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META-ANALYSIS

Physical activity and the risk of type 2 diabetes: a systematic review and dose–response meta-analysis

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Abstract We investigated the association between specific types of physical activity and the risk of type 2 diabetes in a systematic review and meta-analysis of published studies. PubMed, Embase and Ovid databases were searched for prospective studies and randomized trials up to 2nd of March 2015. Summary relative risks (RRs) were calculated using a random effects model. Eighty-one studies were included. The summary RRs for high versus low activity were 0.65 (95 % CI 0.59–0.71, $I^2 = 18$ %, n = 14) for total physical activity, 0.74 (95 % CI 0.70–0.79, $I^2 = 84$ %, n = 55) for leisure-time activity, 0.61 (95 % CI 0.51–0.74, $I^2 = 73$ %, n = 8) for vigorous activity, 0.68 (95 % CI 0.52–0.90, $I^2 = 93$ %, n = 5) for moderate activity, 0.66 (95 % CI 0.47–0.94, $I^2 = 47$ %, n = 4) for low intensity activity, and 0.85 (95 % CI 0.79–0.91, $I^2 = 0$ %, n = 7) for walking. Inverse associations were also observed for increasing activity over time, resistance exercise, occupational activity and for cardiorespiratory fitness. Nonlinear relations were observed for leisure-time activity, vigorous activity, walking and resistance exercise ($p_{\text{nonlinearity}} < 0.0001$ for all), with steeper reductions in type 2 diabetes risk at low activity levels than high activity levels. This meta-analysis provides strong evidence for an inverse association between physical activity and risk of type 2 diabetes, which may partly be mediated by reduced adiposity. All subtypes of physical activity appear to be beneficial. Reductions in risk are observed up to 5–7 h of leisure-time, vigorous or low intensity physical activity per week, but further reductions cannot be excluded beyond this range.

Keywords Physical activity · Sports · Exercise · Walking · Type 2 diabetes · Systematic review · Meta-analysis

Introduction

The prevalence of type 2 diabetes is increasing rapidly around the world parallel to the increase in obesity, reduction in physical activity and dietary changes. In 2011, an estimated 366 million people had diabetes (most of which is type 2) and that number is projected to increase to 552 million by 2030 [1].

Many studies have investigated the association between physical activity and risk of type 2 diabetes [2–88], and most studies reported an inverse association between the two [2–13, 16–18, 20, 21, 23, 24, 26–32, 34–36, 38–51, 53–63, 65–79, 87], with only a few studies finding no association [15, 22, 25, 33, 37, 64]. However, it is not clear whether specific types of activity are more effective in reducing risk than others. Although most studies have

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reported reduced risk with greater leisure-time activity [4, 6–8, 11, 14, 16, 20–24, 28, 29, 31, 34, 36, 39–44, 48, 50–52, 56, 57, 59, 64, 66–68, 80–82], or vigorous activity [6, 21, 23, 24, 31, 74–76] data are less consistent for studies investigating moderate intensity activity such as walking [5, 11, 16, 21, 29, 37, 71, 75], with some studies reporting an inverse association between walking and type 2 diabetes [5, 11, 37, 75], while other studies found no significant association [16, 21, 29, 71]. In addition, some studies have indicated reduced type 2 diabetes risk in subjects who increased their physical activity level over time [5, 26, 63, 72, 73, 86, 87], but to our knowledge these results have not been summarized in a meta-analysis.

It is not clear what level of physical activity is needed to reduce the risk of type 2 diabetes. Some studies have reported a dose-dependent inverse association between physical activity and diabetes risk [5–7, 17, 20, 24, 26, 29, 36, 39, 40, 60–62, 75]. However, other studies suggested that most of the benefit was observed when increasing physical activity from a low level to a moderate level [11, 13, 18, 28, 43, 44, 50, 63]. A systematic review from 2007 suggested an inverse association between high versus low physical activity of moderate intensity and type 2 diabetes risk [89], but that review did not conduct a dose–response analysis. Since that review 59 additional studies (63 publications) have been published [12–20, 33–71, 73, 75–88] and we therefore conducted an updated systematic review and meta-analysis of physical activity and risk of type 2 diabetes with the specific aims of exploring associations with specific types of physical activity, assessing a possible dose–response relationship, and addressing potential confounding.

Methods

Search strategy

We searched the PubMed, Embase and Ovid databases up to 2nd of March 2015 for studies of physical activity and type 2 diabetes risk. We used the following search terms: ("physical activity" OR exercise OR sports OR walking OR biking OR running OR fitness OR "exercise test" OR inactivity OR "sedentary activity") AND diabetes AND ("case–control" OR retrospective OR cohort OR cohorts OR prospective OR longitudinal OR "follow-up" OR "cross-sectional" OR trial) (Supplemental Table S1, S2). No language restrictions were imposed. In addition, studies which reported data on physical activity and type 2 diabetes risk that were identified by searches on adiposity, resting heart rate, pesticides and smoking in relation to type 2 diabetes in separate reviews that we are working on were included in the analysis (these were studies where there was no mention of physical activity in the title or abstract, and was therefore not retrieved by the main search strategy). The reference list of a previous review on the subject was also searched [89]. We followed standard criteria for conducting meta-analyses [90].

Study selection

To be included, the study had to be a prospective cohort, case-cohort, nested case–control study or randomized trial investigating the association between physical activity and risk of type 2 diabetes. We did not consider retrospective case–control studies or cross-sectional studies. Abstracts, unpublished studies and grey literature were excluded. We imposed no age restriction. Relative risk estimates (hazard ratios, risk ratios, odds ratios) adjusted for at least one variable with the 95 % confidence intervals had to be available. For the dose–response meta-analysis, a quantitative measure of activity level had to be available in the publication. When several publications from the same study were identified, we used the publication with the largest number of cases or the publication which provided the most detail in the information needed for dose–response analyses. When several models were presented we used the most adjusted models for the main analysis. Because the diagnostic criteria for diabetes changed during the period of the studies covered, we used whatever diabetes definition had been used in each of the underlying papers (i.e. based on self-report, physician-diagnosed, record linkage, diabetes diagnosis based on medication use). We identified 87 publications that were included in the analysis [2–88]. A list of the excluded studies and the exclusion reasons is found in the Supplemental Table S3. For one study, we used results from a duplicate publication [31] in the subgroup analysis of gender because results were not stratified by gender in the most recent study [62] and for another study we used data from the publication with the largest number of cases for the high versus low analysis [59], but we used data from an overlapping publication [65] for the dose–response analysis because there was not sufficient information in the former publication. For several studies, different publications reported on different types of physical activity and all these publications were included in the respective analyses, but each study was represented only once in each specific analysis. Two studies of leisure-time physical activity and type 2 diabetes risk in subjects with cardiovascular disease were analysed separately from the remaining studies [69, 70].

Data extraction and quality assessment

We extracted the following data from each study: The first author's last name, publication year, country where the study was conducted, study name, follow-up period,

sample size, gender, age, number of cases, exposure, physical activity level, RRs and 95 % CIs for each physical activity level and variables adjusted for in the analysis. Study quality was assessed using the Newcastle–Ottawa scale [91].

Statistical methods

We used random effects models to calculate summary RRs and 95 % CIs for the highest versus lowest level of physical activity and for the dose–response analysis [92]. The average of the natural logarithm of the RRs was estimated and the RR from each study was weighted using random effects weighting [92]. A two-tailed $p < 0.05$ was considered statistically significant. For studies that reported results separately, but not combined, by gender or other subgroups, we combined the results using a fixed-effects model to obtain an overall estimate which was used for the main analysis. For studies not using the lowest category of physical activity as the reference category, we recalculated the RRs so that the lowest category became the reference category using the method by Hamling et al. [93].

We used the method described by Greenland and Longnecker [94] for the dose–response analysis and computed study-specific slopes (linear trends) and 95 % CIs from the natural logs of the RRs and CIs across categories of physical activity. The median or mean physical activity level in each category was assigned to the corresponding relative risk for each study. For studies that reported the physical activity by ranges of activity we estimated the midpoint for each category by calculating the average of the lower and upper bound. When the highest or lowest category was open-ended we assumed the open-ended interval length to have the same width as the adjacent interval. For studies that reported physical activity by frequency per week or month [3, 6, 17, 40, 64, 74] we converted the frequencies to hours per week by assigning a dose of 45 min per session [95] and this was based on an estimated mean duration of activity per session from the HUNT study [96].

We conducted separate dose–response analyses for studies reporting physical activity in metabolic equivalent task (MET)-hours per week and for studies reporting on kcal of energy expenditure. The MET is an index of the intensity of physical activity and is defined as the caloric expenditure per kilogram of body weight per hour of activity, divided by the equivalent per hour at rest and one MET is considered to be equal to the energy cost of a person during quiet sitting [97]. We used the classification by Ainsworth et al. [97] to categorize physical activity of low (1.6–2.9 METs), moderate (3–5.9 METs) and vigorous (≥6 METs) intensity. Results from one study which used ≥5.5 and <5.5 METs as cut-off points to categorize physical activity were included in the vigorous and moderate activity analyses, respectively [23].

We examined a potential nonlinear dose–response relationship between physical activity and type 2 diabetes by restricted cubic splines with 3 knots at 10, 50 and 90 % percentiles of the distribution which was combined using multivariate meta-analysis [98, 99]. A likelihood ratio test was used to assess the difference between the nonlinear and linear models to test for nonlinearity [100]. Because one of the proposed mechanisms relating physical activity to type 2 diabetes risk is through reduced adiposity, we conducted analyses with and without adjustment for BMI when possible to assess the potentially mediating role of BMI.

Heterogeneity between studies was assessed by the Q test and I^2 [101]. I^2 is the amount of total variation that is explained by between study variation. I^2 values of approximately 25, 50 and 75 % are considered to indicate low, moderate and high heterogeneity, respectively. Subgroup analyses by study characteristics such as gender, duration of follow-up, geographic location, number of cases, and adjustment for confounding factors were conducted to investigate sources of heterogeneity. Publication bias was assessed with Egger's test [102] when there were 6 or more studies in the analysis and the results were considered to indicate publication bias when $p < 0.10$. We conducted sensitivity analyses excluding one study at a time to ensure that the results were not simply due to one large study or a study with an extreme result when there were at least five studies in the analysis. The statistical analyses were conducted using Stata, version 10.1 software (StataCorp, College Station, TX, USA).

Results

We identified 78 cohort studies (84 publications) [2–85] and three randomized trials [86–88] that could be included in the meta-analysis of physical activity and type 2 diabetes (Supplemental Table S4, Fig. 1). Two publications reported results from two studies each [52, 68] and one publication reported results from three studies [22], while three publications [40, 71, 79] reported combined results from two studies each.

Total physical activity

Fourteen cohort studies [2, 8–10, 12–14, 18–20, 35, 47, 79, 81] including 18,276 cases and 104,908 participants were included in the analysis of total physical activity (sum of leisure-time, occupational, and transport activity). The summary RR for high versus low total activity was 0.65 (95 % CI 0.59–0.71, $I^2 = 18$ %, $p_{\text{heterogeneity}} = 0.24$) (Fig. 2). There was some indication of publication bias

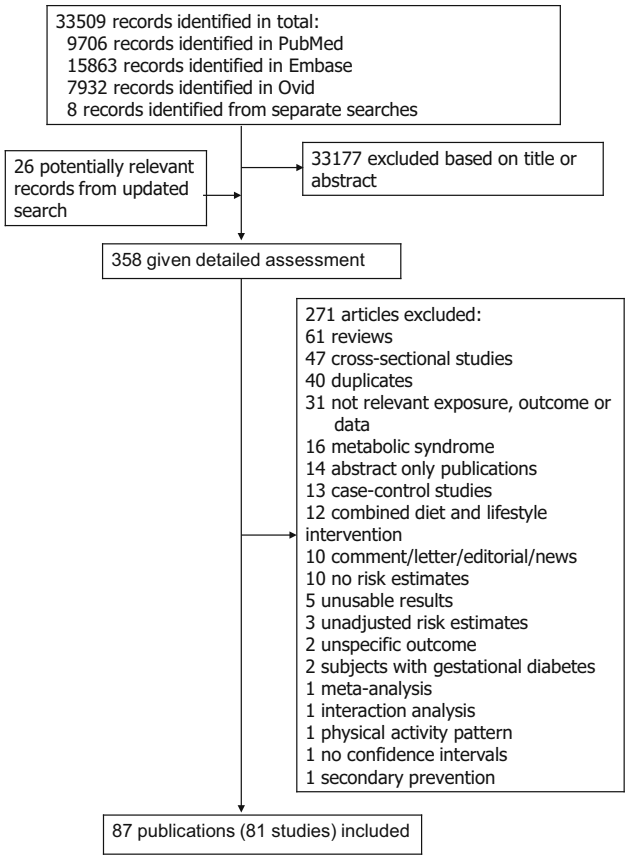

Fig. 1 Flow-chart of study selection

with Egger's test ($p = 0.05$) (Supplemental Figure S1), but this was driven by an outlying study [19], and when excluded Egger's test was no longer significant ($p = 0.11$), and the results were similar, summary RR = 0.65 (95 % CI 0.60–0.71, $I^2 = 13$, $p_{heterogeneity} = 0.31$). Because of differences in the way the results were reported (for example in MET-hours, steps per week or simply low, moderate and high categories) and because only one study provided results in MET-hours per week it was not possible to conduct dose–response analyses for total physical activity.

Leisure-time physical activity

A total of 55 cohort studies (52 publications) [4, 6–8, 10, 11, 16, 20–22, 24–26, 28–30, 32–34, 37–40, 42–64, 66–68, 80, 82, 83] including 151,677 cases and 1820,188 participants were included in the high versus low analysis of leisure-time activity (sports, exercise, recreational activity or activity excluding occupational activity) and type 2 diabetes risk. The summary RR was 0.74 (95 % CI 0.70–0.79, $I^2 = 84$ %, $p_{heterogeneity} < 0.0001$) (Fig. 3). There was evidence of publication bias with Egger's test ($p < 0.0001$) (Supplemental Figure S2), however, this was driven by one very large Korean study [59], which found a very weak association and when this was excluded, Egger's test was no longer significant, $p = 0.10$, and the association was similar, and heterogeneity was also reduced, summary RR = 0.75 (95 % CI 0.71–0.79, $I^2 = 55$ %).

Five studies [5, 11, 16, 27, 67] could be included in the dose–response analysis of MET-hours per week of leisure-time activity and the summary RR was 0.85 (95 % CI 0.81–0.89, $I^2 = 0$ %, $p_{heterogeneity} = 0.88$) per 20 MET-

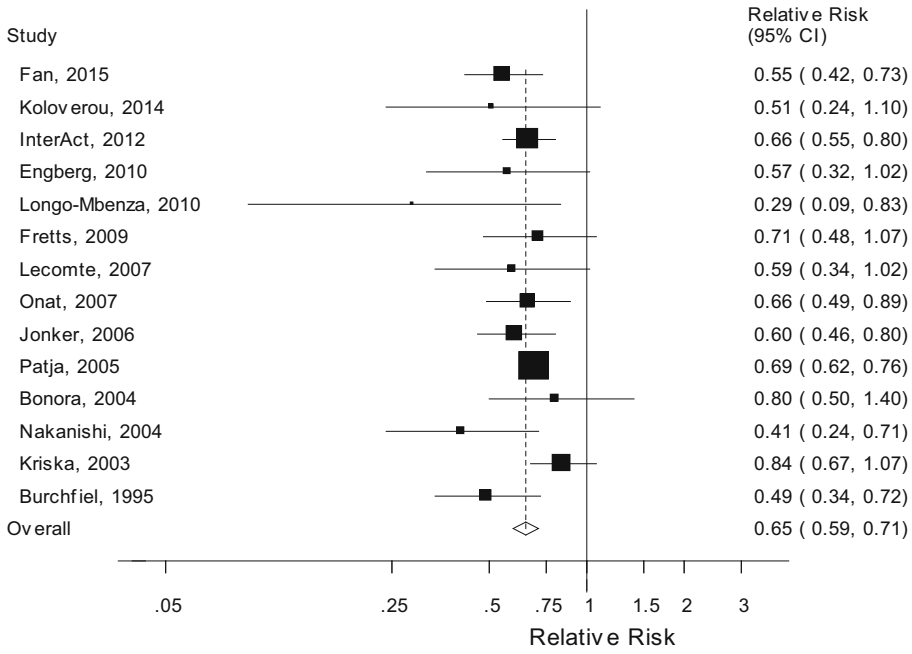

Fig. 2 Total physical activity and type 2 diabetes

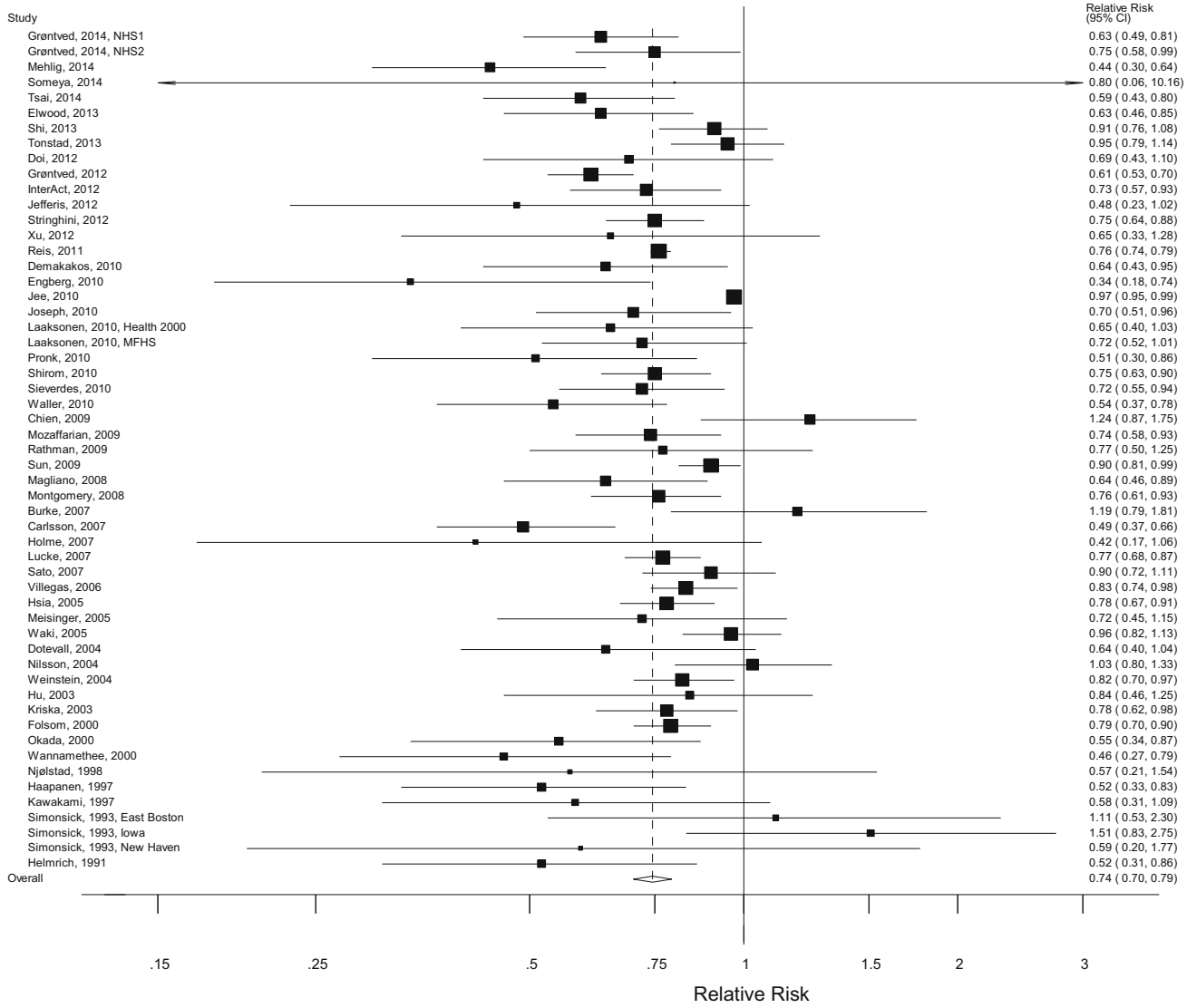

Fig. 3 Leisure-time physical activity and type 2 diabetes

hours per week (Fig. 4a). In an analysis of four studies [5, 16, 27, 67] without BMI adjustment the summary RR was 0.76 (95 % CI 0.72–0.80, $I^2 = 0$ %, $p_{\text{heterogeneity}} = 0.42$) per 20 MET-hours per week. There was evidence of a nonlinear association between MET-hours per week of leisure-time physical activity and type 2 diabetes ($p_{\text{nonlinearity}} < 0.0001$), with a slightly more pronounced reduction in risk at low levels of activity than at high levels (Fig. 4b, Supplemental Table S5).

Ten studies (9 publications) [3, 16, 26, 40, 41, 43, 61, 65, 68] were included in the dose–response analysis of hours per week of leisure-time activity (two of these studies provided only a continuous risk estimate [3, 41]) and the summary RR was 0.75 (95 % CI 0.67–0.85, $I^2 = 89$ %, $p_{\text{heterogeneity}} < 0.0001$) per 5 h per week (Fig. 4c). There was evidence of a nonlinear association between hours per week of leisure-time activity and type 2 diabetes, $p_{\text{nonlinearity}} < 0.0001$, with a slightly more pronounced reduction in risk at low levels of activity than at high levels (Fig. 4d). Analyses of hours per week of leisure-time activity stratified by adjustment for BMI also showed a slightly stronger association without BMI adjustment than with such adjustment, although the number of studies for each analysis differed (Supplemental Figure S3a-d, Supplemental Table S6). When the analysis was restricted to the three studies (two publications) [61, 68] which provided reported risk estimates both adjusted and not adjusted for BMI, the summary RR per 5 h per week was 0.68 (95 % CI 0.59–0.78, $I^2 = 31$ %, $p_{\text{heterogeneity}} = 0.23$) with BMI adjustment and 0.58 (95 % CI 0.53–0.62, $I^2 = 0$ %, $p_{\text{heterogeneity}} = 0.48$) without BMI adjustment.

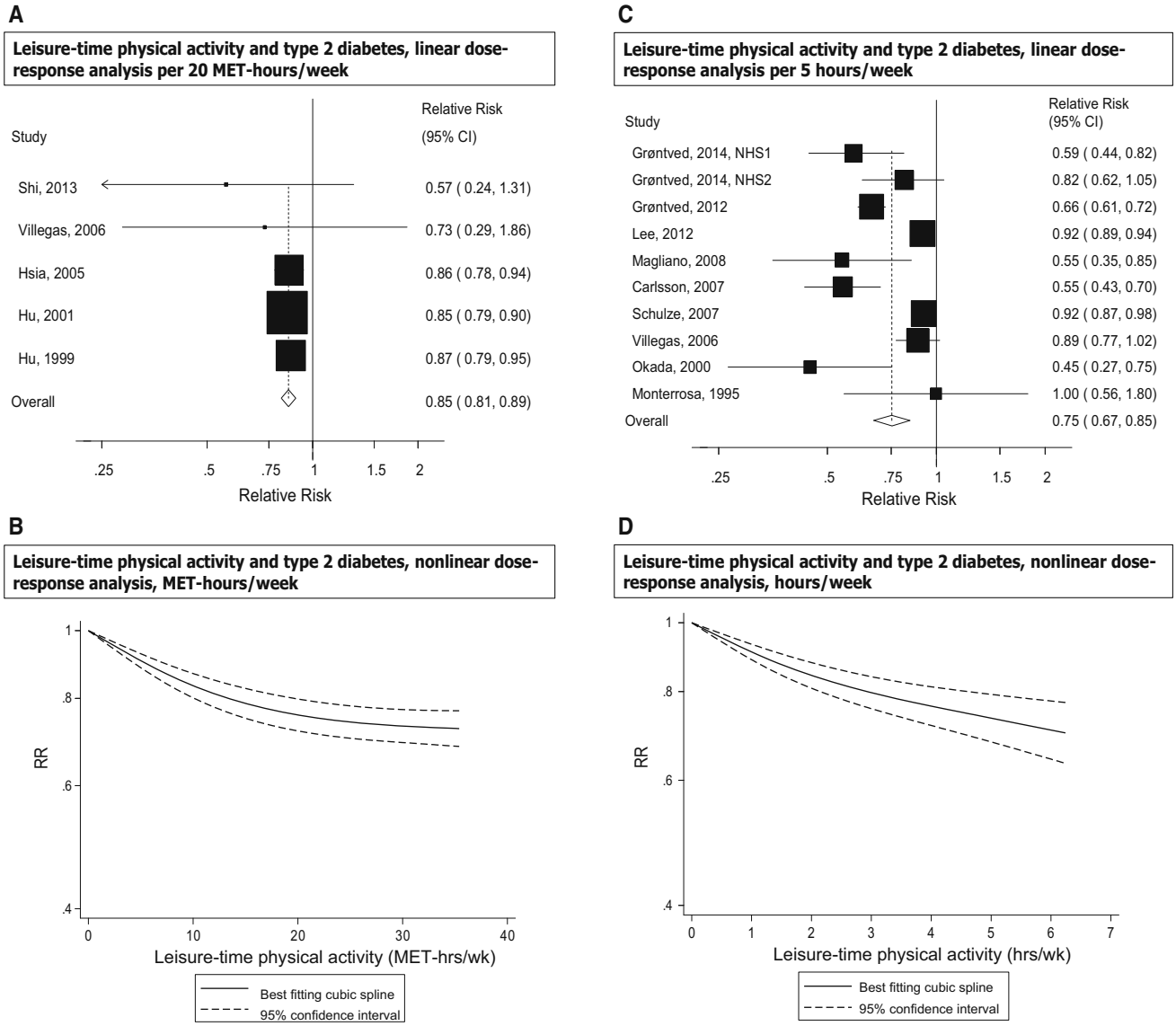

Fig. 4 Leisure-time physical activity and type 2 diabetes, linear and nonlinear dose–response analyses (MET-hours per week and hours per week)

Four studies [21, 24, 29, 42] were included in the dose–response analysis of kcal of energy expenditure per week from leisure-time activity and the summary RR was 0.87 (95 % CI 0.79–0.95, $I^2 = 43$ %, $p_{\text{heterogeneity}} = 0.15$) per 1000 kcal per week increase in energy expenditure (Supplemental Figure S4a). Although the test for nonlinearity was significant, $p_{\text{nonlinearity}} < 0.0001$, for the association between kcal per week of leisure-time activity and type 2 diabetes, the association appeared to be approximately linear across most of the range of activity (Supplemental Figure S4b, Supplemental Table S7). An analysis of two studies which reported on leisure-time activity and risk of type 2 diabetes in subjects with cardiovascular disease [69, 70] yielded a summary RR of 0.66 (95 % CI 0.54–0.79) for the highest versus the lowest level of activity.

Change in physical activity

Five cohort studies [5, 26, 63, 72, 73] and two randomized trials [86, 87] including 2711 cases and 93,371 participants were included in the analysis of change in physical activity and risk of type 2 diabetes. The summary RR was 0.91 (95 % CI 0.46–1.83, $I^2 = 76.3$ %, $p_{\text{heterogeneity}} = 0.002$) for five studies [26, 63, 72, 73, 86] where participants reduced their level of physical activity, 0.64 (95 % CI 0.54–0.76, $I^2 = 0$ %, $p_{\text{heterogeneity}} = 0.64$) for seven studies

[5, 26, 63, 72, 73, 86, 87] where participants increased their physical activity from low to moderate or high levels, and 0.59 (95 % CI 0.50–0.70, $I^2 = 0$ %, $p_{heterogeneity} = 0.64$) for four studies [5, 26, 63, 72] for participants with a consistently moderate to high level of physical activity (Supplemental Figure S5).

Vigorous physical activity

Eight cohort studies [6, 17, 21, 23, 24, 74–76] including 17,062 cases and 272,599 participants were included in the high versus low analysis of vigorous activity (activity with a MET value of 6 or more) and type 2 diabetes. The summary RR was 0.61 (95 % CI 0.51–0.74, $I^2 = 73$ %, $p_{heterogeneity} < 0.0001$) (Fig. 5a). Two outlying studies [74, 76] appeared to explain the heterogeneity and when excluded the summary RR was 0.54 (95 % CI 0.47–0.62, $I^2 = 0$ %, $p_{heterogeneity} = 0.59$). There was some suggestion of publication bias with Egger's test ($p = 0.07$) (Supplemental Figure S6). In the dose–response analysis the summary RR was 0.69 (95 % CI 0.58–0.82, $I^2 = 86$ %, n = 5) per 5 h per week (Supplemental Figure S7a). There was evidence of a nonlinear association between vigorous activity and risk of type 2 diabetes ($p_{nonlinearity} < 0.0001$) (Supplemental Figure 7b, Supplemental Table S8). In analyses restricted to four studies [6, 17, 74, 75] with and without BMI adjustment, the summary RR was 0.67 (95 % CI 0.54–0.83, $I^2 = 85$ %) with BMI adjustment and 0.53 (95 % CI 0.48–0.59, $I^2 = 86$ %) without BMI adjustment per 5 h per week

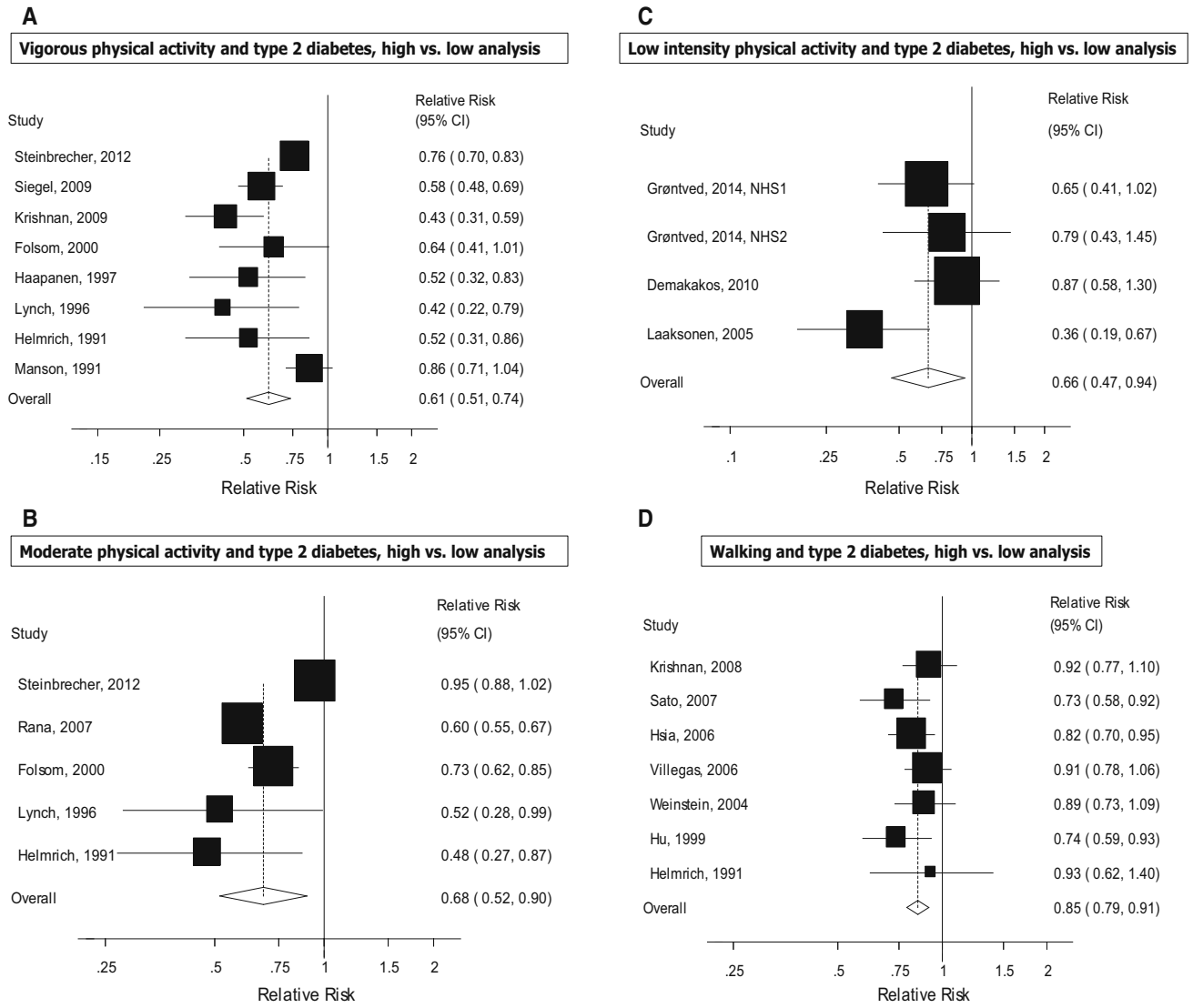

Fig. 5 Vigorous physical activity, moderate physical activity, low intensity physical activity, and walking and type 2 diabetes, high versus low analyses

(Supplemental Figure S8a, Supplemental Figure S8c, Supplemental Table S8), and there was still evidence of nonlinearity, $p_{nonlinearity} < 0.0001$ (Supplemental Figure S8b, Supplemental Figure S8d, Supplemental Table S8).

Moderate physical activity

Five cohort studies [6, 21, 23, 36, 76] reported on moderate activity (activity with a MET value of 3 to <6) and included 14,790 cases and 184,067 participants. The summary RR comparing extreme categories moderate activity was 0.68 (95 % CI 0.52–0.90, $I^2 = 93$ %, n = 5) (Fig. 5b). It was not possible to conduct dose–response analyses because of heterogeneity in the way the data were reported.

Low intensity activity

Three cohort studies (two publications) [60, 68] and one randomized trial [86] reported on low intensity activity (activity with a MET value of <3, for example yoga, stretching, toning) and type 2 diabetes risk and included 3856 cases and 107,269 participants (although the randomized trial reported on change in low intensity activity we included it in the analysis because of few studies available). The summary RR for high versus low activity with low intensity was 0.66 (95 % CI 0.47–0.94, $I^2 = 47$ %, $p_{heterogeneity} = 0.13$) (Fig. 5c). The summary RR per 5 h per week of low intensity activity was 0.71 (95 % CI 0.52–0.97, $I^2 = 0$ %, $p_{heterogeneity} = 0.44$, n = 2) with BMI adjustment (Supplemental Figure S9a) and 0.60 (95 % CI 0.44–0.82, $I^2 = 0$ %, $p_{heterogeneity} = 0.58$, n = 2) without BMI adjustment (Supplemental Figure 9c). There was no evidence of nonlinearity with BMI adjustment, $p_{nonlinearity} = 0.60$ (Supplemental Figure S9b, Supplemental Table S9) or without BMI adjustment, $p_{nonlinearity} = 0.57$ (Supplemental Figure S9d, Supplemental Table S9).

Walking

Seven cohort studies [5, 9, 11, 16, 21, 29, 75] including 11,032 cases and 326,779 participants were included in the high versus low analysis of walking and type 2 diabetes. The summary RR was 0.85 (95 % CI 0.79–0.91, $I^2 = 0$ %, $p_{heterogeneity} = 0.52$) (Fig. 5d). There was no evidence of publication bias with Egger's test ($p = 0.66$) (Supplemental Figure S10). One publication with a combined analysis of two studies provided only a continuous risk estimate and was only included in the dose–response analysis [71]. In the dose–response analysis the summary RR was 0.95 (95 % CI 0.88–1.02, $I^2 = 76$ %, $p_{heterogeneity} = 0.02$, n = 3) per 10 MET-hours per week of walking (Supplemental Figure S11a) and it was 0.92 (95 % CI 0.85–0.99, $I^2 = 62$ %, $p_{heterogeneity} = 0.05$, n = 4) per 2 h per week (Supplemental Figure S11c). There was evidence of a nonlinear association between walking and risk of type 2 diabetes ($p_{nonlinearity} = 0.006$ for MET-hours per week and $p_{nonlinearity} = 0.0001$ for hours per week), with reductions in risk up to 10–15 MET-hours of walking per week (Supplemental Figure S11b, Supplemental Table S10) or up to 2–3 h of walking per week (Supplemental Figure S11d, Supplemental Table S11), but there was no further reduction in risk above these levels.

Resistance exercise

Three cohort studies (two publications) [61, 68] were included in the analysis of resistance training (exercise with free weights, weight machines, exercise against own weight, yoga and outdoor work) and included 5769 cases among 131,318 participants. The summary RR was 0.72 (95 % CI 0.57–0.91, $I^2 = 0$ %, $p_{heterogeneity} = 0.90$, n = 3) for high versus low resistance exercise (Supplemental Figure S12). The summary RR per 5 h per week was 0.70 (95 % CI 0.58–0.84, $I^2 = 0$ %, $p_{heterogeneity} = 0.75$) (Supplemental Figure S13a). There was evidence of a nonlinear association between resistance exercise and type 2 diabetes, $p_{nonlinearity} < 0.0001$, with a more pronounced reduction in risk at low levels of activity (Supplemental Figure S13b, Supplemental Table S12). These associations were stronger without adjustment for BMI (Supplemental Figure S13c, Supplemental Figure S13d, Supplemental Table S12).

Occupational physical activity

Three cohort studies [28, 46, 76] including 9246 cases and 91,139 participants were included in the analysis of occupational activity and risk of type 2 diabetes. The summary RR for high versus low occupational activity was 0.85 (95 % CI 0.79–0.92, $I^2 = 0$ %, $p_{heterogeneity} = 0.41$) (Supplemental Figure S14).

Cardiorespiratory fitness

Five cohort studies (seven publications) [23, 50, 77, 78, 83–85] including 1273 cases and 38,870 participants were included in the analysis of cardiorespiratory fitness and type 2 diabetes risk. Two publications reported separately on men and women from the same study, Ref. [50, 78] and one publication was only included in the dose–response analysis as it reported a continuous estimate only [85]. The summary RR for high versus low cardiorespiratory fitness was 0.45 (95 % CI 0.29–0.70, $I^2 = 75$ %, $p_{heterogeneity} = 0.001$) (Supplemental Figure S15). The summary RR was 0.74

(95 % CI 0.56–0.98, $I^2 = 77$ %, $p_{heterogeneity} = 0.004$) per 20 mL O_2/kg/min (Supplemental Figure 16a). There was no evidence of a nonlinear association between cardiorespiratory fitness and type 2 diabetes risk, $p_{nonlinearity} = 0.14$ (Supplemental Figure 16b, Supplemental Table S13).

Subgroup, sensitivity and meta-regression analyses

In meta-regression analyses, there was generally little evidence of heterogeneity between subgroups (Supplemental Table S14, S15). In the analysis of total physical activity there was heterogeneity by whether studies adjusted for family history of diabetes and triglycerides ($p_{heterogeneity} = 0.03$ and $p_{heterogeneity} = 0.04$, respectively), with stronger associations among studies with compared to without such adjustments (Supplemental Table S14, S15). In the analysis of leisure-time activity, there was heterogeneity by geographic location ($p_{heterogeneity} = 0.002$), number of cases ($p_{heterogeneity} = 0.004$) and adjustment for age ($p_{heterogeneity} = 0.05$), with a weaker association in Asian studies than in European or American studies, and among studies with a large compared to a low number of cases, and in studies with adjustment for age compared to without such adjustment (Supplemental Table S14, S15). However, the inverse association between leisure-time activity and type 2 diabetes was highly statistically significant in almost all subgroups. There was no significant heterogeneity when studies were stratified by study quality scores (Supplemental Table S14, S15) and there was no significant heterogeneity between any of the remaining subgroups using meta-regression analyses. The results persisted in sensitivity analyses excluding one study at a time from the analyses (Supplemental Figure S17-S22).

Discussion

In this meta-analysis high versus low total physical activity, leisure-time activity, low, moderate and vigorous intensity activity, resistance exercise, occupational activity and walking, cardiorespiratory fitness were each associated with a statistically significant reduction in the risk of type 2 diabetes. Most of these activities were associated with a 25–40 % reduction in the relative risk of type 2 diabetes, while walking, occupational activity and cardiorespiratory fitness was associated with a 15, 15 and 55 % decrease in the relative risk of type 2 diabetes, respectively. In addition, subjects who increased their activity levels or those with consistently high levels of activity over time had a 36 and 41 % lower subsequent risk of type 2 diabetes. There was some suggestion of nonlinear relations of leisure-time activity, vigorous activity, walking and resistance exercise to type 2 diabetes risk, with more pronounced reductions in risk at low activity levels and less pronounced reductions in risk at high levels of leisure-time activity and vigorous activity and no further reduction in risk with high levels of walking. This suggests that targeting very sedentary individuals might be particularly important from a public health perspective. Nevertheless, further benefit was also observed at higher physical activity levels. Vigorous activity appeared to be more strongly associated with reduced type 2 diabetes risk than walking.

The results from this meta-analysis are consistent with a previous meta-analyses of cohort studies which also found an inverse association between high versus low moderate intensity physical activity and risk of type 2 diabetes [89]. Our study differs from the previous meta-analysis in that we included a larger number of studies, and further quantified the association between total physical activity and different subtypes of activity and type 2 diabetes risk, and conducted both linear and nonlinear dose–response analyses to clarify the amount of physical activity needed for reducing type 2 diabetes risk. This is important with regard to developing physical activity recommendations for the general population.

As in any meta-analysis of observational studies, certain limitations may have affected the results. It is possible that the observed inverse association between physical activity and risk of type 2 diabetes risk was influenced by unmeasured or residual confounding. Higher physical activity may be associated with other risk factors for type 2 diabetes, including lower prevalence of obesity, lower prevalence of smoking, and higher intakes of dietary fiber and whole grains, and lower intakes of red and processed meat. However, many of the studies included in this meta-analysis adjusted for known confounding factors and most of the results persisted in subgroup analyses with adjustment for confounding factors (such as age, BMI, smoking, fiber, and energy intake) and when stratified by other study characteristics.

Although there was high heterogeneity in the analysis of leisure-time activity, this was partly explained by a Korean study which reported results by only two activity categories [59] and when excluded the heterogeneity was considerably lower. In the analysis of vigorous activity there was also high heterogeneity, but this appeared to be explained more by differences in the size of the effect estimates than differences in the direction of an association. Two outlying studies [74, 76] appeared to explain the heterogeneity for vigorous activity and when excluded there was no heterogeneity. In meta-regression analyses, we found in general little evidence of heterogeneity between subgroups. There was heterogeneity in the analysis of leisure-time activity when stratified by geographic location with a weaker association among Asian studies compared to European and American studies, but the reason for this heterogeneity

is not clear. It is possible that it is due to differences in the type, level and ranges of activity between the populations. Alternatively, differences in the assessment of type 2 diabetes may have contributed to some of the heterogeneity. Publication bias may have affected the results for leisure-time activity. However, this appeared to be explained by one very large Korean study with a limited range of activity [59], and when excluded Egger's test was no longer significant. The results were robust and were not materially altered in sensitivity analyses excluding one study at a time.

Although many studies were included in the high versus low analyses, fewer studies could be included in the dose–response analyses due to differences in the way the results were reported. For example, only 16 out of 55 studies could be included in dose–response analyses of leisure-time activity and type 2 diabetes. The remaining studies did not report the quantity of physical activity or simply categorized physical activity as low, moderate, or high, or had less than three categories of physical activity. In addition, for the 16 studies that did quantify the physical activity level, the studies differed in their measurement of physical activity, with some reporting on MET-hours per week, while others reported the results in hours per week or kcal of energy expenditure per week. For future comparisons between studies, it would be important for new studies to report their results in more detail and preferably in a manner that allows combining the data from different studies, for example by using MET-hours per week and/or hours per week of activity as the underlying measure of exposure. Measurement error in the assessment of physical activity is known to bias effect estimates, however, none of the studies corrected for measurement error.

Several biological mechanisms could explain an inverse association between physical activity and type 2 diabetes. Physical activity improves energy balance and reduces adiposity [103], which is the main risk factor for type 2 diabetes [36, 104]. Comparing the risk estimates from the analyses of leisure-time, vigorous, and low intensity activity and resistance exercise with and without BMI-adjustment the results with BMI adjustment were approximately 20–30 % weaker compared with the results not adjusted for BMI, suggesting that approximately 20–30 % of the association may be explained by reduced adiposity. However, we found a clinically relevant reduction in risk even with adjustment for BMI, and several other mechanisms may explain an effect of physical activity on type 2 diabetes risk independent of adiposity.

An acute bout of exercise (muscle contraction) improves glucose homeostasis by increasing skeletal muscle glucose uptake by translocation of the GLUT4 glucose transporters to the skeletal muscle cell membranes and by increased activity of glycogen synthase [105, 106]. There is experimental evidence that both aerobic and resistance exercise increases GLUT4 translocation and blood glucose uptake [107], consistent with our finding of an inverse association between both leisure-time activity and resistance exercise and type 2 diabetes risk. Both observational studies and randomized trials have reported that regular physical activity improves insulin sensitivity, glycemic control, and the metabolic profile of persons with and without diabetes [108, 109]. Improvements in insulin sensitivity and reductions in blood glucose are related to the duration and intensity of exercise, with greater effects of more prolonged and intense physical activity than for non-vigorous physical activity [109]. This is consistent with our observation of a stronger association for type 2 diabetes with vigorous activity than with walking. Long-term physical activity leads to a number of adaptions in skeletal muscle, including transformation of muscle fiber types, increased mitochondrial activity and content, and increases in GLUT4 protein expression, which may contribute to reduced type 2 diabetes risk [105].

Our meta-analysis has several strengths. Because our analyses only included prospective studies we effectively avoided recall bias and reduced the potential for selection bias. The large number of studies included in the analysis, with >150,000 cases among >1.8 million participants in the analysis of leisure-time physical activity, provided ample statistical power to detect modest associations. We conducted analyses of total physical activity and specific subtypes of physical activity in relation to type 2 diabetes, and we also conducted linear and nonlinear dose–response analyses to investigate whether specific levels of physical activity were associated with type 2 diabetes risk as well the potential mediating effect of reduced obesity. Finally, we conducted detailed subgroup and sensitivity analyses of physical activity in relation to diabetes risk and found that the results persisted across all subgroups and that there was little evidence of heterogeneity between subgroups. The consistency of findings across different types of physical activity, evidence of a dose–response relationship, and stability of results in numerous subgroup and sensitivity analyses, a strong mechanistic basis, and confirming evidence from randomized trials [86, 110], all point to a causal association between increased physical activity and reduced type 2 diabetes risk.

Our findings have important public health implications as lifestyles are becoming increasingly sedentary around the globe, and suggest a dose-dependent reduction of type 2 diabetes risk with greater physical activity. Our finding that all types of activity including light, moderate, and vigorous activity, as well as resistance exercise, occupational activity and walking is associated with reduced type 2 diabetes risk has important public health implications as

persons with physical impairments and older persons may have difficulties performing vigorous activities, but may still benefit from other types of activities. Any further studies should report more detailed results for subtypes and intensities of physical activity. Current guidelines for physical activity among adults recommend at least 150 min per week of moderate-intensity activity, or at least 75 min per week of vigorous-intensity activity, and for additional health benefits up to 300 min per week of moderate-intensity activity, or 150 min per week of vigorous-intensity activity [111]. The current findings confirm that reductions in risk of type 2 diabetes are observed with up to 5–7 h per week (which was the high end of the range observed in the present studies based on the nonlinear analyses) of leisure-time, vigorous and low intensity physical activity, at or above the high end of the current recommendations. We found that for each 20 MET-hours per week of leisure-time physical activity there was a 15 % reduction in diabetes risk. This corresponds to walking briskly at 6.4 km per hour for 1 h 5 days per week or running at 7.4 km per hour for 30 min 5 days per week.

In conclusion, this meta-analysis provides strong evidence for an inverse dose–response relationship between physical activity and risk of type 2 diabetes. All subtypes of physical activity appear to be beneficial. Physical activity may reduce type 2 diabetes risk partly by improving body weight control, but also independently of adiposity. Reductions in risk are observed with up to 5–7 h of leisure-time, vigorous or low intensity physical activity per week, but further reductions with higher physical activity levels cannot be excluded.

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