I^2 = 7%, *n* = 11]) (Table 1 and Fig. 2*B*). A 10 MET-h/week increase in physical activity was associated with an 18% risk decrease of CVD mortality (0.82 [0.74, 0.90]; I^2 = 82, *n* = 7]) (Table 1). There was evidence for nonlinearity (*P* for nonlinearity $<$0.001). The steepest decrease in relative risk of CVD mortality was observed for up to 40 MET-h of physical activity per week, and after this, no further decrease was observed (Fig. 3*D*). The certainty of evidence was moderate (Supplementary Table 5).

Three studies included investigation of the association between total physical activity and CHD mortality (25,48,56). In high versus low physical activity meta-analysis, the relative risk of CHD mortality was decreased by 10% but imprecisely estimated (SRR 0.90 [95% CI 0.54, 1.51; I^2 = 42%, *n* = 3]) (Table 1 and Fig. 2*B*). No dose-response meta-analysis could be conducted. The certainty of evidence for CHD mortality was very low (Supplementary Table 5).

MVD Incidence

For total microvascular complications, we identified eight studies. Of these, in five studies, incidence of retinopathy was investigated (21,45,46,52,58), in two nephropathy was examined (22,45), and one had a combined end point (incidence of major microvascular events) (44). In

Table 1—Physical activity and risk of incident diabetes-related complications in individuals with diabetes: findings from meta-analyses

Outcome	High vs. low physical activity meta-analysis			Linear dose-response meta-analysis (physical activity per 10 MET-h/week)			Certainty of evidence
	SRR (95% CI)	I^2	*n* participants (*n* studies)	SRR (95% CI)	I^2	*n* participants (*n* studies)	
CVD incidence	0.84 (0.77, 0.92)	0	34,503 (7)	0.97 (0.93, 1.00)	6	16,040 (4)	Moderate
CHD incidence	0.84 (0.76, 0.93)	0	31,768 (5)	0.89 (0.77, 1.03)	45	15,871 (3)	Low
Cerebrovascular event incidence	0.74 (0.65, 0.84)	26	928,076 (6)	0.92 (0.80, 1.04)	1	13,229 (2)	Low
HF incidence*	0.76 (0.65, 0.88)	0	3,047(3)	—	—	—	Low
MACE incidence*	0.82 (0.70, 0.97)	0	11,617(2)	—	—	—	Low
CVD mortality	0.62 (0.55, 0.69)	0	51,804 (11)	0.82 (0.74, 0.90)	82	29,822 (7)	Moderate
CHD mortality*	0.90 (0.54, 1.51)	42	1,327 (3)	—	—	—	Very low
MVD incidence	0.76 (0.67, 0.86)	0	27,645 (8)	0.93 (0.88, 0.98)	45	14,472 (3)	Moderate
Diabetes-related retinopathy	0.68 (0.55, 0.84)	0	14,041 (5)	0.95 (0.91, 0.98)	0	3,332 (2)	Moderate
Diabetes-related nephropathy*	0.97 (0.46, 2.07)	75	2,464 (2)	—	—	—	Very low

*Linear dose-response meta-analyses could not be conducted because of lack of data from primary studies. *n*, number of.

the meta-analysis combining the studies to total microvascular complications (21,22,44–46,52,58), the relative risk was 24% lower (SRR 0.76 [95% CI 0.67, 0.86; I^2 = 0%, *n* = 8]) in high versus low levels of physical activity (Table 1 and Fig. 2*C*). With each 10 MET-h/week increase in physical activity, the SRR decreased by 7% (0.93 [0.88, 0.98; I^2 = 45%, *n* = 3]) (Table 1). There was indication for a nonlinear association (*P* for nonlinearity = 0.022), with the steepest decrease of risk shown for MVD incidence between 0 and 20 MET-h/week (Fig. 3*E*). Certainty of evidence for the summarized outcome of MVD was moderate (Supplementary Table 5).

For retinopathy, a 32% decreased relative risk was observed for high versus low physical activity (SRR 0.68 [95% CI 0.55, 0.84; I^2 = 0%, *n* = 5]) (Table 1 and Fig. 2*C*). The SRR for an increase of 10 MET-h/week of total physical activity and risk of retinopathy was 0.95 (0.91, 0.98; I^2 = 0%, *n* = 2) (Table 1). The curve showed the strongest risk reduction for physical activity up to 50 MET-h/week, with no further benefit after this level (Fig. 3*F*) (*P* for nonlinearity = 0.201). The certainty of evidence was moderate for this outcome (Supplementary Table 5). For nephropathy, no clear association was observed in the high versus low physical activity meta-analysis [0.97 (0.46, 2.07; I^2 = 75%, *n* = 2)] (Table 1), and we could not conduct a dose-response analysis due to lack of data. The certainty of evidence was rated as very low (Supplementary Table 5).

Subgroup Analyses and Publication Bias

There were no differences between subgroups after stratification for ROB, sex, type of diabetes, geographic location, and adjustment of relevant confounders for the outcomes CVD, CHD, cerebrovascular event, HF incidence, CVD and CHD mortality, and incidence of retinopathy (Supplementary Tables 6–12). In addition, whenever possible, we conducted subgroup meta-analyses by type of physical activity (total physical activity, LTPA, MVPA, and walking), and we did not observe differences in the magnitude of the associations by type of exercise (Supplementary Table 13). The dose-response meta-analysis of MVPA, including a publication by Ried-Larsen et al. (24) excluded from the primary analysis due

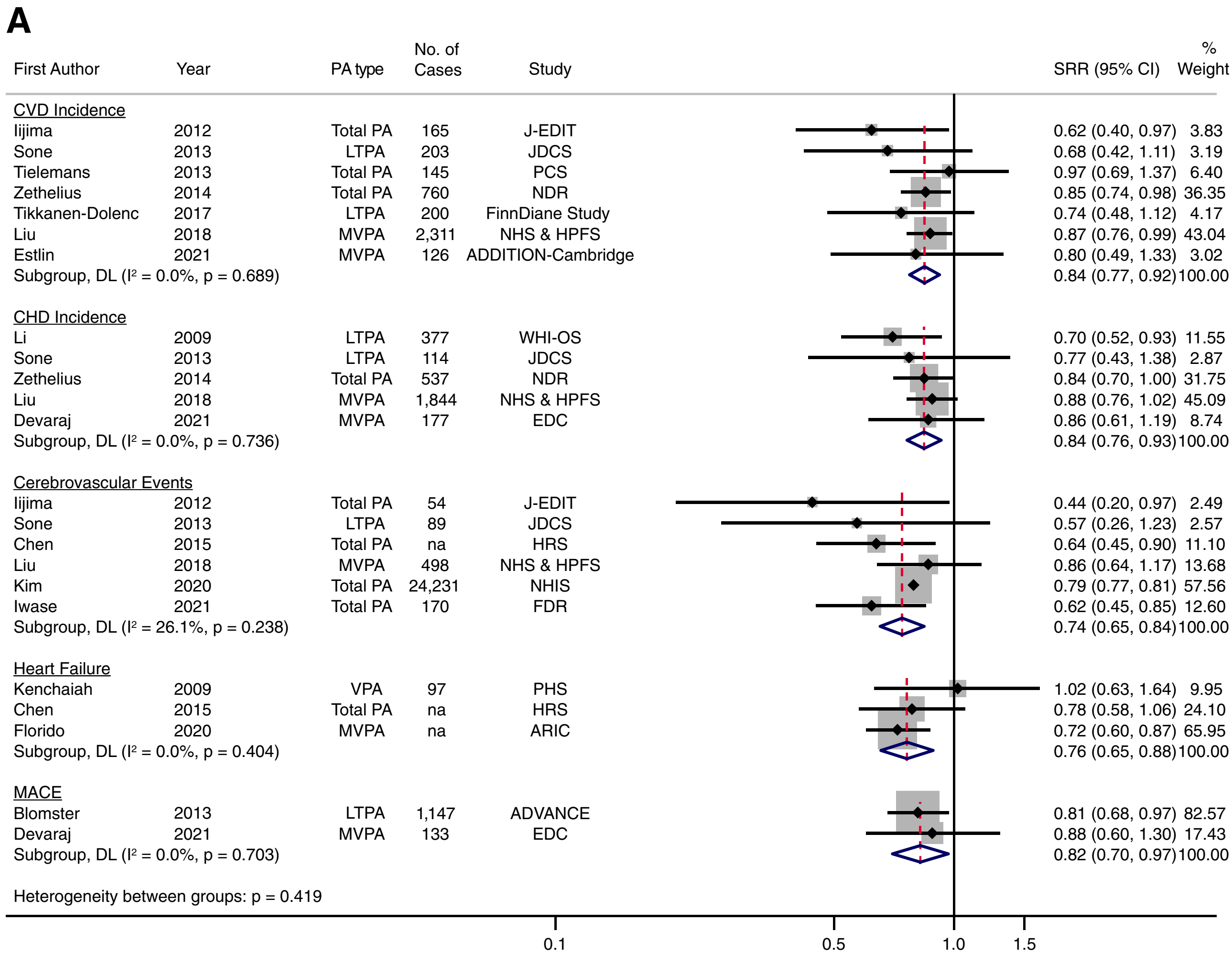

Figure 2—*A*–*C*: Forest plot of associations between total physical activity (high vs. low) and CVD incidence (*A*), CVD mortality (*B*), and incidence of MVD (*C*). MACE includes death from CVD or nonfatal stroke and nonfatal myocardial infarction; major MVD includes new or worsening diabetic renal disease and retinopathy. ADDITION, Anglo-Danish-Dutch Study of Intensive Treatment in People with Screen-Detected Diabetes in Primary Care; ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation; ARIC, Atherosclerosis Risk in Communities; DDCRT, Diabetes Distress and Care Registry at Tenri; DL, DerSimonian-Laird; EDC, Epidemiology of Diabetes Complications; EPIC, European Prospective Investigation into Cancer and Nutrition; FDR, Fukuoka Diabetes Registry; FinnDiane, Finnish Diabetic Nephropathy; HPFS, Health Professionals Follow-Up Study; HRS, Health and Retirement Study; HSfE, Health Survey for England; JDCS, Japan Diabetes Complications Study; J-EDIT, Japanese Elderly Diabetes Intervention Trial; na, not available; NDR, Swedish National Diabetes Register; NHANES, National Health and Nutrition Examination Survey; NHIS, National Health Insurance System; NHS, Nurses' Health Study; NW&R, National Walkers' and Runners' Health Studies; PA, physical activity; PCS, EURODIAB Prospective Complications Study; PHS, Physicians' Health Study; RBS, Rancho Bernardo Study; SHeS, Scottish Health Survey; Taichung Diabetes, Taichung Diabetes Study; WESDR, Wisconsin Epidemiologic Study of Diabetic Retinopathy; WHI-OS, Women's Health Initiative Observational Study; 45 and Up, 45 and Up Study; %Weight, weights from random-effects analysis.

to a duplicate cohort, showed a reduced relative risk of CVD mortality with a threshold of up to ∼20 MET-h/week (Supplementary Fig. 3).

In addition, for CVD mortality, ≥10 studies were included in the meta-analysis, and thus we explored small study effects and publication bias. There was no indication of publication bias in the funnel plot (Supplementary Fig. 4) and Egger test (*P* = 0.41).

DISCUSSION

In this systematic review and meta-analysis, we investigated the prospective association of physical activity with incident major diabetes-related complications in individuals with diabetes. There was moderate certainty of evidence that physical activity was associated with a decreased relative risk of CVD incidence and CVD mortality as well as with total microvascular complications, particularly retinopathy. There was an inverse dose-response relation between physical activity and incidence of the investigated outcomes. However, the relationship was nonlinear for CVD mortality and incidence of MVD. The strongest risk reductions were observed for up to 20 and 40 MET-h/week, respectively. These findings indicate that a physical activity level even below the WHO recommendations likely reduces the relative risk for diabetes-related complications.

In a previous systematic review and meta-analysis, a 29% risk decrease for CVD incidence in individuals with diabetes was reported in comparing the highest and lowest levels of physical activity (16). While this aligns with the findings of this study (SRR 0.84 [95% CI 0.77, 0.92]), current evidence describes significantly lower risk reductions than seen in the work by Kodama et al. (16).

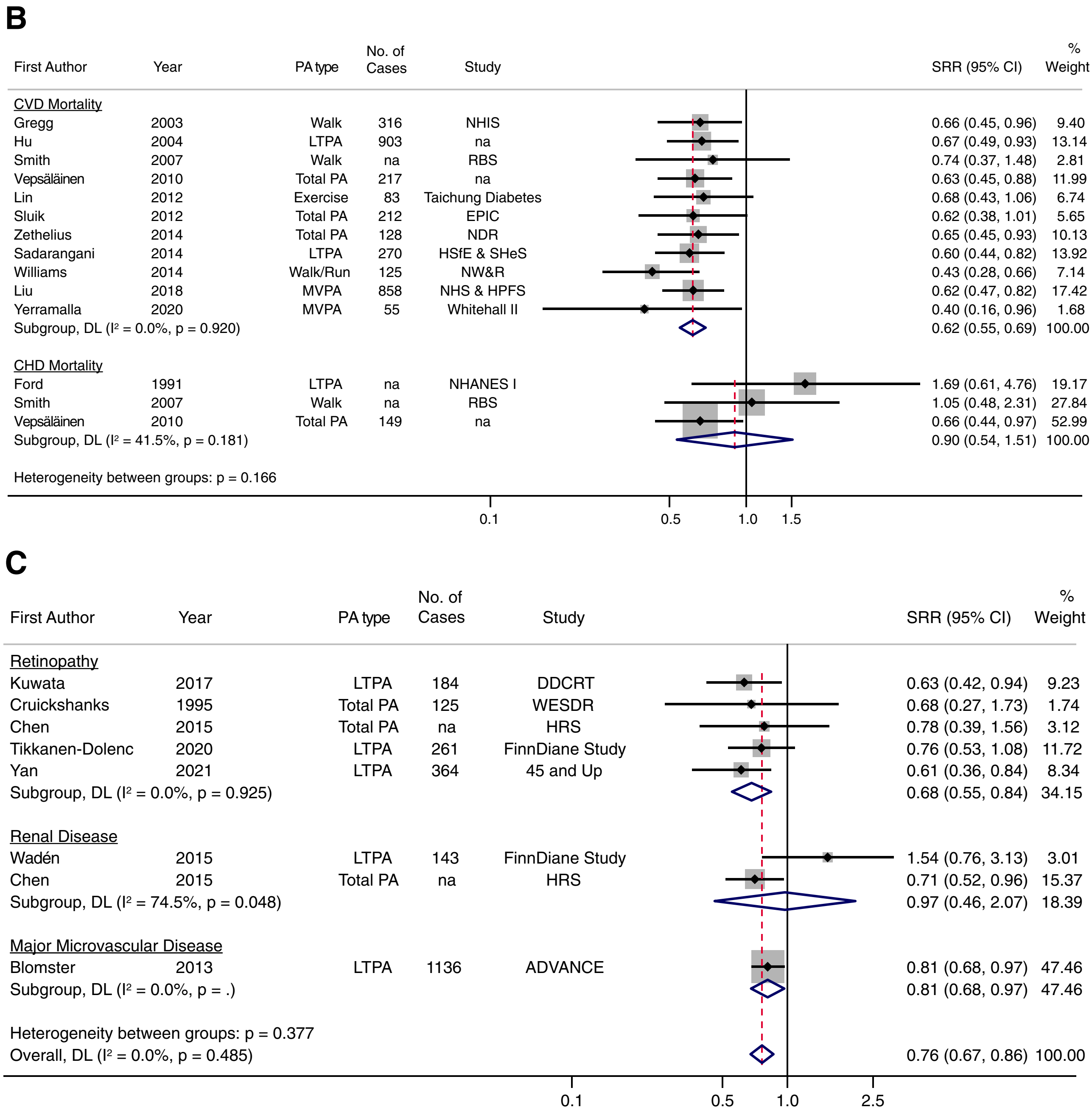

Figure 2—*Continued.*

Additionally, in our meta-analysis we separately report on more specific outcomes such as cerebrovascular events, HF incidence, and MACE and include several publications that were published after their literature search, that was completed in September 2011 (6,17,18,20,26,36,37,44,45,51,55). In addition, the findings of our systematic review and meta-analysis of prospective observational studies are in agreement with those of several meta-analyses of randomized controlled trials. For instance, Mannucci et al. (61) reported a significant decrease in cardiovascular risk factors (e.g., HbA_{1c}, systolic blood pressure, and body fat) in randomized controlled trials where the effect of exercise in individuals with diabetes was investigated. Similarly, findings of systematic reviews and meta-analyses showed that physical activity was associated with microvascular diabetes-related complications, but evidence came mainly from cross-sectional studies (62,63).

Possible Explanations

It is likely that individuals with high levels of physical activity follow an overall healthy lifestyle, such as avoiding smoking and eating a healthy diet. However, our stratified analysis by smoking status indicated that findings were robust even after smoking was considered as a confounder. In addition, some of the studies were adjusted for dietary factors and associations persisted (51,54,57). Moreover, participants with longer duration of and more advanced diabetes may be less active compared with participants with less severe disease presentation, suggesting that physical activity may also be an indicator of diabetes

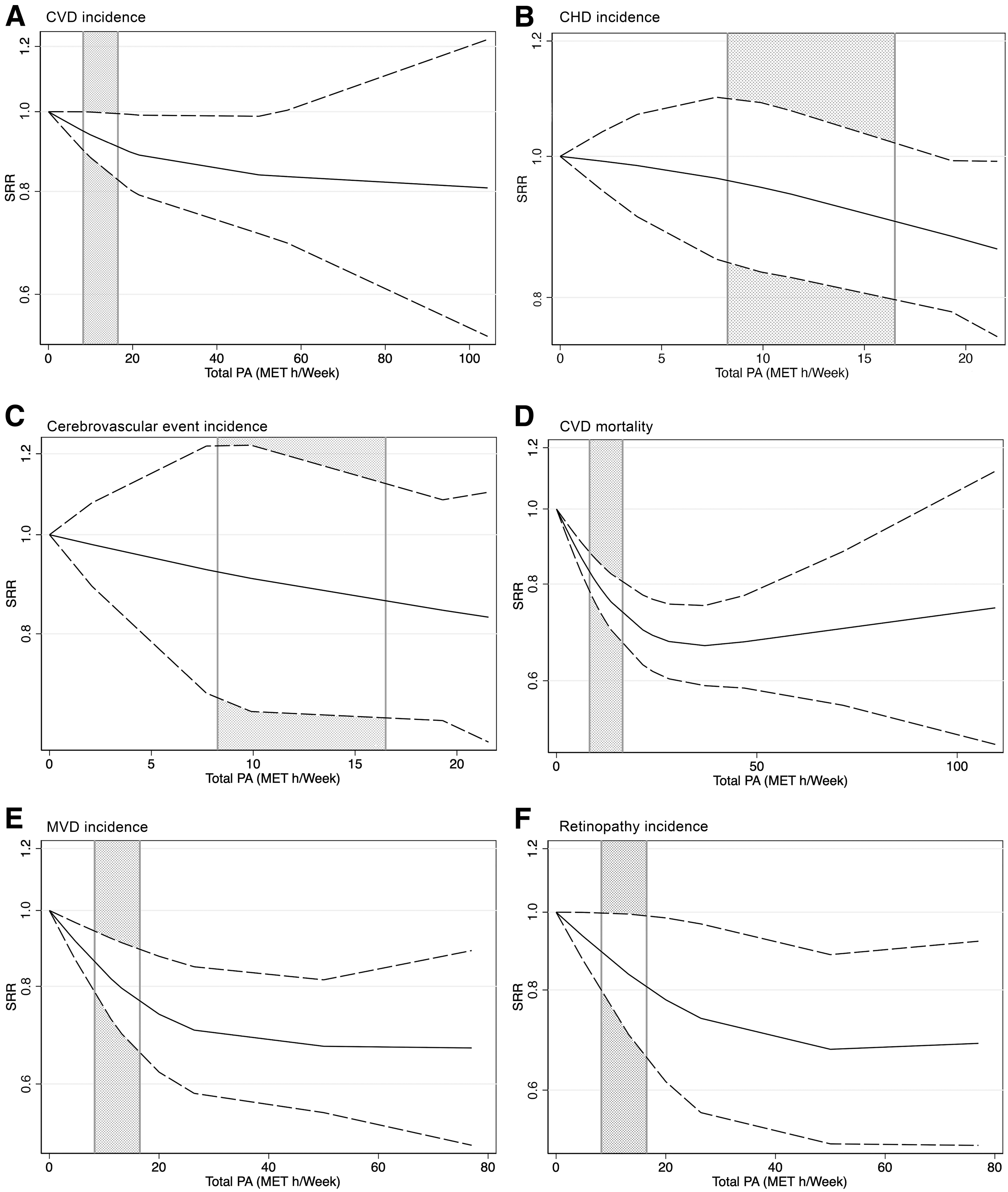

Figure 3—*A*–*F*: Nonlinear dose-response meta-analyses, with presentation of association between physical activity and CVD incidence (*A*), CHD incidence (*B*), cerebrovascular event incidence (*C*), CVD mortality (*D*), MVD incidence (*E*), and retinopathy incidence (*F*). The graph includes a dose-response curve (solid line) with 95% CI (dashed line). The shaded area between the grey lines indicates the minimum recommended amount of moderate physical activity (150–300 min) for individuals with diabetes (8.25–16.5 MET-h) per week (10). MVD includes new or worsening diabetic renal disease and retinopathy. PA, physical activity; SRR, summary risk ratio.

severity. Thus, we considered adjustment for diabetes duration—as indicator for diabetes severity—in our subgroup meta-analysis, and findings were robust after adjustment. Moreover, there are different potential direct mechanisms for physical activity that may influence the development of diabetes-related complications. Regular physical activity may promote glycemic control and may therefore improve individuals' blood pressure, lipid profiles, and other metabolic and cardiovascular risk factors (64,65). In addition, physical activity has been suggested to help to control weight, strengthen muscles, and improve insulin sensitivity in individuals with type 2 diabetes—all aspects likely to be associated with incidence of diabetes-related complications (64).

Strengths and Limitations

Strengths of the present systematic review and meta-analyses include the prospective study design of the included studies, which avoids recall bias and reduces selection bias. In addition, to our knowledge, this is the first report including linear and nonlinear dose-response meta-analyses for the prospective association of physical activity and risk of incidence of major diabetes-related complications. Thus, in this meta-analysis we were able to highlight that the risk of diabetes-related complications was already reduced at lower levels of physical activity. Furthermore, we conducted extensive subgroup and sensitivity analyses, and our findings were robust across the subgroups. We assessed the ROB of each included study and evaluated the certainty of evidence for each association by using validated tools (30,42). Finally, this study included six large studies carried out in Asian populations contributing eight unique risk estimates, while for a previous meta-analysis investigators reported the lack of studies in this geographic region as a limitation (16).

However, there are limitations of our findings that should be discussed. Most included studies had a serious ROB, mainly due to insufficient adjustment for potential confounders (e.g., socioeconomic status and diabetes duration) or assessment of physical activity with nonvalidated tools. Yet, we conducted subgroup meta-analyses, and the findings were robust in analyses with stratification for ROB. Since the included studies were of an observational nature, residual confounding cannot be ruled out, and findings of this study do not allow for causal inferences (66). In addition, it is likely that healthier individuals with diabetes are more active than those with more severe diabetes and/or other medical conditions. Therefore, the findings are at a substantial risk of reverse causation. Nonetheless, we considered this aspect in the ROB assessment, and studies were rated to have serious ROB when severity of diabetes (e.g., as indicated by diabetes duration) and reverse causation (exclusion of cases that occurred within the first 2 years after baseline) were not considered (Supplementary Table 2). Of the 31 included studies, 5 were rated to have serious ROB in this domain (Supplementary Fig. 2). However, we conducted stratified analysis by ROB and did not find substantial differences in the results (Supplementary Tables 6–12). As all studies relied on self-reported physical activity, studies were at risk for measurement error and it is possible that participants overestimated their physical activity (67). However, we do not expect differential misclassification, and, thus, this could potentially lead to an underestimation of the effect sizes. Third, most of the studies did not include repeated recording of physical activity and only included recording of baseline physical activity. At long durations of follow-up, changes in physical activity may have distorted results. Fifth, many studies did not differentiate between type 1 and type 2 diabetes, but due to the low number of individuals with type 1 diabetes, it is expected that the proportion of participants with type 1 diabetes is also very low in large-scale epidemiological studies. However, whenever possible, we conducted subgroup analyses, and the stratified meta-analyses did not show important differences in the results for participants with type 1 versus type 2 diabetes. The effect estimates pointed in the same direction; though, due to the small number of studies regarding/number of participants with type 1 diabetes, the findings were imprecisely estimated. Finally, for some of the subgroup meta-analyses, e.g., different physical activities, only a small number of studies could be included, and, thus, more studies on specific types of physical activity/exercise are warranted.

Implications and Future Research

Our findings implicate, with moderate certainty of evidence, that physical activity is inversely associated with CVD incidence and mortality as well as with incidence of MVD, such as diabetes-related retinopathy. The clinical implication of our study is that individuals with diabetes may be encouraged to be physically active and even low levels of physical activity might be effective for the prevention of diabetes-related complications, as demonstrated by the findings of our dose-response meta-analyses. Considering the limitations of this study, this leads to the recommendation that for people with diabetes, every step toward a more active lifestyle can be important. This is in line with the current consensus statement from the American College of Sports Medicine on exercise/physical activity in individuals with type 2 diabetes, which states that some physical activity is better than none (64). For instance, 1 h of Nordic walking per week, corresponding to 4.8 MET-h (28), could, considering our dose-response meta-analysis, decrease the relative risk of CVD mortality by ∼10%.

However, as our findings show that the largest relative risk reductions were within the range of current WHO recommendations for physical activity, exercise should be recommended to individuals with diabetes at a level of at least 8.25 MET-h/week (9). For example, this could mean bicycling to work for 1 h (4.0 MET-h) and 1 h of brisk walking for exercise (4.3 MET-h), 40 min of circuit training (4.3 MET-h) 3 days a week, or even 40 minutes of slow walking for 5 days a week (2.5 MET-h) (28).

For provision of more specific recommendations for individuals with diabetes, future research should investigate the effects of different types of physical activity, such as resistance training, aerobic training, a combined training, or flexibility training, on development of diabetes-related complications and explore differences according to diabetes type. In addition, there is a lack of studies on physical activity and specific diabetes-related complications, especially peripheral vascular diseases and microvascular complications (e.g., retinopathy, nephropathy), as well as neuropathy, and foot ulcers and amputations. To address the limitation of self-reported physical activity, we recommend use of objective exposure measures, such as an accelerometer, for future studies investigating the association between physical activity and diabetes-related complications. Since our findings are based only on observational data, large randomized controlled trials are needed to investigate the beneficial effects of physical activity in individuals with diabetes.

Conclusion

In conclusion, this systematic review and meta-analysis of 31 prospective cohort studies showed an inverse association between physical activity and risk of diabetes-related complications, including CVD incidence and mortality, cerebrovascular diseases, HF, and MACE as well as MVD incidence. The certainty of evidence ranged from moderate to very low, and major limitations were self-reported physical activity, risk of reverse causation, and residual bias. Although evidence needs to be strengthened, these findings suggest that physical activity, even at lower levels, may be beneficial in reducing the relative risk of major diabetes-related complications.

Funding. The German Diabetes Center is funded by the German Federal Ministry of Health (Berlin, Germany) and the Ministry of Culture and Science of the state North Rhine-Westphalia (Düsseldorf, Germany) and receives additional funding from the German Federal Ministry of Education and Research (BMBF) through the German Center for Diabetes Research (DZD e.V.).

The funders had no role in study design, data collection, data analysis, data interpretation, or writing of the manuscript.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. M.R., A.Le., and S.S. designed the research. M.R., A.Le., J.B., and S.S. developed the search term of the systematic review and meta-analysis. M.R., A.Le., E.M., A.La., T.S., M.N., and S.S. conducted the systematic literature search and were involved in data acquisition. M.R., E.S., and S.S. conducted the assessment of ROB. M.R. and A.Le. conducted the statistical analyses, and J.B. and S.S. assisted with the statistical analysis. M.R. and S.S. rated the certainty of evidence and drafted the manuscript. E.M., E.S., C.H., N.S., W.G., J.B., and M.N. made critical revisions to the manuscript for important intellectual content. All authors read and approved the final manuscript.

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