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Muscle-strengthening activities are associated with lower risk and mortality in major non-communicable diseases: a systematic review and meta-analysis of cohort studies

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ABSTRACT

Objective To quantify the associations between muscle-strengthening activities and the risk of non-communicable diseases and mortality in adults independent of aerobic activities.

Design Systematic review and meta-analysis of prospective cohort studies.

Data sources MEDLINE and Embase were searched from inception to June 2021 and the reference lists of all related articles were reviewed.

Eligibility criteria for selecting studies Prospective cohort studies that examined the association between muscle-strengthening activities and health outcomes in adults aged ≥18 years without severe health conditions.

Results Sixteen studies met the eligibility criteria. Muscle-strengthening activities were associated with a 10–17% lower risk of all-cause mortality, cardiovascular disease (CVD), total cancer, diabetes and lung cancer. No association was found between muscle-strengthening activities and the risk of some site-specific cancers (colon, kidney, bladder and pancreatic cancers). J-shaped associations with the maximum risk reduction (approximately 10–20%) at approximately 30–60 min/week of muscle-strengthening activities were found for all-cause mortality, CVD and total cancer, whereas an L-shaped association showing a large risk reduction at up to 60 min/week of muscle-strengthening activities was observed for diabetes. Combined muscle-strengthening and aerobic activities (versus none) were associated with a lower risk of all-cause, CVD and total cancer mortality.

Conclusion Muscle-strengthening activities were inversely associated with the risk of all-cause mortality and major non-communicable diseases including CVD, total cancer, diabetes and lung cancer; however, the influence of a higher volume of muscle-strengthening activities on all-cause mortality, CVD and total cancer is unclear when considering the observed J-shaped associations.

Systematic review registration PROSPERO CRD42020219808.

INTRODUCTION

Physical inactivity is a global public health problem. Several national and international physical activity guidelines recommend regular muscle-strengthening activities for adults.[1–5] For example, the recent WHO guidelines recommend that adults should perform muscle-strengthening activities ≥2 days/week.[4] Regular engagement in muscle-strengthening activities (eg, resistance training) increases or preserves skeletal muscle strength,[3] which has been shown to be inversely associated with mortality[6 7] and the risk of non-communicable diseases (NCDs) such as cardiovascular disease (CVD) and cancer.[7] Therefore, promoting muscle-strengthening activities may help in reducing the risk of premature death and NCDs.

Compared with aerobic activities, muscle-strengthening activities have been less frequently investigated in terms of their influence on the prevention of premature death and NCDs. Saeidifard *et al* conducted the first systematic review and meta-analysis of 11 published studies that focused on mortality.[8] Although no clear association was observed between resistance training and mortality from CVD and cancer, resistance training was found to be inversely associated with all-cause mortality.[8] Moreover, a recent meta-analysis that focused on cancer incidence and mortality showed that muscle-strengthening activities were associated with a lower incidence of kidney cancer.[9] Although these findings suggested a favourable influence of muscle-strengthening activities on the risk of NCDs and mortality, the dose–response association was not quantified. In some countries such as Japan,[10] a revision of the national physical activity guidelines is under way, and there is a debate regarding whether muscle-strengthening activities should be included in the guidelines. Existing physical activity guidelines primarily focus on the musculoskeletal health benefits of muscle-strengthening activities.[11–13] A systematic evaluation of the associations of muscle-strengthening activities with mortality and NCDs will aid in determining whether muscle-strengthening activities need to be included in the guidelines. In addition, investigating the dose–response association is also necessary to determine the amount of muscle-strengthening activities that should be recommended for public health purposes. A recent narrative review suggested the existence of dose–response associations between muscle-strengthening activities and mortality and major NCDs.[14] With the increasing number of relevant cohort studies, it is now possible to systematically update and expand on previous reviews that did not directly provide the optimal dose of muscle-strengthening activities.

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We therefore conducted a systematic review and meta-analysis of prospective cohort studies on muscle-strengthening activities and the risk of mortality and NCDs among adults aged ≥18 years. In addition to examining the health benefits of engaging in muscle-strengthening activities compared with the absence of muscle-strengthening activities independent of aerobic activities, we quantified the dose–response association between muscle-strengthening activities and health outcomes. We also focused on the additional benefits of combined muscle-strengthening and aerobic activities for health outcomes.

METHODS

This systematic review was performed following the MOOSE[15] and PRISMA 2020[16] guidelines and was registered a priori in the PROSPERO database (CRD42020219808).

Data sources and searches

A systematic literature search was conducted in MEDLINE and Embase from the inception of the databases to 25 October 2020. The search syntax was designed by professional research agencies (International Medical Information Centre, Tokyo, Japan and Inforesta Co Ltd, Tokyo, Japan) with input from two authors (HM and RK) (see online supplemental table 1). We focused on the literature on the association between muscle-strengthening activities and health outcomes among adults aged ≥18 years without diagnosed severe health conditions (eg, cancer or disability) at baseline. Studies were considered eligible if they (1) had a prospective observational design; (2) had a minimum follow-up period of 2 years; (3) examined the influence of muscle-strengthening activities on the outcomes independent of and in combination with aerobic activities; and (4) were published in English. We included studies that used any health outcomes except for those that used a surrogate marker as an outcome.

Study selection

To select articles for full-text reading, two authors (HM and RK) independently screened the titles and abstracts using EndNote X9.2 (Clarivate Analytics, Pennsylvania, USA) and Microsoft Excel (Microsoft Corporation, Redmond, Washington, USA) after the exclusion of duplicates. Articles with ambiguous eligibility were included in the full-text reading step. The two authors also independently performed full-text reading of each article and a hand-search of the reference lists in the selected articles. No additional studies were found. Disagreements were resolved through discussion. An update of the primary search was conducted in June 2021.

Data extraction

Three authors (HM, RK, and TH) independently extracted the following information from each eligible study after dividing the selected papers among them: first author, publication year, study location, cohort name, sex, age of participants, number of participants and person-years, years of follow-up, number of deaths, cause of death, number of incident outcomes, subtype of incident outcome, assessment details for outcomes, assessment details for muscle-strengthening activities, covariates included in the analyses, and effect estimates and 95% confidence intervals (CIs) of mortality or incidence of NCDs. If relevant information about the assessment of outcomes and exposures was missing from the eligible studies, we obtained the information from other studies of the same cohort. The most adjusted effect estimates in the main and sensitivity analyses were extracted. For each study, one of the three authors extracted the data and the remaining two authors cross-checked the data. Disagreements were resolved through deliberation to achieve consensus. Because most of the studies eligible for our meta-analyses reported hazard ratios, if other effect estimates such as ORs were reported, we asked the corresponding authors to provide the hazard ratios.[17 18] Moreover, if information about the effect estimate was not reported, we asked the corresponding authors to provide the hazard ratios using a template.[19–21] Three authors provided additional data.[17 19 20] When multiple articles involving the same cohort for the same outcome were identified, only data from the most recently published article were used. In all such cases, the most recently published articles had the largest number of cases in our systematic review. When the publication year was the same, the article with the largest number of participants and cases was included.

Quality assessment

The quality of the studies was assessed using a modification of the Newcastle–Ottawa Scale (NOS) for Quality Assessment of Prospective Cohort Studies (see online supplemental table 2).[22] We excluded the 'representativeness of the exposed cohort' item of the original NOS because our quality assessment was planned to evaluate internal validity, not external validity. Therefore, 8 stars in total were achievable, and a higher score indicated higher study quality. HM and RK independently assessed the studies and resolved any inconsistencies through discussion.

Data synthesis and analysis

A meta-analysis was conducted if at least two studies reported the effect estimate for the same outcome. Reported hazard ratios were considered equivalent to relative risks (RRs). When only ORs were available,[18] they were considered equivalent to RRs because the overall cumulative incidence of the outcome was relatively low (16.5%). Although we tried to convert ORs to RRs, we could not obtain an assumed control risk from the study because the number of cases was not provided. We assessed the influence of the inclusion of this study by performing a leave-one-out analysis. For the meta-analysis of the influence of muscle-strengthening activities, the effect estimates for any muscle-strengthening activities compared with no muscle-strengthening activities were combined using the random-effects model of DerSimonian and Laird.[23] When the included studies had two or more exposed groups, the effect estimates among the exposed groups were synthesised to obtain a pooled effect estimate using a fixed-effects model with the inverse variance method.[24 25]

We also conducted a dose–response meta-analysis to investigate the influence of muscle-strengthening activities on health outcomes using the method described by Greenland and Longnecker[26] and Orsini *et al*.[27] This method allows estimating study-specific linear trends (slopes) considering the covariance for each exposure category within each study because they are calculated relative to a common reference group.[26 27] The method requires data including distribution of cases, person-years and adjusted RR with 95% CI across three or more quantitative categories. If only the total number of cases or person-years was reported, the distribution of cases or person-years was estimated using the total number of cases and person-years and the RR according to the previous study.[28] If the total number of person-years was not reported, we approximated it by multiplying the total number of participants by the median or mean of the follow-up period. The median or mean of the time of muscle-strengthening activities

within the exposure categories was assigned to the corresponding RR. If these were not reported, the midpoint between the lower and upper limits was calculated. For open-ended categories, we assumed that they had the same widths as the closest category. We used 'none' as the reference group, and there was no study in which the reference category was not the lowest category. The study-specific slopes were pooled using the DerSimonian and Laird random-effects model.[23] A potential non-linear association was also examined using a restricted cubic spline model with three knots at fixed percentiles (10%, 50% and 90%) of time of the exposure.[29] Non-linearity was assessed by testing the null hypothesis that the coefficient of the second spline was equal to zero using a Wald test.[29]

The joint benefit of muscle-strengthening activities and aerobic activities was also examined using the studies that reported the effect estimates of both muscle-strengthening and aerobic activities. The categories of muscle-strengthening (eg, none vs any or ≥2 vs <2 times/week) and aerobic activity (eg, ≥150 vs <150 min/week or low vs high) were defined on the basis of the included studies.

Statistical heterogeneity between studies was examined using Cochrane's Q test and I^2 statistic. I^2 statistic with values of 25%, 50% and 75% corresponded to low, moderate and high level of heterogeneity, respectively.[30] To examine the effect of individual studies on the pooled point estimate and 95% CI of each outcome, we performed a sensitivity analysis by serially excluding each study and evaluated the corresponding changes in the effect estimate (leave-one-out analysis).

Subgroup analyses were performed according to sex (men only, women only, or men and women), age (>65 or ≤65 years), exposure assessment (post hoc, questionnaire or interview) and NOS quality score (post hoc, <7 or ≥7). However, subgroup analyses according to age and sex with cancer as the outcome were not performed owing to insufficient data.

Publication bias was assessed by visually inspecting the funnel plots of estimates against the SE of each study and by using Egger's test of funnel plot asymmetry[31] if the number of included studies was ≥10.[32]

All analyses were performed using Stata 17 (StataCorp, College Station, Texas, USA). Statistical significance was set at $p<0.05$.

Grading the evidence

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to assess the overall certainty of evidence for outcomes.[33–38] One reviewer (HM) assessed the certainty of the evidence while two reviewers (RK and TH) examined and revised the certainty of assessments as necessary. A GRADE evidence profile was developed (see online supplemental table 3).[39]

RESULTS

Literature search

A total of 1252 records were identified through systematic searches in MEDLINE and Embase after the removal of duplicates. Of these, 47 records were retrieved for full-text review and 29 studies were eligible based on the inclusion criteria.[17–21 40–63] Among them, although a total of 28 outcomes were reported, only nine outcomes (all-cause mortality, CVD, total cancer, diabetes and site-specific cancers (colon, kidney, bladder, lung and pancreatic cancers)) were examined in two or more studies. Therefore, 17 outcomes were excluded from our meta-analyses (see online supplemental table 4), resulting in the exclusion of three studies.[60–62] Moreover, prostate cancer and lymphoma were also excluded because of discrepancies in the definition of outcomes across the studies.[45 50] Of the remaining 26 studies we excluded eight because of multiple publications from the same cohort (see online supplemental table 5).[52–59] One study was further excluded because of insufficient information about the effect estimate[21] and another study was excluded because the exposure could not be integrated.[63] Finally, 16 studies were included in the meta-analysis (figure 1).[17–20 40–51]

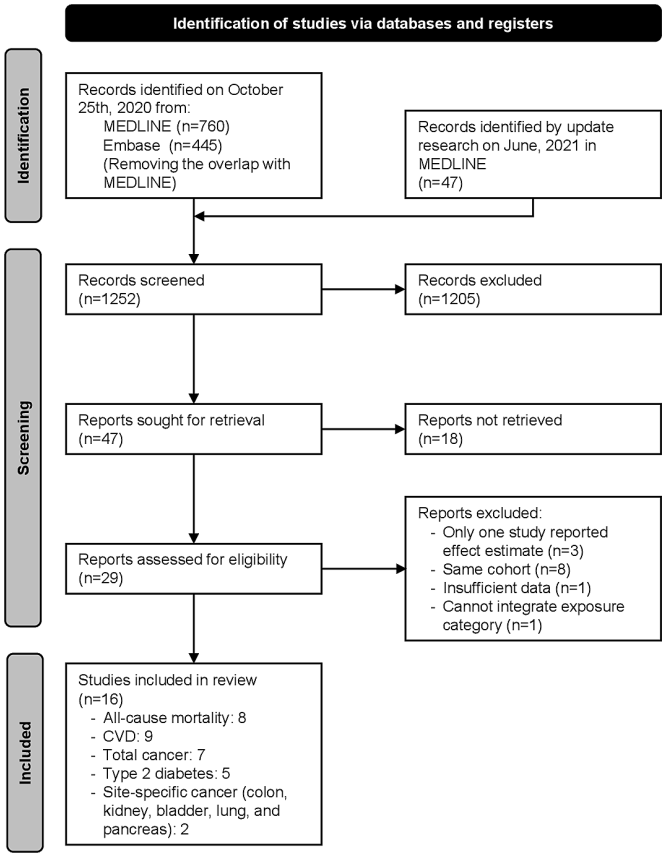

Figure 1 Flowchart of the selection of studies included in the meta-analysis.

Study characteristics

The detailed characteristics of the studies included in the meta-analysis are presented in online supplemental table 6. The publication years ranged from 2012 to 2020. Most studies were conducted in the USA.[18 19 40 42–51] Other studies were from England and Scotland,[20] Australia[17] and Japan.[41] The number of participants varied considerably (from 3809 to 479 856). The maximum follow-up duration was 25.2 years (median).[46] The age of participants ranged from 18 to 97.8 years. Twelve studies included both men and women,[17 18 20 41 44–49 51] two studies included men only[19 50] and three studies included women only.[40 42 43] Adjustment for confounders varied widely across studies, with most studies adjusting for age, body mass index, alcohol intake and smoking status, whereas several studies adjusted for sex, race/ethnicity, dietary habits, disease history and sociodemographic status. All studies considered aerobic or other types of physical activity. Thirteen studies used self-reporting methods to measure muscle-strengthening activities[17–20 40–46 48 50] and three studies used interview methods.[47 49 51] All studies focused on muscle-strengthening exercises such as

resistance/strength/weight training and callisthenics, but not on muscle-strengthening activities such as carrying heavy loads and heavy gardening.

Risk of bias and certainty of evidence

In the risk of bias assessment using the NOS (online supplemental table 2), the included studies were assigned 4–7 stars. For all-cause mortality, four studies were assigned 7 stars, three studies were assigned 6 stars and one study was assigned 5 stars. For CVD, four studies were assigned 7 or 6 stars whereas one study was assigned 5 stars. For total cancer, four and three studies were assigned 7 and 6 stars, respectively, whereas one study was assigned 5 stars. For diabetes, four studies were assigned 6 stars and one study was assigned 4 stars.

The overall certainty of the evidence for each outcome and its details are shown in table 1 and online supplemental table 3. The grading of the certainty of the evidence was generally very low. The main reason for downgrading the evidence was indirectness because most of the studies included in this review were conducted in the USA.

All-cause mortality

Seven studies with 42 133 cases of all-cause mortality among 263 058 participants were included in the two-group analysis. Muscle-strengthening activities were associated with a 15% lower risk of all-cause mortality (RR 0.85; 95% CI 0.79 to 0.93; p<0.001) (figure 2). Although the heterogeneity was high (I^2=83.0%; p<0.001), the association was in the same direction, with an RR of <1.00 in all studies. A similar result was obtained when Sheehan's study,[18] which provided ORs, was excluded (RR 0.84; 95% CI 0.76 to 0.92; p<0.001) (see online supplemental figure 1). Moreover, the exclusion of any other individual study did not substantially change this result, and the high heterogeneity was not explained by sex, quality score or exposure assessment (see online supplemental figures 1-4).

Six studies were eligible for the dose–response analysis of muscle-strengthening activities per 10 min/week increase, with a total of 236 331 participants and 37 178 cases. Although there was no clear linear association (figure 3), a non-linear association was observed (figure 4). The lowest RR (RR 0.83; 95% CI 0.79 to 0.86) was observed at 40 min/week of muscle-strengthening activities, and the RR estimate for up to approximately 140 min/week was <1.00.

Three studies examined the joint benefit of muscle-strengthening and aerobic activities for all-cause mortality, with a total of 581 194 participants and 68 637 cases. Combined muscle-strengthening and aerobic activities (vs none) were associated with a 40% lower risk of all-cause mortality (RR 0.60; 95% CI 0.54 to 0.67; I^2=59.3%) (figure 5).

The overall quality of the evidence on all-cause mortality was rated as 'very low'.

CVD

Seven studies with 16 056 cases of CVD among 257 888 participants were included in the two-group analysis. Three studies focused on CVD mortality or CVD morbidity,[43 44 46] whereas other studies focused on CVD mortality.[19 20 42 48 49 51] Muscle-strengthening activities were associated with a 17% lower risk of CVD (RR 0.83; 95% CI 0.73 to 0.93; p=0.002), with a high level of heterogeneity (I^2=72.9%; p=0.001) (figure 2). Although the high heterogeneity was not completely explained by the quality score and exposure assessment, the heterogeneity disappeared (I^2=0.0%) when the study by Liu *et al*[44] was excluded (online

Table 1 Summary of the association between muscle-strengthening activities and health outcomes

Outcomes	Two-group (no vs any muscle-strengthening activities) meta-analysis					Dose–response meta-analysis (10 min/week increase)					
	N	Cases/participants	RR (95% CI)	P value	I^2, p value	N	Cases/participants	RR (95% CI)	P value	I^2, p value	GRADE*
All-cause mortality	7	42 133/263 058	0.85 (0.79 to 0.93)	<0.001	83%,<0.001	6	37 178/236 331	0.99 (0.98 to 1.00)†	0.05	75%, 0.001	⊕◯◯◯
CVD	7	16 056/257 888	0.83 (0.73 to 0.93)	0.002	73%,<0.001	5	11 263/226 746	0.996 (0.99 to 1.003)‡	0.26	0%, 0.46	⊕◯◯◯
Total cancer	6	21 253/540 543	0.88 (0.80 to 0.97)	0.008	76%,<0.001	4	13 033/212 323	0.99 (0.98 to 1.004)§	0.15	80%, 0.002	⊕◯◯◯
Diabetes	5	9548/202 486	0.83 (0.77 to 0.89)	<0.001	36%, 0.18	3	7511/167 072	0.98 (0.97 to 0.99)¶	0.003	59%, 0.09	⊕⊕◯◯
Colon cancer	2	2415/248 909	0.96 (0.91 to 1.01)	0.09	0%,<0.35	2	2415/248 909	0.998 (0.96 to 1.04)	0.91	94%,<0.001	⊕◯◯◯
Kidney cancer	2	1063/248 909	0.88 (0.76 to 1.02)	0.08	0%,<0.52	2	1063/248 909	0.98 (0.96 to 1.002)	0.08	9%, 0.29	⊕◯◯◯
Bladder cancer	2	2341/248 909	0.94 (0.84 to 1.05)	0.27	19%,<0.27	2	2341/248 909	0.98 (0.95 to 1.02)	0.34	77%, 0.04	⊕◯◯◯
Lung cancer	2	4075/248 909	0.90 (0.83 to 0.98)	0.01	0%,<0.69	2	4075/248 909	0.99 (0.98 to 1.00)	0.045	0%, 0.81	⊕◯◯◯
Pancreatic cancer	2	1028/248 909	1.12 (0.98 to 1.28)	0.11	0%,<0.84	2	1028/248 909	1.004 (0.99 to 1.02)	0.65	0%, 0.89	⊕◯◯◯

*⊕◯◯◯: very low; ⊕⊕◯◯: low; ⊕⊕⊕◯: moderate; ⊕⊕⊕⊕: high.
†A J-shaped association with the maximum risk reduction (17%) at 40 min/week.
‡A J-shaped association with the maximum risk reduction (18%) at 60 min/week.
§A J-shaped association with the maximum risk reduction (9%) at 30 min/week.
¶An L-shaped association with a large risk reduction up to 60 min/week.
CVD, cardiovascular diseases; GRADE, Grading of Recommendations Assessment, Development and Evaluation; RR, relative risk.

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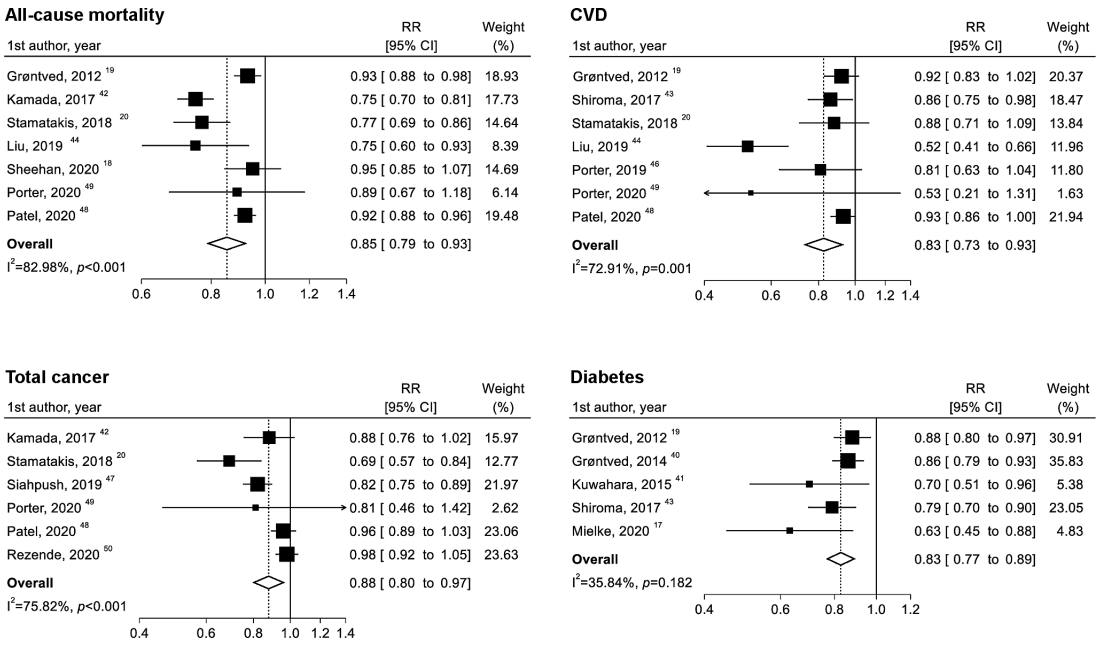

Figure 2 Two-group meta-analysis of the associations between no versus any muscle-strengthening activities and all-cause mortality, cardiovascular disease (CVD), total cancer and diabetes. RR, relative risk.

supplemental figure 1). Moreover, a similar result was obtained when the analysis was limited to CVD mortality (online supplemental figure 5).

Five studies were eligible for the dose–response analysis of muscle-strengthening activities per 10 min/week increase, with a total of 226 746 participants and 11 263 cases. Although there was no clear linear association (figure 3), a non-linear association was observed (figure 4). The lowest RR (RR 0.82; 95% CI 0.76 to 0.90) was observed at 60 min/week of muscle-strengthening activities, and the RR estimate for up to approximately 130 min/week was <1.00.

Three studies examined the joint benefit of muscle-strengthening and aerobic activities for CVD mortality, with a total of 582 672 participants and 15 643 cases. Combined muscle-strengthening and aerobic activities were associated with a 46% lower risk of CVD (RR 0.54; 95% CI 0.41 to 0.70; I^2=62.6%) (figure 5).

The overall quality of the evidence on CVD was rated as 'very low'.

Total cancer

Six studies with 21 253 cases of total cancer among 540 543 participants were included in the two-group analysis. One study focused on total cancer incidence,[50] whereas the other studies focused on total cancer mortality.[20 42 47–49] Muscle-strengthening activities were associated with a 12% lower risk of total cancer (RR 0.88; 95% CI 0.80 to 0.97; p=0.008), with a high level of

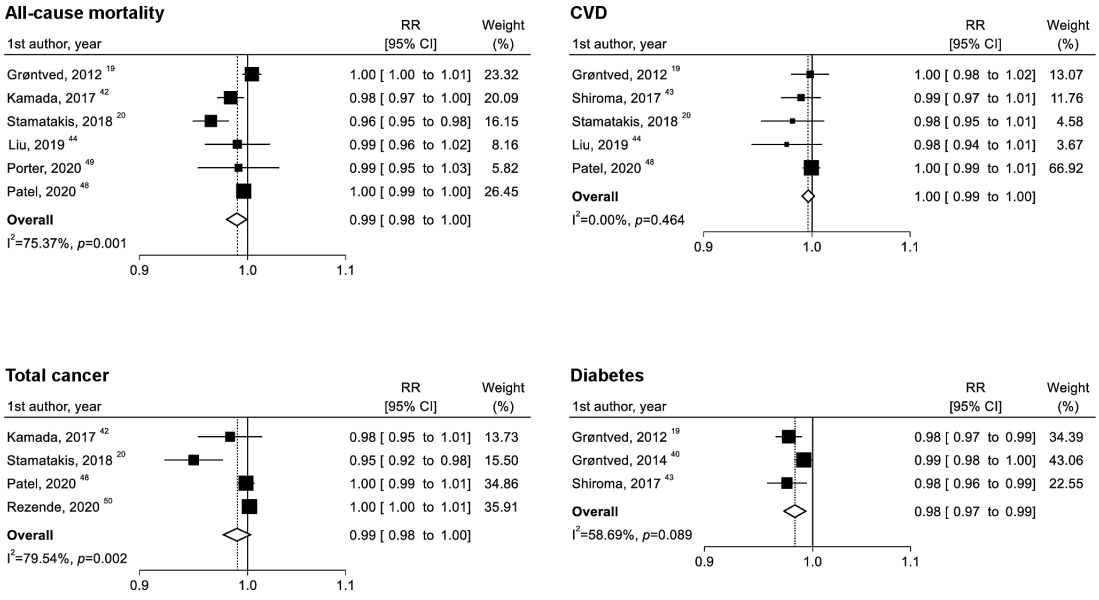

Figure 3 Linear dose–response meta-analysis of the associations between muscle-strengthening activities (per 10 min/week increase) and all-cause mortality, cardiovascular disease (CVD), total cancer and diabetes. RR, relative risk.

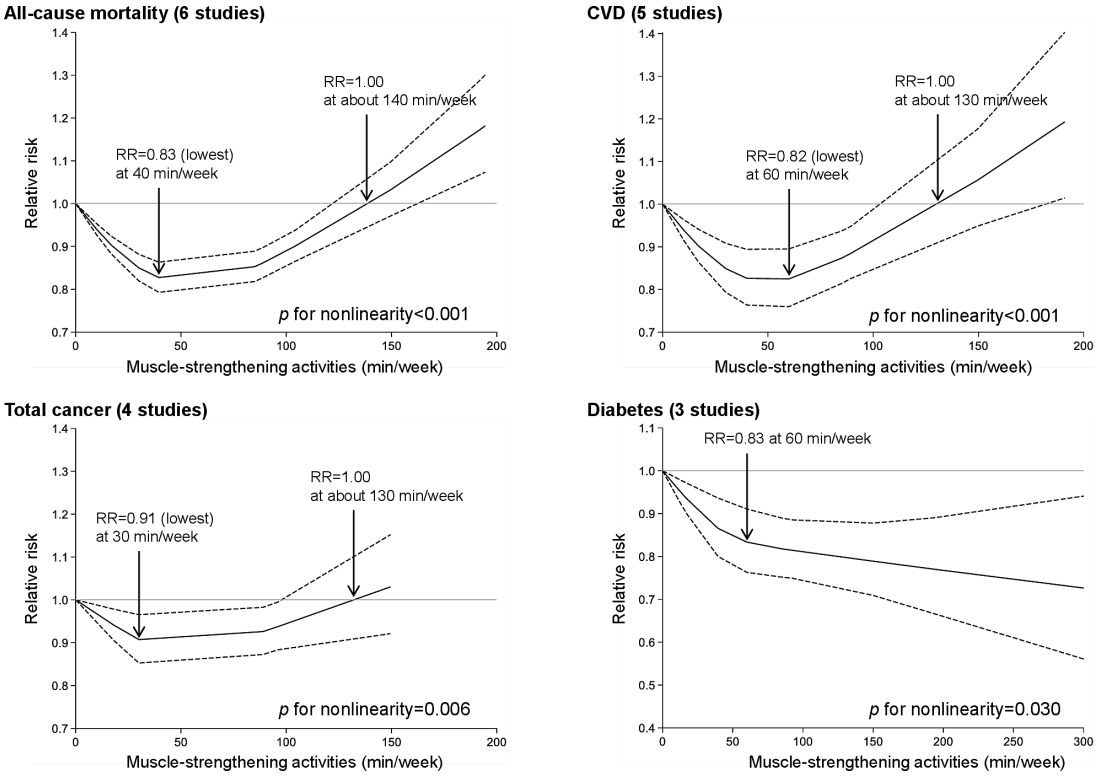

Figure 4 Non-linear dose–response meta-analysis of the associations between muscle-strengthening activities and all-cause mortality, cardiovascular disease (CVD), total cancer and diabetes. Muscle-strengthening activities were modelled with restricted cubic splines in a random-effects dose–response model. The black line indicates the spline model and dashed lines represent 95% confidence intervals. RR, relative risk.

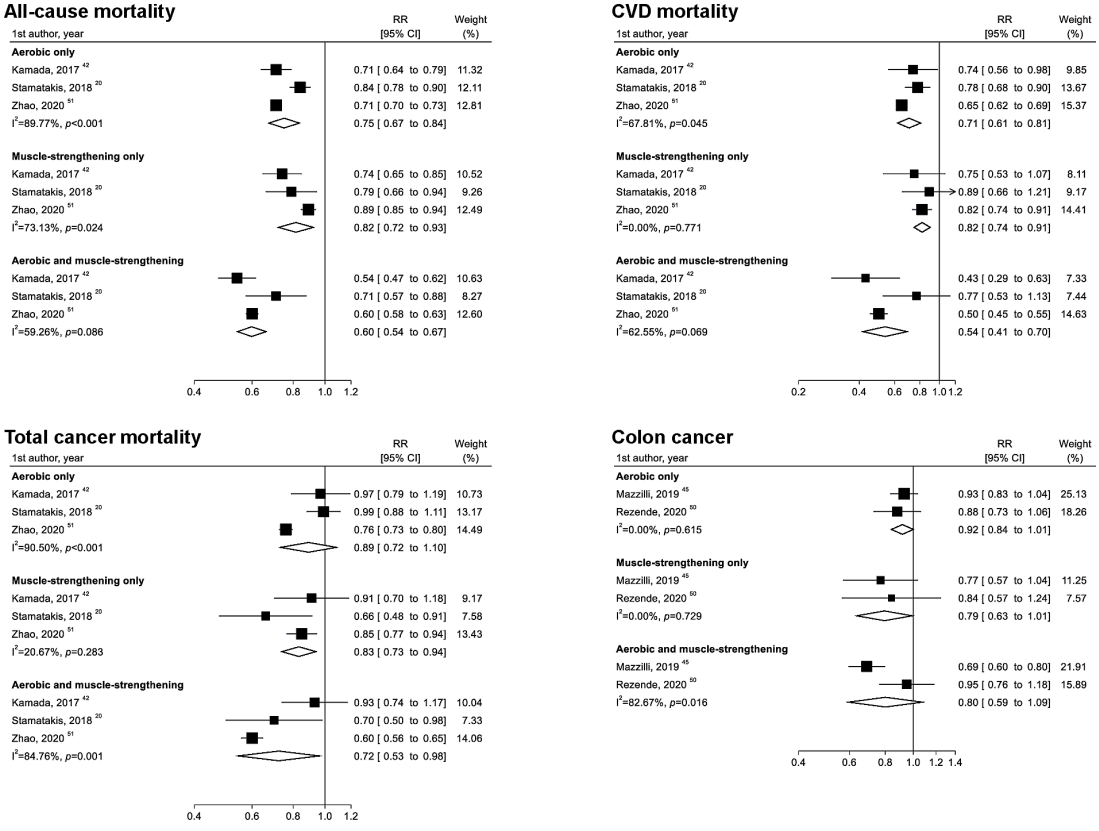

Figure 5 Meta-analysis of the joint associations of muscle-strengthening and aerobic activities with all-cause mortality, cardiovascular disease (CVD) mortality, total cancer mortality and colon cancer incidence. The definitions of groups for muscle-strengthening and aerobic activities were based on the categories described in online supplemental table 6. RR, relative risk.

heterogeneity (I^2=75.8%; p<0.001) (figure 2). The exclusion of any individual study did not substantially change this result, and the high heterogeneity was not explained by the quality score or exposure assessment (online supplemental figures 1-3). When the analysis was limited to total cancer mortality (ie, excluding the study by Rezende *et al*[50]), a similar result was obtained (online supplemental figure 1).

Four studies were eligible for the dose–response analysis of muscle-strengthening exercise per 10 min/week increase, with a total of 212 323 participants and 13 033 cases. Although there was no linear association (figure 3), a non-linear association was observed (figure 4). The lowest RR (RR 0.91; 95% CI 0.85 to 0.97) was observed at 30 min/week of muscle-strengthening activities and the RR estimate for up to approximately 130 min/week was <1.00.

Three studies examined the joint benefit of muscle-strengthening and aerobic activities for total cancer mortality, with a total of 585 930 participants and 17 212 cases. Combined muscle-strengthening and aerobic activities were associated with a 28% lower risk of total cancer mortality (RR 0.72; 95% CI 0.53 to 0.98; I^2=84.8%) (figure 5).

The overall quality of the evidence on total cancer was rated as 'very low'.

Diabetes

Five studies with 9548 cases of diabetes among 202 486 participants were included in the two-group analysis. Muscle-strengthening activities were associated with a 17% lower incidence of diabetes (RR 0.83; 0.77 to 0.89; p<0.001), with a low to moderate level of heterogeneity (I^2=35.8%; p=0.18) (figure 2). The heterogeneity was substantially reduced (I^2=9.5%) when the study by Mielke *et al*[17] with low quality (NOS=4) was excluded (online supplemental figure 1). An inverse association was obtained when the analysis was limited to studies focused on women (two studies) (online supplemental figure 5).

Three studies were eligible for the dose–response analysis of muscle-strengthening activities per 10 min/week increase, with a total of 167 072 participants and 7511 cases. Each 10 min/week increase in muscle-strengthening activities was inversely associated with the risk of diabetes, with moderate evidence of heterogeneity (RR 0.98; 95% CI 0.97 to 0.99; p=0.003; I^2=58.7%; p=0.09) (figure 3). Moreover, an L-shaped relationship was found, and the risk markedly decreased until up to 60 min/week of muscle-strengthening activities (figure 4).

The overall quality of the evidence on diabetes was rated as 'low'.

Site-specific cancers

Two studies were included in the two-group and dose–response analyses for the incidence of site-specific cancers (colon, kidney, bladder, lung and pancreatic cancers).[45 50] The total number of cases/participants was 2415/248 909 for colon cancer, 1063/248 909 for kidney cancer, 2341/248 909 for bladder cancer, 4075/248 909 for lung cancer and 1028/248 909 for pancreatic cancer. Muscle-strengthening activities were associated with a 10% lower incidence of lung cancer (RR 0.90; 95% CI 0.83 to 0.98; p=0.01; I^2=0.0%; p=0.69) (online supplemental figure 6). A linear association was obtained for lung cancer (RR 0.99; 95% CI 0.98 to 1.00; p=0.045; I^2=0.0%; p=0.81) (online supplemental figure 7). For other site-specific cancers, no association was confirmed in the two-group, dose–response and joint analyses (figure 5 and online supplemental figures 6 and 7).

Sensitivity analysis and any subgroup analysis were not performed because of the small number of included studies.

The overall quality of the evidence on the incidence of each site-specific cancer was rated as 'very low'.

Publication bias

For all outcomes included in the meta-analysis, the test for funnel plot asymmetry was not performed because of the small number of included studies (n≤7).

DISCUSSION

This systematic review and meta-analysis of cohort studies found that muscle-strengthening activities were inversely associated with the risk of CVD, total cancer, diabetes, lung cancer and all-cause mortality independent of aerobic activities among adults aged ≥18 years without severe health conditions. Moreover, J-shaped associations were found between muscle-strengthening activities and all-cause mortality, CVD and total cancer, with the maximum risk reduction (approximately 10–20%) at approximately 30–60 min/week of muscle-strengthening activities. We also observed an L-shaped association between muscle-strengthening activities and diabetes, showing a large risk reduction before 60 min/week. Finally, combined muscle-strengthening and aerobic activities (vs none) were associated with a lower risk of all-cause, CVD and total cancer mortality.

Saeidifard *et al* reported that engaging in muscle-strengthening activities was associated with a lower risk of all-cause mortality, although there was no clear association with CVD mortality and total cancer mortality.[8] Moreover, another meta-analysis showed no clear association with total cancer mortality.[9] Our systematic review updated the literature and expanded on previous studies,[8 9] showing that muscle-strengthening activities were inversely associated with the risk of CVD, total cancer and all-cause mortality. We obtained similar results when the analysis was limited to CVD and total cancer mortality. In addition, muscle-strengthening activities were associated with a lower incidence of lung cancer in our review, although Nascimento *et al* showed an inverse association for kidney cancer, but not lung cancer, even when the same studies were included.[9] The reason for this discrepancy may be derived from the extracted effect estimates. Nascimento *et al* extracted the effect estimate from the highest category of muscle-strengthening activities whereas we used pooled effect estimates when the included studies had two or more exposed groups.

Joint analysis between muscle-strengthening and aerobic activities showed that a greater benefit for all-cause, CVD and total cancer mortality was obtained when these two types of activities were combined. These results confirm the findings of previous meta-analyses.[8 9] Therefore, beyond aerobic activities, muscle-strengthening activities may provide additional benefits for preventing mortality.

One of the strengths of this study was the quantification of the dose–response association between muscle-strengthening activities and health outcomes. Several previous cohort studies have reported a non-linear association between muscle-strengthening activities and health outcomes.[42–44 48] For example, Kamada *et al* showed a quadratic association between strength training and all-cause and CVD mortality, and the lowest risk of all-cause mortality was observed at 82 min/week of strength training.[42] Furthermore, the abovementioned previous meta-analysis reported that performing resistance training 1–2 times/week was associated with a lower all-cause mortality, but increasing the volume to >2 times/week was not.[8] This result supports a potential non-linear

association between muscle-strengthening activities and all-cause mortality. In our systematic review, J-shaped associations with the maximum risk reduction (10–20%) at approximately 30–60 min/week of muscle-strengthening activities were observed for all-cause mortality, CVD and total cancer. These results suggest that optimal doses of muscle-strengthening activities for the prevention of all-cause death, CVD and total cancer may exist.

In addition, our study is the first to systematically evaluate the longitudinal association between muscle-strengthening activities and the risk of diabetes. Although the potential of muscle-strengthening activities to reduce the risk of diabetes is supported by several biological mechanisms,[64 65] many of the previous studies on this topic were limited to short-term randomised controlled trials examining surrogates of diabetes.[66] Our findings showed that muscle-strengthening activities were associated with a 17% lower incidence of diabetes, with the risk of diabetes sharply decreasing until up to 60 min/week of muscle-strengthening activities followed by a gradual decrease. Because muscle-strengthening activities increase or preserve skeletal muscle mass, which has been identified as the major tissue in glucose metabolism, a clear dose–response association can be established.

Our systematic review has some limitations. The first and most important limitation is that the meta-analysis included only a small number of studies. The limited number of studies precluded some examinations. For example, it did not allow us to conduct some subgroup analyses to explain the heterogeneity in our findings and, even when performed, few studies were included. Moreover, we could not test for publication bias. Therefore, the pooled estimates in this study might have been overestimated because of potential publication bias. Second, the included studies evaluated muscle-strengthening activities using a self-reported questionnaire or the interview method. Although measures of muscle-strengthening activities have been reported to have higher reliability than those of aerobic activities,[67] this may have contributed to the heterogeneity in our results. Indeed, the heterogeneities in this review were partially explained by differences in exposure assessment, although only a few studies were included. Third, because most of the included studies were conducted in the USA, the generalisability of our findings is limited. Fourth, observational studies were included in the meta-analysis and were thus potentially influenced by residual, unknown and unmeasured confounding factors. Finally, only two databases were searched, and therefore some relevant studies may have been missed.

Several physical activity guidelines recommend that adults perform muscle-strengthening activities at least twice a week.[1–5] Although the recommendation is primarily based on the benefit for musculoskeletal health,[11–13] these guidelines are partly supported by our results in terms of preventing premature death and NCDs. However, the influence of a higher volume of muscle-strengthening activities on health benefits is unclear. Our findings showed that the maximum risk reduction for all-cause mortality, CVD and total cancer was obtained at approximately 30–60 min/week of muscle-strengthening activities, and the RR was low for up to approximately 130–140 min/week. Given this result, the current recommendation of at least 2 days/week could be reasonable, although a higher volume may require caution. However, our findings should be interpreted with caution because the number of included studies was small and we could not directly examine the frequency of muscle-strengthening activities. Large-scale studies are needed to examine the health benefits of high-volume muscle-strengthening activities. Moreover, attention should also be paid to evidence that most programmes providing benefits for musculoskeletal health in elderly people are performed ≥2 days/week.[12] The longitudinal influence of muscle-strengthening activities on mortality and NCDs should be further investigated with a focus on the elderly population in future studies.

What is already known?

⇒ Physical activity guidelines recommend regular muscle-strengthening activities for adults, and this recommendation is primarily based on the benefits for musculoskeletal health.
⇒ Previous meta-analyses have shown that muscle-strengthening activities are associated with a decreased risk of all-cause mortality and kidney cancer, although the dose–response association is unknown.
⇒ Further studies are needed to update the literature and expand on previous studies that did not provide evidence on the optimal dose of muscle-strengthening activities.

What are the new findings?

⇒ Muscle-strengthening activities were associated with a 10–17% lower risk of CVD, total cancer, diabetes, lung cancer and all-cause mortality independent of aerobic activities among adults.
⇒ The maximum risk reduction for all-cause mortality, CVD and total cancer was obtained at approximately 30–60 min/week of muscle-strengthening activities, and the risk of diabetes sharply decreased until 60 min/week of muscle-strengthening activities, followed by a gradual decrease.

CONCLUSION

Engaging in muscle-strengthening activities was associated with a lower risk of all-cause mortality and major NCDs such as CVD, total cancer, diabetes and lung cancer. However, the influence of a higher volume of muscle-strengthening activities on all-cause mortality, CVD and total cancer is unclear, considering the observed J-shaped associations. In addition, the combination of muscle-strengthening and aerobic activities may provide a greater benefit for reducing all-cause, CVD and total cancer mortality. Given that the available data are limited, further studies—such as studies focusing on a more diverse population—are needed to increase the certainty of the evidence.

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Contributors HM and RK contributed equally to this work. HM, RK, TH and SSS have full access to all the data in this review and take full responsibility as guarantors for the integrity of the data and the accuracy of the data analysis. HM and RK conceived and designed the study. HM, RK and TH contributed to study selection, data extraction and data analyses. RK conducted the meta-analysis. HM drafted the manuscript. All authors contributed to data interpretation and critically revised the manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Appendix Table 1. Search strategy for Ovid MEDLINE and Embase

Ovid MEDLINE

#	Searches
1	exp resistance training/
2	((resistance adj2 (exercise* OR training*)) OR (weight bearing adj2 (exercise* OR training* OR strengthening*)) OR (strength adj2 (exercise* OR training*)) OR (strengthening adj2 activit*) OR weightlifting OR (weight adj1 training) OR (weight adj1 lifting) OR ((muscular OR muscle) adj1 strengthening) OR (circuit adj1 training) OR (isometric adj1 exercise) OR (resistance exercise* OR resistance training OR weight bearing exercise* OR weight bearing training OR weight bearing strengthening OR strength exercise OR strength training OR strengthening activit* OR weight training OR weight lifting OR muscular strengthening OR muscle strengthening OR circuit training OR isometric exercise)).mp.
3	exp cohort studies/ OR (cohort OR prospective OR retrospective OR longitudinal OR (follow adj1 up) OR follow up).mp. OR observational study.pt. OR (exp health surveys/ OR health surve*.ti.)
4	mortality.mp. OR exp cause of death/ OR (death OR mortality).hw.
5	exp risk/ OR exp causality/ OR exp mortality/ OR (etiology or mortality).fs. OR exp morbidity/ OR (prevalen* OR morbidity or incidence).mp. OR (risk* OR mortality OR death OR cause* OR causality OR etiology OR incidence).ti.
6	(1 or 2) and 3 AND (4 OR 5)
7	((systematic adj1 review*) OR (meta adj1 analys*) OR (random* OR case report*) OR (phase adj1 (II OR III OR "2" OR "3")) OR phase II OR phase III OR phase 2 OR phase 3).ti. OR (clinical trial, all OR meta analysis OR systematic reviews OR case reports OR guideline OR review OR practice guideline OR comment OR letter ORor news).pt.
8	6 NOT 7
9	l/8 en=y
10	l/9 hu=y
11	exp muridae/ or (animals or animal).hw. or (in vitro or in vivo or mouse or mice or rat or rats).ti.
12	9 NOT 11
13	10 OR 12

EMBASE

#	Searches
L1	SEA RESISTANCE TRAINING+PFT,NT/CT
L2	SEA (RESISTANCE OR STRENGTH)(2A)(EXERCISE? OR TRAINING?) OR WEIGHT(W)BEARING(2A)(EXERCISE? OR TRAINING? OR STRENGTHENING?) OR STRENGTHENING(2A)ACTIVIT? OR WEIGHTLIFTING OR WEIGHT(1A)(TRAINING OR LIFTING) OR (MUSCULAR OR MUSCLE)(1A)STRENGTHENING OR CIRCUIT(1A)TRAINING OR ISOMETRIC(1A)EXERCIS
L3	SEA (COHORT ANALYSIS+PFT,NT OR OBSERVATIONAL STUDY+PFT,NT OR HEALTH SURVEY+PFT,NT)/CT OR COHORT OR PROSPECTIVE OR RETROSPECTIVE OR LONGITUDINAL OR FOLLOW(1A)UP OR HEALTH(W)SURVE?/TI
L4	SEA MORTALITY OR CAUSE OF DEATH+PFT,NT/CT E DEATH+KT/CT
L5	SEA (DEATH/CT OR "BH3 INTERACTING DOMAIN DEATH AGONIST PROTEIN"/CT OR "BCL 2 INTERACTING MEDIATOR OF CELL DEATH"/CT OR "BCL ASSOCIATED DEATH PROTEIN"/CT OR "BCL-ASSOCIATED DEATH PROTEIN"/CT OR "DISC (DEATH INDUCING SIGNALING COMPLEX)"/CT OR "DEATH ANXIETY SCALE"/CT OR "DEATH DEPRESSION SCALE"/CT OR "EDAR ASSOCIATED DEATH DOMAIN PROTEIN"/CT OR "EDAR-ASSOCIATED DEATH DOMAIN PROTEIN"/CT OR "FAS ASSOCIATED DEATH DOMAIN LIKE INTERLEUKIN 1BETA CONVERTING ENZYME"/CT OR "FAS ASSOCIATED DEATH DOMAIN LIKE INTERLEUKIN 1BETA CONVERTING ENZYME 2"/CT OR "FAS ASSOCIATED DEATH DOMAIN LIKE INTERLEUKIN 1BETA CONVERTING ENZYME INHIBITORY PROTEIN"/CT OR "FAS ASSOCIATED DEATH DOMAIN PROTEIN"/CT OR "FAS ASSOCIATED DEATH DOMAIN PROTEIN INTERLEUKIN1BETA CONVERTING ENZYME 2"/CT OR "FAS ASSOCIATING DEATH DOMAIN PROTEIN"/CT OR "FAS-ASSOCIATED DEATH DOMAIN PROTEIN"/CT OR "IUFD (INTRAUTERINE FETAL DEATH)"/CT OR "MN-INDUCED NEURONAL CELL DEATH"/CT OR "MN-INDUCED NEURONAL DEATH"/CT OR "PARP-1-DEPENDENT CELL DEATH"/CT OR "PARP-DEPENDENT CELL DEATH"/CT OR "PROGRAMMED DEATH-LIGAND 1 IMMUNOHISTOCHEMISTRY ASSAY"/CT OR "PROGRAMMED DEATH-LIGAND 1 TEST KIT"/CT OR "RIP ASSOCIATED PROTEIN WITH A DEATH DOMAIN"/CT OR "TNF RECEPTOR ASSOCIATED DEATH DOMAIN PROTEIN"/CT OR "TNF RECEPTOR-ASSOCIATED DEATH DOMAIN PROTEIN"/CT OR "TNF RELATED DEATH LIGAND 1"/CT OR "ACCIDENTAL DEATH"/CT OR "ACTIVATION INDUCED CELL DEATH"/CT OR "AFTER-DEATH CARE"/CT OR "ANTEPARTUM DEATH"/CT OR "APOPTOTIC CELL DEATH"/CT OR "APOPTOTIC CELLULAR DEATH"/CT OR "APOPTOTIC DEATH"/CT OR "APOPTOTIC NERVE CELL DEATH"/CT OR "APOPTOTIC NEURON DEATH"/CT OR "APOPTOTIC NEURONAL CELL DEATH"/CT OR "APOPTOTIC NEURONAL DEATH"/CT OR "APOPTOTIC-LIKE CELL DEATH"/CT OR "APOPTOTIC-LIKE NEURON DEATH"/CT OR "APOPTOTIC-LIKE NEURONAL CELL DEATH"/CT OR "APOPTOTIC-LIKE NEURONAL DEATH"/CT OR "APOPTOTIC-MEDIATED NEURONAL DEATH"/CT OR "ATTITUDE TO DEATH"/CT OR "AUTOPHAGIC CELL DEATH"/CT OR "AUTOPHAGIC PROGRAMMED CELL DEATH"/CT OR "AUTOPHAGY-DEPENDENT CELL DEATH"/CT OR "BATHTUB DEATH"/CT OR "BRAIN DEATH" E MORTALITY+KT/CT
L6	SEA (MORTALITY/CT OR "100% MORTALITY TIME"/CT OR "50% MORTALITY LETHAL TIME"/CT OR "GRACE MORTALITY SCORE"/CT OR "GLOBAL REGISTRY OF ACUTE CORONARY EVENTS MORTALITY RISK SCORE"/CT OR "PAEDIATRIC INDEX OF MORTALITY"/CT OR "PAEDIATRIC INDEX OF MORTALITY 2"/CT OR "PEDIATRIC INDEX OF

	MORTALITY"/CT OR "PEDIATRIC INDEX OF MORTALITY 2"/CT OR "PEDIATRIC INDEX OF MORTALITY 2 SCORE"/CT OR "SMR (STANDARDISED MORTALITY RATIO)"/CT OR "SMR (STANDARDIZED MORTALITY RATIO)"/CT OR "SMRS (STANDARDISED MORTALITY RATIOS)"/CT OR "SMRS (STANDARDIZED MORTALITY RATIOS)"/CT OR "SOCIETY OF THORACIC SURGEONS MORTALITY RISK SCORE"/CT OR "ALL CAUSE MORTALITY"/CT OR "CANCER MORTALITY"/CT OR "CARDIOVASCULAR MORTALITY"/CT OR "CHILD MORTALITY"/CT OR "CHILDHOOD MORTALITY"/CT OR "DRUG MORTALITY"/CT OR "EMBRYO MORTALITY"/CT OR "EMBRYONIC MORTALITY"/CT OR "EXCESS MORTALITY"/CT OR "FETAL MORTALITY"/CT OR "FETUS MORTALITY"/CT OR "FOETAL MORTALITY"/CT OR "FOETUS MORTALITY"/CT OR "HOSPITAL MORTALITY"/CT OR "INFANT MORTALITY"/CT OR "INFANTILE MORTALITY"/CT OR "INTRAUTERINE MORTALITY"/CT OR "LETHAL TIME FOR 50% MORTALITY"/CT OR "LETHAL TIME OF MORTALITY"/CT OR "MATERNAL MORTALITY"/CT OR "MORTALITY CAUSE"/CT OR "MORTALITY MODEL"/CT OR "MORTALITY PREDICTION SCALE"/CT OR "MORTALITY PREDICTION SCORE"/CT OR "MORTALITY RATE"/CT OR "MORTALITY RISK"/CT OR "MORTALITY RISK INDEX"/CT OR "MORTALITY RISK SCALE"/CT OR "MORTALITY RISK SCORE"/CT OR "MORTALITY, CANCER"/CT OR "MORTALITY, CHILDHOOD"/CT OR "MORTALITY, FETAL"/CT OR "MORTALITY, FOETAL"/CT OR "MORTALITY, INFANT"/CT OR "MORTALITY, MATERNAL"/CT OR "MORTALITY, NEONATAL"/CT OR "MORTALITY, PERINATAL"/CT OR "MORTALITY, PREMATURE"/CT OR "MORTALITY, PRENATAL"/CT OR "MOTHER MORTALITY"/CT OR "NEONATAL MORTALITY"/CT OR "NEONATUS MORTALITY"/CT OR "NEWBORN MORTALITY"/CT OR "OPERATION MORTALITY"/CT OR "OPERATIVE MORTALITY"/CT OR "PERINATAL MORTALITY"/CT OR "POSTNEONATAL MORTALITY"/CT OR "POSTOPERATIVE MORTALITY"/CT OR "POULTENTERITIS MORTALITY SYNDROME"/CT OR "PREMATURE MORTALITY"/CT OR "PRENATAL MORTALITY"/CT OR "
L7	QUE (RISK+PFT,NT OR CAUSALITY+PFT,NT OR MORTALITY+PFT,NT OR MORBIDITY+PFT,NT)/CT OR ET/CT OR PREVALEN? OR MORBIDITY OR INCIDENCE OR (RISK? OR MORTALITY OR DEATH OR CAUSE? OR CAUSALITY OR ETIOLOGY OR INCIDENCE)/TI
L8	SEA (L1 OR L2) AND L3 AND (L4 OR L5 OR L6 OR L7)
L9	SEA (SYSTEMATIC(1A)REVIEW? OR META(1A)ANALYS? OR RANDOM? OR CASE(W)REPORT? OR PHASE(1A)(II OR III OR 2 OR 3))/TI OR (LETTER OR REVIEW)/DT
L10	QUE (CLINICAL TRIAL+PFT,NT OR META ANALYSIS+PFT,NT OR SYSTEMATIC REVIEW+PFT,NT OR CASE REPORT+PFT,NT OR REVIEW+PFT,NT OR PRACTICE GUIDELINE+PFT,NT OR LETTER+PFT,NT)/CT
L11	SEA L8 NOT (L9 OR L10)
L12	SEA L11 AND ENGLISH/LA
L13	SEA L12 AND HUMAN+AUTO/CT
L14	QUE MURIDAE+PFT,NT/CT OR (IN(W)VITRO OR IN(W)VIVO OR MOUSE OR MICE OR RAT OR RATS)/TI E ANIMALS+KT/CT
L15	SEA (ANIMALS/CT OR "ADULT ANIMALS"/CT OR "ANIMALS BY OUTER APPEARANCE"/CT OR "ANIMALS, CONGENIC"/CT OR "ANIMALS, DOMESTIC"/CT OR "ANIMALS, EXOTIC"/CT OR "ANIMALS, GENETICALLY MODIFIED"/CT OR "ANIMALS, INBRED STRAINS"/CT OR "ANIMALS, LABORATORY"/CT OR "ANIMALS, NEWBORN"/CT OR "ANIMALS, OUTBRED STRAINS"/CT OR "ANIMALS, POISONOUS"/CT OR "ANIMALS, SUCKLING"/CT OR "ANIMALS, TRANSGENIC"/CT OR "ANIMALS, WILD"/CT OR "ANIMALS, ZOO"/CT OR "BULLOCKS (DRAFT

	ANIMALS)"/CT OR "CANINES (ANIMALS)"/CT OR "CONGENIC ANIMALS"/CT OR "CONTAMINATED ANIMALS"/CT OR "CRUELTY TO ANIMALS"/CT OR "DAMS (ANIMALS)"/CT OR "DOMESTIC ANIMALS"/CT OR "DOMESTICATED ANIMALS"/CT OR "EXOTIC ANIMALS"/CT OR "EXPERIMENTAL ANIMALS"/CT OR "FARM ANIMALS"/CT OR "FERAL ANIMALS"/CT OR "FOSSIL ANIMALS"/CT OR "GENETICALLY MODIFIED ANIMALS"/CT OR "ILLEGAL TRADE IN WILD ANIMALS"/CT OR "ILLEGAL TRADE OF WILD ANIMALS"/CT OR "ILLEGAL TRADING OF WILD ANIMALS"/CT OR "INBRED STRAINS ANIMALS"/CT OR "LABORATORY ANIMALS"/CT OR "MATURE ANIMALS"/CT OR "MYTHICAL ANIMALS"/CT OR "NON-NATIVE ANIMALS"/CT OR "OUTBRED STRAINS ANIMALS"/CT OR "PET ANIMALS"/CT OR "POISONOUS ANIMALS"/CT OR "POLLINATION BY ANIMALS"/CT OR "POLLUTED ANIMALS"/CT OR "SEX WITH ANIMALS"/CT OR "SUCKLING ANIMALS"/CT OR "TOXIC ANIMALS"/CT OR "TRANSGENIC ANIMALS"/CT OR "VENOMOUS ANIMALS"/CT OR "WILD ANIMALS"/CT OR "WORKING ANIMALS"/CT OR "ZOO ANIMALS"/CT) E ANIMAL+KT/CT
L16	QUE (ANIMAL/CT OR "AFRICAN ANIMAL TRYPANOSOMIASIS"/CT OR "AFRICAN ANIMAL TRYPANOSOMOSIS"/CT OR "DIO ANIMAL"/CT OR "MEAT ANIMAL RESEARCH CENTER-145 (MARC-145) CELL LINE"/CT OR "MEAT ANIMAL RESEARCH CENTER-145 (CELL LINE)"/CT OR "PHOLIDOTA (ANIMAL)"/CT OR "ABNORMAL ANIMAL BEHAVIOR"/CT OR "ABNORMAL BEHAVIOR (ANIMAL)"/CT OR "ADULT ANIMAL"/CT OR "ALPHA ANIMAL"/CT OR "ALTRICIAL ANIMAL"/CT OR "ANATOMY, ANIMAL"/CT OR "ANIMAL AFRICAN TRYPANOSOMIASIS"/CT OR "ANIMAL ABNORMAL BEHAVIOR"/CT OR "ANIMAL ABNORMAL BEHAVIOUR"/CT OR "ANIMAL ABUSE"/CT OR "ANIMAL ANAESTHESIA"/CT OR "ANIMAL ANATOMY"/CT OR "ANIMAL ANESTHESIA"/CT OR "ANIMAL ASSISTED THERAPY"/CT OR "ANIMAL BEHAVIOR"/CT OR "ANIMAL BEHAVIOR PROBLEM"/CT OR "ANIMAL BEHAVIORAL PROBLEM"/CT OR "ANIMAL BEHAVIOUR"/CT OR "ANIMAL BEHAVIOUR PROBLEM"/CT OR "ANIMAL BITE"/CT OR "ANIMAL BREEDING"/CT OR "ANIMAL CAGE"/CT OR "ANIMAL CARE"/CT OR "ANIMAL CARE COMMITTEES"/CT OR "ANIMAL CARE HOSPITAL"/CT OR "ANIMAL CARE TECHNICIAN"/CT OR "ANIMAL CARE TECHNICIANS"/CT OR "ANIMAL CASTE"/CT OR "ANIMAL CELL"/CT OR "ANIMAL CELL CULTURE"/CT OR "ANIMAL COLONY"/CT OR "ANIMAL COMFORT"/CT OR "ANIMAL COMMUNICATION"/CT OR "ANIMAL COMMUNITIES"/CT OR "ANIMAL COMMUNITY"/CT OR "ANIMAL CONIINE"/CT OR "ANIMAL CRUELTY"/CT OR "ANIMAL CULLING"/CT OR "ANIMAL DERIVED BIOABSORBABLE BONE MATRIX IMPLANT"/CT OR "ANIMAL DERIVED BONE MATRIX IMPLANT"/CT OR "ANIMAL DISEASE"/CT OR "ANIMAL DISEASE MODEL"/CT OR "ANIMAL DISEASE MODELS"/CT OR "ANIMAL DISEASES"/CT OR "ANIMAL DISPERSAL"/CT OR "ANIMAL DISTRIBUTION"/CT OR "ANIMAL DOCTOR"/CT OR "ANIMAL EMBRYO"/CT OR "ANIMAL EUTHANASIA"/CT OR "ANIMAL EXPERIMENT"/CT OR "ANIMAL EXPERIMENTATION"/CT OR "ANIMAL EXTRACT"/CT OR "ANIMAL EXTRACTS"/CT OR "ANIMAL FACILITATED THERAPY"/CT OR "ANIMAL FEED"/CT OR "ANIMAL FIBER"/CT OR "ANIMAL FIBRE"/CT OR "ANIMAL FIN"/CT OR "ANIMAL FINS"/CT OR "ANIMAL FLIGHT"/CT OR "ANIMAL FOOD"/CT OR "ANIMAL FUR"/CT OR "ANIMAL GENETICS"/CT OR "ANIMAL HEALTH"/CT OR "ANIMAL HEALTH AIDES"/CT OR "ANIMAL HEALTH ASSISTANT"/CT OR "ANIMAL HEALTH TECHNICIAN"/CT OR "
L17	SEA L12 NOT (L14 OR L15 OR L16)
L18	SEA L13 OR L17
L19	SEA L18 NOT CONFERENC?/DT

	ACT HTITLE/Q
L20-188	We entered the information about the records identified through MEDLINE searching and removed the overlaps with MEDLINE

Appendix Table 2. Quality assessment of included studies according to Newcastle-Ottawa Scale

First author, year	Newcastle-Ottawa Scale items for cohort studies								
	Selection			Comparability		Outcome			Stars
	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome was not present at start of study	Multivariate adjustment	Aerobic physical activity	Assessment of outcome	Length of follow-up	Adequacy of follow-up	
All-cause mortality									
Grøntved, 2012[19]	A*	C	A*	A*	A*	A*	A*	B*	7
Kamada, 2017[42]	A*	C	A*	A*	A*	A*	A*	A*	7
Stamatakis, 2018[20]	A*	C	A*	A*	A*	A*	A*	D	6
Liu, 2019[44]	A*	C	A*	A*	A*	A*	A*	C	6
Sheehan, 2020[18]	A*	B*	B	A*	A*	A*	A*	B*	7
Porter, 2020[49]	A*	B*	B	A*	A*	A*	A*	A*	7
Patel, 2020[48]	A*	C	A*	A*	A*	A*	A*	D	6
Zhao, 2020[51]	A*	B*	B	A*	-	A*	A*	D	5
CVD									
Grøntved, 2012[19]	A*	C	A*	A*	A*	A*	A*	B*	7
Kamada, 2017[42]	A*	C	A*	A*	A*	A*	A*	A*	7
Shiroma, 2017[43]	A*	C	A*	A*	A*	C	A*	A*	6
Stamatakis, 2018[20]	A*	C	A*	A*	A*	B*	A*	D	6
Liu, 2019[44]	A*	C	A*	A*	A*	A*	A*	C	6
Porter, 2019[46]	A*	B*	A*	A*	A*	B*	A*	D	7
Porter, 2020[49]	A*	B*	B	A*	A*	B*	A*	A*	7
Patel, 2020[48]	A*	C	A*	A*	A*	B*	A*	D	6
Zhao, 2020[51]	A*	B*	B	A*	-	A*	A*	D	5

Total cancer/site-specific cancers incidence									
Kamada, 2017[42]	A*	C	A*	A*	A*	A*	A*	A*	7
Stamatakis, 2018[20]	A*	C	A*	A*	A*	A*	A*	D	6
Siahpush, 2019[47]	A*	B*	B	A*	A*	A*	A*	B*	7
Mazzilli, 2019[45]	A*	C	A*	A*	A*	A*	A*	D	6
Porter, 2020[49]	A*	B*	B	A*	A*	A*	A*	A*	7
Patel, 2020[48]	A*	C	A*	A*	A*	A*	A*	D	6
Rezende, 2020[50]	A*	C	A*	A*	A*	A*	A*	B*	7
Zhao, 2020[51]	A*	B*	B	A*	-	A*	A*	D	5
Diabetes incidence									
Grøntved, 2012[19]	A*	C	A*	A*	A*	B	A*	B*	6
Grøntved, 2014[40]	A*	C	A*	A*	A*	B	A*	B*	6
Kuwahara, 2015[41]	A*	C	A*	B	A*	A*	A*	B*	6
Shiroma, 2017[43]	A*	C	A*	A*	A*	B	A*	A*	6
Mielke, 2020[17]	A*	C	A*	B	A*	B	A*	C	4

Quality Assessment

The quality of the studies was assessed using a modification of the Newcastle-Ottawa Scale (NOS) for quality assessment of prospective cohort studies.[22] We excluded the "representativeness of the exposed cohort" item of the original NOS because our quality assessment was planned to evaluate internal validity, not external validity. Therefore, 8 stars in total were achievable. HM and RK independently assessed the studies and resolved any inconsistencies through a discussion.

Criteria of quality assessment

1. Selection of the nonexposed cohort

A: Participants with and without muscle-strengthening activities were selected from the same source population. (*)
B: Participants with and without muscle-strengthening activities were not selected from the same source population.
C: No description.

2. Ascertainment of exposure

A: An objective method was used to assess muscle-strengthening activities. (*)
B: A structured interview was used to assess muscle-strengthening activities. (*)

C: A self-reported questionnaire was used to assess muscle-strengthening activities.
D: No description.

3. Demonstration that the outcome of interest was not present at the start of the study
A: Exclusion of participants with baseline cardiovascular diseases (both stroke or coronary heart disease) and/or cancer in analyses of all-cause mortality, participants with baseline cardiovascular diseases in analyses of cardiovascular disease mortality, participants with cancer in analyses of cancer mortality, and participants with baseline outcomes of interest in analyses of incidence of noncommunicable diseases. (*)
B: No exclusion of participants with the abovementioned outcomes.
C: No description.

4. Comparability of cohorts on the basis of the design or analysis
(1) Multivariate adjustment
A: The study adjusted for at least three of five covariates (smoking, alcohol consumption, diet, body composition, socioeconomic status) in addition to age, sex, and race/ethnicity, if relevant. (*)
B: The study did not adjust for these covariates.
(2) Aerobic physical activity
A: The study adjusted for aerobic physical activity. (*)
B: The study did not adjust for aerobic physical activity.

5. Assessment of outcome
A: Patient registers or death certificates for mortality and clinical assessment, medical records, or record linkage for incidence. (*)
B: Self-report.
C: No description.

6. Length of follow-up
A: The follow-up period was a mean/median of ≥5 years. (*)
B: The follow-up period was <5 years.

7. Adequacy of follow-up of cohorts
A: Participants were completely (≥99%) followed up. (*)
B: Approximately ≥80% of the participants were followed up or the description of participants lost to follow-up indicated that bias was unlikely to have been introduced. (*)
C: Less than 80% of the participants were followed up.
D: No description.

Reference
22 Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2009. Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp accessed January 5th, 2021.

Appendix Table 3. GRADE evidence profiles for the association of muscle-strengthening activities and the risk of mortality and noncommunicable disease

Grading the evidence

The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach was used to assess the overall certainty of evidence for outcomes with results from two or more studies.[33] GRADE assesses the evidence as very low, low, moderate, or high quality. One reviewer (HM) assessed the certainty of evidence, whereas two reviewers (RK and TH) examined and revised the certainty of assessments, as necessary. The certainty of evidence starts at a low level because of the inherent limitations of observational studies. The downgraded criteria included risk of bias (weight of studies showing a risk of bias according to a low NOS [<6]), inconsistency (similarity of point estimates, extent of overlap of confidence intervals [CIs], same direction of effects, I^2≥50%, and p<0.10),[34] indirectness (presence of factors that limit the generalizability of the results),[35] imprecision,[36] and publication bias.[37] On the basis of the literature,[36] we considered the optimal information size to be 400 cases and 4000 participants with a 25% relative risk (RR) reduction. If the optimal information size criterion was not met, the evidence was downgraded for imprecision.[36] We also downgraded for imprecision when the optimal information size criterion was met but the 95% CI included 1.00 and the upper and lower bounds of 95% CI were <0.75 and >1.25, respectively.[36] The upgraded criteria included a large magnitude of effect (RR>2 or RR<0.5 in the absence of plausible confounders), dose-response gradient, or opposing residual confounding.[38] A GRADE evidence profile was developed.[39]

Certainty assessment								Summary of findings			Certainty
								No. of participants		Effect	
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Other considerations	Participants	Cases	Relative (95% CI)	
All-cause mortality											
7	Observational studies	Not serious	Not serious[a]	Serious[b]	Not serious	NA[c]	NA	263 058	42 133	0.85 (0.79 to 0.93)	⨁◯◯◯ VERY LOW
Cardiovascular diseases											
7	Observational studies	Not serious	Not serious[a]	Serious[b]	Not serious	NA[c]	NA	257 888	16 056	0.83 (0.73 to 0.93)	⨁◯◯◯ VERY LOW
Total cancer											
6	Observational studies	Not serious	Not serious[a]	Serious[b]	Not serious	NA[c]	NA	540 543	21 253	0.88 (0.80 to 0.97)	⨁◯◯◯ VERY LOW
Diabetes incidence											
5	Observational studies	Not serious	Not serious	Not serious	Not serious	NA[c]	Dose-response gradient[d]	202 486	9548	0.83 (0.77 to 0.89)	⨁⨁◯◯ LOW
Colon cancer incidence											

Certainty assessment								Summary of findings			Certainty
								No. of participants		Effect	
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Other considerations	Participants	Cases	Relative (95% CI)	
2	Observational studies	Not serious	Not serious	Serious[b]	Not serious	NA[c]	NA	248 909	2415	0.96 (0.91 to 1.01)	⨁◯◯◯ VERY LOW
Kidney cancer incidence											
2	Observational studies	Not serious	Not serious	Serious[b]	Serious[e]	NA[c]	NA	248 909	1063	0.88 (0.76 to 1.02)	⨁◯◯◯ VERY LOW
Bladder cancer incidence											
2	Observational studies	Not serious	Not serious	Serious[b]	Not serious	NA[c]	NA	248 909	2341	0.94 (0.84 to 1.05)	⨁◯◯◯ VERY LOW
Lung cancer incidence											
2	Observational studies	Not serious	Not serious	Serious[b]	Not serious	NA[c]	Dose-response gradient[n]	248 909	4075	0.90 (0.83 to 0.98)	⨁◯◯◯ VERY LOW
Pancreatic cancer incidence											
2	Observational studies	Not serious	Not serious	Serious[b]	Serious[e]	NA[c]	NA	248 909	1028	1.12 (0.98 to 1.28)	⨁◯◯◯ VERY LOW

CI: Confidence interval
[a] Despite the high I^2 and $p<0.10$ judged as not serious because of the overlapping CI and same direction of effects in the forest plots
[b] Downgraded by one level because all studies were conducted in Western countries, especially in USA
[c] Publication bias could not be assessed due to limited number of studies
[d] Not upgraded despite the dose-response gradient because publication bias could not be assessed
[e] Serious imprecision because optimal information size was not met
[f] Serious imprecision because the 95% CI include the null value (1.00) and the upper bound=1.25, although optimal information size met (cases=1028, participants=248 909)

Reference

33 Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol 2011;64(4):383-94. doi: 10.1016/j.jclinepi.2010.04.026
34 Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines: 7. Rating the quality of evidence--inconsistency. J Clin Epidemiol 2011;64(12):1294-302. doi: 10.1016/j.jclinepi.2011.03.017

35 Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines: 8. Rating the quality of evidence--indirectness. J Clin Epidemiol 2011;64(12):1303-10. doi: 10.1016/j.jclinepi.2011.04.014
36 Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines 6. Rating the quality of evidence--imprecision. J Clin Epidemiol 2011;64(12):1283-93. doi: 10.1016/j.jclinepi.2011.01.012
37 Guyatt GH, Oxman AD, Montori V, et al. GRADE guidelines: 5. Rating the quality of evidence--publication bias. J Clin Epidemiol 2011;64(12):1277-82. doi: 10.1016/j.jclinepi.2011.01.011
38 Guyatt GH, Oxman AD, Sultan S, et al. GRADE guidelines: 9. Rating up the quality of evidence. J Clin Epidemiol 2011;64(12):1311-6. doi: 10.1016/j.jclinepi.2011.06.004
39 Guyatt GH, Oxman AD, Santesso N, et al. GRADE guidelines: 12. Preparing summary of findings tables-binary outcomes. J Clin Epidemiol 2013;66(2):158-72. doi: 10.1016/j.jclinepi.2012.01.012

Appendix Table 4. Outcomes excluded from our meta-analysis

First author, year	Country; Cohort	Participants characteristics	Outcome; Case ascertainment; Case/Participants	Follow-up	Exposure measurement	Exposure category	Effect estimates	Covariates	Quality assessment
Chronic lower respiratory tract diseases mortality									
Zhao, 2020[51]	USA; NHIS	Men and women; ≥18 years	Chronic lower respiratory tract diseases mortality; NDI; 3188/479 856	8.75 years (median)	Interview	Neither guideline Aerobic only Strength only Both guideline	1 0.42 (0.37 to 0.47) 0.76 (0.62 to 0.93) 0.29 (0.23 to 0.37)	Sex, age, race/ethnicity, education, marital status, BMI, smoking status, alcohol intake, and chronic conditions (hypertension, heart disease, stroke, cancer, and diabetes)	5
Accidents and injuries mortality									
Zhao, 2020[51]	USA; NHIS	Men and women; ≥18 years	Accidents and injuries mortality; NDI; 2477/479 856	8.75 years (median)	Interview	Neither guideline Aerobic only Strength only Both guideline	1 0.82 (0.73 to 0.93) 1.08 (0.87 to 1.35) 0.71 (0.60 to 0.84)	Sex, age, race/ethnicity, education, marital status, BMI, smoking status, alcohol intake, and chronic conditions (hypertension, heart disease, stroke, cancer, and diabetes)	5
Alzheimer's disease mortality									
Zhao, 2020[51]	USA; NHIS	Men and women; ≥18 years	Alzheimer's disease mortality; NDI; 1470/479 856	8.75 years (median)	Interview	Neither guideline Aerobic only Strength only Both guideline	1 0.74 (0.62 to 0.87) 0.88 (0.64 to 1.23) 0.64 (0.48 to 0.86)	Sex, age, race/ethnicity, education, marital status, BMI, smoking status, alcohol intake, and chronic conditions (hypertension, heart disease, stroke, cancer, and diabetes)	5
Diabetes mellitus mortality									
Zhao, 2020[51]	USA; NHIS	Men and women; ≥18 years	Diabetes mellitus mortality; NDI; 1803/479 856	8.75 years (median)	Interview	Neither guideline Aerobic only Strength only Both guideline	1 0.63 (0.53 to 0.74) 0.96 (0.73 to 1.27) 0.47 (0.36 to 0.62)	Sex, age, race/ethnicity, education, marital status, BMI, smoking status, alcohol intake, and chronic conditions (hypertension, heart disease, stroke, cancer, and diabetes)	5
Influenza and pneumonia mortality									
Zhao, 2020[51]	USA; NHIS	Men and women; ≥18 years	Influenza and pneumonia mortality; NDI; 1135/479 856	8.75 years (median)	Interview	Neither guideline Aerobic only Strength only Both guideline	1 0.55 (0.44 to 0.68) 0.87 (0.62 to 1.24) 0.46 (0.32 to 0.64)	Sex, age, race/ethnicity, education, marital status, BMI, smoking status, alcohol intake, and chronic conditions (hypertension, heart disease, stroke, cancer, and diabetes)	5

First author, year	Country; Cohort	Participants characteristics	Outcome; Case ascertainment; Case/Participants	Follow-up	Exposure measurement	Exposure category	Effect estimates	Covariates	Quality assessment
Nephritis, nephrotic syndrome, or nephrosis mortality									
Zhao, 2020[51]	USA; NHIS	Men and women; ≥18 years	Nephritis, nephrotic syndrome, or nephrosis mortality; NDI; 1129/479 856	8.75 years (median)	Interview	Neither guideline Aerobic only Strength only Both guideline	1 0.48 (0.40 to 0.59 0.71 (0.50 to 1.01) 0.52 (0.36 to 0.76)	Sex, age, race/ethnicity, education, marital status, BMI, smoking status, alcohol intake, and chronic conditions (hypertension, heart disease, stroke, cancer, and diabetes)	5
Other cause-specific mortality									
Hsu, 2018[21]	Australia; CHAMP	Men; ≥70 years (mean 77 years)	Cancer mortality; New South Wales Registry of Births, Deaths, and Marriages; -/958	7 years (median)	Questionnaire	No Yes	1 -	Age, comorbidity, smoking status, alcohol, BMI, ethnicity, education, diabetes, health-related quality of life, activities of daily living disability, depression, and PASE score	5
Breast cancer incidence									
Mazzilli, 2019[45]	USA, NIH-AARP DHS	Men and women; 50-71 years	Breast cancer; Cancer registries; 3288/215 122	10 years (max)	Questionnaire	None 5-90 min/week ≥120 min/week	1 1.02 (0.93 to 1.11) 0.99 (0.83 to 1.17)	Age, sex, BMI, smoking status, race, education, alcohol intake, MVPA not including weight lifting, oral birth control use, age of menarche, age of menopause, postmenopausal hormone use, and parity	6
Lymphoma incidence									
Mazzilli, 2019[45]	USA, NIH-AARP DHS	Men and women; 50-71 years	Non-Hodgkin's lymphoma; Cancer registries; 1187/215 122	10 years (max)	Questionnaire	None 5-90 min/week ≥120 min/week	1 0.90 (0.78 to 1.05) 0.96 (0.75 to 1.23)	Age, sex, BMI, smoking status, race, education, alcohol intake, and MVPA not including weight lifting	6

First author, year	Country; Cohort	Participants characteristics	Outcome; Case ascertainment; Case/Participants	Follow-up	Exposure measurement	Exposure category	Effect estimates	Covariates	Quality assessment
Rezende, 2020[50]	USA, HPSF	Men; 40-75 years (mean 67.5 years)	Lymphoma; Self-reported cancer diagnosis confirmed from medical records or NDI; 484/33 787	24 years (max)	Questionnaire	None 1-59 min/week ≥60 min/week	1 1.02 (0.81 to 1.29) 1.08 (0.79 to 1.50)	Race, height, family history of cancer, physical exam in past two years, history of colonoscopy or sigmoidoscopy, smoking in pack years, regular aspirin use, multivitamin use, alcohol consumption, red and processed meat intake, Alternate Healthy Eating Index, prostate-specific antigen test in past 2 years, total physical activity except for resistance training, total energy intake, and BMI	7
Prostate cancer incidence									
Mazzilli, 2019[45]	USA, NIH-AARP DHS	Men and women; 50-71 years	Prostate cancer; Cancer registries; 7213/215 122	10 years (max)	Questionnaire	None 5-90 min/week ≥120 min/week	1 1.03 (0.97 to 1.09) 1.05 (0.96 to 1.15)	Age, sex, BMI, smoking status, race, education, alcohol intake, and MVPA not including weight lifting	6
Rezende, 2020[50]	USA, HPSF	Men; 40-75 years (mean 67.5 years)	Advanced prostate cancer; Self-reported cancer diagnosis confirmed from medical records or NDI; 657/33 787	24 years (max)	Questionnaire	None 1-59 min/week ≥60 min/week	1 0.96 (0.77 to 1.20) 0.89 (0.66 to 1.19)	Race, height, family history of cancer, physical exam in past two years, history of colonoscopy or sigmoidoscopy, smoking in pack years, regular aspirin use, multivitamin use, alcohol consumption, red and processed meat intake, Alternate Healthy Eating Index, prostate-specific antigen test in past 2 years, total physical activity except for resistance training, total energy intake, and BMI	7
Rectum cancer incidence									
Mazzilli, 2019[45]	USA, NIH-AARP DHS	Men and women; 50-71 years	Rectum cancer; Cancer registries; 527/215 122	10 years (max)	Questionnaire	None 5-90 min/week ≥120 min/week	1 0.68 (0.52 to 0.88) 1.01 (0.69 to 1.48)	Age, sex, BMI, smoking status, race, education, alcohol intake, and MVPA not including weight lifting	6
Melanoma incidence									

First author, year	Country; Cohort	Participants characteristics	Outcome; Case ascertainment; Case/Participants	Follow-up	Exposure measurement	Exposure category	Effect estimates	Covariates	Quality assessment
Mazzilli, 2019[45]	USA, NIH-AARP DHS	Men and women; 50-71 years	Melanoma; Cancer registries; 2454/215 122	10 years (max)	Questionnaire	None 5-90 min/week ≥120 min/week	1 1.18 (1.07 to 1.30) 1.03 (0.88 to 1.20)	Age, sex, BMI, smoking status, race, education, alcohol intake, and MVPA not including weight lifting	6
Leukemia incidence									
Rezende, 2020[50]	USA, HPSF	Men; 40-75 years (mean 67.5 years)	Leukemia; Self-reported cancer diagnosis confirmed from medical records or NDI; 188/33 787	24 years (max)	Questionnaire	None 1-59 min/week ≥60 min/week	1 0.81 (0.55 to 1.19) 1.00 (0.59 to 1.70)	Race, height, family history of cancer, physical exam in past two years, history of colonoscopy or sigmoidoscopy, smoking in pack years, regular aspirin use, multivitamin use, alcohol consumption, red and processed meat intake, Alternate Healthy Eating Index, prostate-specific antigen test in past 2 years, total physical activity except for resistance training, total energy intake, and BMI	7
Multiple myeloma incidence									
Rezende, 2020[50]	USA, HPSF	Men; 40-75 years (mean 67.5 years)	Multiple myeloma; Self-reported cancer diagnosis confirmed from medical records or NDI; 112/33 787	24 years (max)	Questionnaire	None 1-59 min/week ≥60 min/week	1 0.99 (0.61 to 1.60) 0.93 (0.46 to 1.89)	Race, height, family history of cancer, physical exam in past two years, history of colonoscopy or sigmoidoscopy, smoking in pack years, regular aspirin use, multivitamin use, alcohol consumption, red and processed meat intake, Alternate Healthy Eating Index, prostate-specific antigen test in past 2 years, total physical activity except for resistance training, total energy intake, and BMI	7
Oesophageal cancer incidence									

First author, year	Country; Cohort	Participants characteristics	Outcome; Case ascertainment; Case/Participants	Follow-up	Exposure measurement	Exposure category	Effect estimates	Covariates	Quality assessment
Rezende, 2020[50]	USA, HPSF	Men; 40-75 years (mean 67.5 years)	Oesophageal cancer; Self-reported cancer diagnosis confirmed from medical records or NDI; 103/33787	24 years (max)	Questionnaire	None 1-59 min/week ≥60 min/week	1 1.27 (0.77 to 2.09) 0.71 (0.30 to 1.72)	Race, height, family history of cancer, physical exam in past two years, history of colonoscopy or sigmoidoscopy, smoking in pack years, regular aspirin use, multivitamin use, alcohol consumption, red and processed meat intake, Alternate Healthy Eating Index, prostate-specific antigen test in past 2 years, total physical activity except for resistance training, total energy intake, and BMI	7
Ovarian cancer									
Buras, 2021[62]	USA, NHS and NHSII	Women; NHS: 30-50 years (mean 65.8 years), NHSII: 25-42 years (mean 46.4 years)	Ovarian cancer. Self-report cancer diagnosis or linkage to the NDI confirmed from review of medical records, including pathology reports, or linkage to the relevant cancer registry; 609/109 294	-	Questionnaire	0 min/week 1-59 min/week ≥60 min/week	1 1.14 (0.93 to 1.39) 0.95 (0.74 to 1.22)	age, calendar year, cohort (NHS and NHSII), BMI, oral contraceptive use, parity, family history of breast or ovarian cancer, menopausal status, smoking, hormone therapy use, tubal ligation, hysterectomy, and other physical activity	6
Hypertension incidence									
Mielke, 2020[17]	Australia; HABITAT	Men and women; 40-65 years	Hypertension; Self-reported hypertension diagnosis; 1028/8784	6 years (max)	Questionnaire	None <1 time/week ≥1 time/week	1 0.89 (0.75 to 1.05) 0.82 (0.70 to 0.97)	Sex, age, education, annual income, living arrangements, cigarette smoking status, physical activity, diabetes, and obesity	4
Hypercholesteremia incidence									

First author, year	Country; Cohort	Participants characteristics	Outcome; Case ascertainment; Case/Participants	Follow-up	Exposure measurement	Exposure category	Effect estimates	Covariates	Quality assessment
Bakker, 2018[61]	USA; ACLS	Men and Women; 18-83 years (mean 43 years)	Hypercholesteremia (NCEP-ATPIII); Clinical assessment; 1430/7317	4 years (median)	Questionnaire	No Yes	1 0.86 (0.76 to 0.98)	Age, examination year, BMI, current smoking, heavy alcohol drinking, abnormalities on electrocardiography, systolic and diastolic blood pressure, parental history of hypercholesterolemia, and aerobic exercise* *Excluded from the joint analysis.	5
						0 min/week 1-59 min/week 60-119 min/week 120-179 min/week ≥180 min/week	1 0.68 (0.54 to 0.86) 0.93 (0.78 to 1.12) 0.86 (0.67 to 1.11) 0.98 (0.77 to 1.24)		
						0 time/week 1 time/week 2 times/week 3 times/week 4 times/week ≥5 times/week	1 0.77 (0.49 to 1.20) 0.69 (0.54 to 0.88) 0.93 (0.79 to 1.10) 0.84 (0.63 to 1.12) 1.02 (0.74 to 1.39)		
						Aerobic exercise (<500 MET• min/week) & Resistance training (<2 days/week) Aerobic exercise (≥500 MET-min/week) & Resistance training (<2 days/week) Aerobic exercise (<500 MET-min/week) & Resistance training (≥2 days/week) Aerobic exercise (≥500 MET-min/week) & Resistance training (≥2 days/week)	1 0.89 (0.79 to 1.01) 0.82 (0.62 to 1.09) 0.79 (0.68 to 0.91)		
Metabolic syndrome incidence									

First author, year	Country; Cohort	Participants characteristics	Outcome; Case ascertainment; Case/Participants	Follow-up	Exposure measurement	Exposure category	Effect estimates	Covariates	Quality assessment
Bakker, 2017[60]	USA; ACLS	Men and women; (mean 46 years)	Metabolic syndrome (NCEP-ATPIII); Clinical assessment; 1147/7418	4 years (median)	Questionnaire	No Yes	1 0.83 (0.72 to 0.95)	Age, sex, examination year, BMI, current smoking, heavy alcohol drinking, abnormal electrocardiographic findings, parental history of cardiovascular disease, hypertension and diabetes, and aerobic exercise* *Excluded from the joint analysis.	5
						0 min/week 1-59 min/week 60-119 min/week 120-179 min/week ≥180 min/week	1 0.71 (0.56 to 0.89) 0.96 (0.80 to 1.16) 0.81 (0.61 to 1.07) 0.78 (0.60 to 1.02)		
						0 time/week 1 time/week 2 times/week 3 times/week 4 times/week ≥5 times/week	1 0.83 (0.54 to 1.27) 0.84 (0.67 to 1.06) 0.88 (0.74 to 1.05) 0.62 (0.44 to 0.89) 0.81 (0.56 to 1.16)		
						Aerobic exercise (<500 MET-min/week) & Resistance training (<2 days/week) Aerobic exercise (≥500 MET-min/week) & Resistance training (<2 days/week) Aerobic exercise (<500 MET-min/week) & Resistance training (≥2 days/week) Aerobic exercise (≥500 MET-min/week) & Resistance training (≥2 days/week)	1 0.93 0.87 0.75 (0.63 to 0.89)		

ACLS, Aerobics Center Longitudinal Study; BMI, body mass index; CHAMP, Concord Health and Aging in Men Project; HABITAT, how areas in Brisbane Influence health and activity; MVPA, moderate-to-vigorous physical activity; NCEP-ATPIII, National Cholesterol Education Program- the third revision of the Adult Treatment Panel III; NDI, national death index; NHIS, National Health Interview Survey; NHS, Nurses' Health Study; NHSII, Nurses' Health Study II; NIH-AARP DHS, National Institutes of Health-American Association for Retired Persons Diet and Health Study

Appendix Table 5. List of publications excluded from meta-analysis because of multiple publication from the same cohort

Reference	Main reason for exclusion
All-cause mortality	
NHANES (**Porter et al. 2020[49] included**)	
Zhao et al. 2014[54]	Older publication year.
Loprinzi et al. 2015[55]	Older publication year.
Dankel et al. 2016 (a)[56]	Older publication year.
Dankel et al. 2016 (b)[57]	Older publication year.
Evenson et al. 2016[58]	Older publication year. Not adjusted for other physical activities.
NHIS (**Sheehan et al. 2020[18] included**)	
Schoenborn et al. 2011[53]	Older publication year.
Kraschnewski et al. 2016[59]	Older publication year.
CVD	
NHANES (**Porter et al. 2020[49] included**)	
Zhao et al. 2014[54]	Older publication year.
Loprinzi et al. 2015[55]	Older publication year.
Dankel et al. 2016 (a)[56]	Older publication year.
Evenson et al. 2016[58]	Older publication year. Not adjusted for other physical activities.
HPFS (**Grøntved et al. 2012[19] included**)	
Tanasescu et al. 2002[52]	Older publication year.

CVD, cardiovascular diseases; HPFS, Health Professionals Follow-Up Study; NHIS, National Health Interview Survey; NHANES, National Health and Nutrition Examination Survey

Appendix Table 6. Characteristics of the studies included in the meta-analysis

First author, year	Country; Cohort	Participants characteristics	Outcome; Case ascertainment; Case/Participants	Follow-up	Exposure measurement	Exposure category	Effect estimates	Covariates	Quality assessment
All-cause mortality									
Grøntved, 2012[19]	USA; HPFS	Men; 40-75 years	All-cause mortality; NDI, next of kin, or postal authorities; 6251/32 002	18 years (max)	Questionnaire	0 min/week 1-59 min/week 60-149 min/week ≥150 min/week	1 0.88 (0.83 to 0.94) 1.04 (0.93 to 1.17) 1.11 (0.90 to 1.37) (personal communication)	Age, smoking, alcohol consumption, coffee intake, race, family history of diabetes, intake of total energy, trans fat, polyunsaturated fat to saturated fat ratio, cereal fiber, whole grain, glycemic load, aerobic exercise, other physical activity of at least moderate intensity, and television viewing	7
Kamada, 2017[42]	USA; WHS	Women; ≥45 years (mean 62.2 years)	All-cause mortality; Family members, postal authorities medical records, death certificates, or NDI; 3055/28 879	12 years (mean)	Questionnaire	0 min/week 1-19 min/week 20-59 min/week 60-149 min/week ≥150 min/week Aerobic MVPA (<150 min/week) & No strength training Aerobic MVPA (≥150 min/week) & No strength training Aerobic MVPA (<150 min/week) & Any strength training Aerobic MVPA (≥150 min/week) & Any strength training	1 0.73 (0.65 to 0.82) 0.71 (0.62 to 0.82) 0.81 (0.67 to 0.97) 1.10 (0.77 to 1.56) 1 0.71 (0.64 to 0.79) 0.74 (0.65 to 0.85) 0.54 (0.47 to 0.61)	Age, trial randomization, race, education, postmenopausal status, hormone use, smoking status, parental history of myocardial infarction or cancer, alcohol intake, energy intake, saturated fat intake, fiber intake, fruit and vegetable intake, physical examination for screening, time per week spent in aerobic MVPA*, BMI, incidence of hypertension, high cholesterol, cardiovascular diseases, diabetes mellitus, and cancer before and during follow-up. *Excluded from the joint analysis.	7

First author, year	Country; Cohort	Participants characteristics	Outcome; Case ascertainment; Case/Participants	Follow-up	Exposure measurement	Exposure category	Effect estimates	Covariates	Quality assessment
Stamatakis, 2018[20]	England and Scotland; HSE and SHS	Men and women; ≥30 years (mean 45.6 years)	All-cause mortality; National Health Service Central Register; 5763/72 459	9.2 years (mean)	Questionnaire	No Yes None <66.0 min/week (women) and <52.5 min/week (men) ≥66.0 min/week (women) and ≥52.5 min/week (men) Neither guideline Aerobic only Strength only Both guideline	1 0.77 (0.69 to 0.87) 1 0.81 (0.69 to 0.95) 0.75 (0.64 to 0.88) 1 0.84 (0.78 to 0.90) 0.79 (0.66 to 0.94) 0.71 (0.57 to 0.87)	Age, sex, long-standing illness, alcohol consumption, psychological distress, BMI, smoking status, educational level, and weekly volume of other physical activity* *Total volume of physical activity was alternatively included in the joint analysis	6
Liu, 2019[44]	USA; ACLS	Men and women; 18-89 years (mean 47 years)	All-cause mortality; NDI; 276/12 591	10.5 years (mean)	Questionnaire	0 min/week 1-59 min/week 60-119 min/week ≥120 min/week 0 time/week 1 time/week 2 times/week 3 times/week ≥4 times/week	1 0.64 (0.47 to 0.88) 0.84 (0.53 to 1.34) 1.03 (0.59 to 1.80) 1 0.65 (0.44 to 0.97) 0.68 (0.46 to 1.01) 0.67 (0.40 to 1.11) 1.29 (0.75 to 2.20)	Baseline examination year, age, sex, smoking status, alcohol consumption, parental history of CVD, BMI, aerobic exercise, hypertension, diabetes, and hypercholesterolemia	6
Sheehan, 2020[18]	USA; NHIS	Men and women; 18-84 years (mean 43.1 years)	All-cause mortality; National vital death registry (NHIS-LMF); 4955/26 727	17 years (max)	Interview	No Yes	1 0.95 (0.85 to 1.07)	Age, sex, nativity status, census region of residence, marital status, race/ethnicity, educational attainment, household income, home ownership, smoking, drinking alcohol, BMI, self-reported health status, physical handicap, health condition, and other exercise types	7
Porter, 2020[49]	USA; NHANES	Men and women; ≥20 years (mean 46.3 years)	All-cause mortality; NDI; 3799/17 938	11.9 years (median)	Interview	No Yes 0 min/week 1-59 min/week ≥60 min/week	1 0.89 (0.67 to 1.17) 1 0.75 (0.49 to 1.16) 0.98 (0.68 to 1.40)	Other leisure-time activities, age, gender, race, education, cigarette use, heavy alcohol consumption, BMI, household activity, transportation activity, and history of diabetes, arthritis, cancer, disability, and CVD	7

First author, year	Country; Cohort	Participants characteristics	Outcome; Case ascertainment; Case/Participants	Follow-up	Exposure measurement	Exposure category	Effect estimates	Covariates	Quality assessment
Patel, 2020[48]	USA; CPS-IINC	Men and women; 59-83 years (mean 70.2 years)	All-cause mortality; NDI; 18 034/72 462	13 years (max)	Questionnaire	0 min/week 1-59 min/week 60-119 min/week ≥120 min/week	1 0.88 (0.82 to 0.94) 0.90 (0.84 to 0.97) 1.01 (0.93 to 1.09)	Sex, age, BMI, survey type, education, self-reported overall health, smoking duration and intensity, alcohol use, marital status, work status, TV sitting time, aspirin use, and comorbidity score (reported personal history of high blood pressure, type 2 diabetes, and high cholesterol), and MVPA	6
Zhao, 2020[51]	USA; NHIS	Men and women; ≥18 years	All-cause mortality; NDI; 59 819/479 856	8.75 years (median)	Interview	Neither guideline Aerobic only Strength only Both guideline	1 0.71 (0.69 to 0.72) 0.89 (0.85 to 0.94) 0.60 (0.57 to 0.62)	Sex, age, race/ethnicity, education, marital status, BMI, smoking status, alcohol intake, and chronic conditions (hypertension, heart disease, stroke, cancer, and diabetes)	5
CVD									
Grøntved, 2012[19]	USA; HPFS	Men; 40-75 years	CVD mortality; NDI, next of kin, or postal authorities; 1901/32 002	18 years (max)	Questionnaire	0 min/week 1-59 min/week 60-149 min/week ≥150 min/week	1 0.90 (0.80 to 1.01) 1.00 (0.80 to 1.26) 0.98 (0.63 to 1.51) (personal communication)	Age, smoking, alcohol consumption, coffee intake, race, family history of diabetes, intake of total energy, trans fat, polyunsaturated fat to saturated fat ratio, cereal fiber, whole grain, glycemic load, aerobic exercise, other physical activity of at least moderate intensity, and television viewing	7

First author, year	Country; Cohort	Participants characteristics	Outcome; Case ascertainment; Case/Participants	Follow-up	Exposure measurement	Exposure category	Effect estimates	Covariates	Quality assessment
Kamada, 2017[42]	USA; WHS	Women; ≥45 years (mean 62.2 years)	CVD mortality; Family members, postal authorities medical records, death certificates, or NDI; 411/28 879	12 years (mean)	Questionnaire	Aerobic MVPA (<150 min/week) & No strength training Aerobic MVPA (≥150 min/week) & No strength training Aerobic MVPA (<150 min/week) & Any strength training Aerobic MVPA (≥150 min/week) & Any strength training	1 0.74 (0.56 to 0.98) 0.75 (0.53 to 1.07) 0.43 (0.29 to 0.63)	Age, trial randomization, race, education, postmenopausal status, hormone use, smoking status, parental history of myocardial infarction or cancer, alcohol intake, energy intake, saturated fat intake, fiber intake, fruit and vegetable intake, physical examination for screening, BMI, incidence of hypertension, high cholesterol, cardiovascular diseases, diabetes mellitus, and cancer before and during follow-up	7
Shiroma, 2017[43]	USA, WHS	Women; 47-97.8 years (mean 62.6 years)	CVD incidence or mortality; Annual follow-up questionnaires and medical records; 1742/35 754	10.7 years (mean)	Questionnaire	0 min/week 1-19 min/week 20-59 min/week 60-119 min/week ≥120 min/week	1 0.82 (0.64 to 1.06) 0.94 (0.73 to 1.21) 0.76 (0.59 to 0.98) 0.97 (0.70 to 1.33)	Age, smoking status, dietary habits, alcohol intake, postmenopausal status, hormone use, parental history of myocardial infarction, trial randomization, time per week spent in lower-intensity activities and aerobic activities, and BMI	6
Stamatakis, 2018[20]	England and Scotland; HSE and SHS	Men and women; ≥30 years (mean 45.6 years)	CVD mortality; National Health Service Central Register; 1723/73 937	9.2 years (mean)	Questionnaire	No Yes None <66.0 min/week (women) and <52.5 min/week (men) ≥66.0 min/week (women) and ≥52.5 min/week (men) Neither guideline Aerobic only Strength only Both guideline	1 0.88 (0.71 to 1.08) 1 0.89 (0.67 to 1.19) 0.86 (0.65 to 1.14) 1 0.78 (0.68 to 0.90) 0.89 (0.65 to 1.14) 0.77 (0.53 to 1.14) (personal communication)	Age, sex, long-standing illness, alcohol consumption, psychological distress, BMI, smoking status, educational level, and weekly volume of other physical activity *Total volume of physical activity was alternatively included in the joint analysis	6

First author, year	Country; Cohort	Participants characteristics	Outcome; Case ascertainment; Case/Participants	Follow-up	Exposure measurement	Exposure category	Effect estimates	Covariates	Quality assessment
Liu, 2019[44]	USA; ACLS	Men and women; 18-89 years (mean 47 years)	CVD mortality or CVD morbidity; NDI for CVD mortality and mail-back health surveys for CVD morbidity; 127/12 591	10.5 years (mean)	Questionnaire	0 min/week 1-59 min/week 60-119 min/week ≥120 min/week 0 time/week 1 time/week 2 times/week 3 times/week ≥4 times/week	1 0.35 (0.24 to 0.51) 0.63 (0.39 to 1.03) 0.93 (0.51 to 1.68) 1 0.28 (0.17 to 0.46) 0.46 (0.29 to 0.70) 0.57 (0.33 to 0.96) 1.33 (0.75 to 2.36)	Baseline examination year, age, sex, smoking status, alcohol consumption, parental history of CVD, BMI, aerobic exercise, hypertension, diabetes, and hypercholesterolemia	6
Porter, 2019[46]	USA, ARICS	Men and women; 45-64 years (mean 54 years)	CVD incidence or mortality; Annual interviews, study visits, and community-wide surveillance of hospitalization discharge listings; 3966/13 204	25.2 years (median)	Interviewer-administered questionnaire	No Yes	1 0.81 (0.62 to 1.02)	Marital status, income, race by study site, smoking, alcohol, education, age*sex, TV watching, BMI, active transportation, and total sport/exercise minutes/week minus minutes/week for weight training	7
Porter, 2020[49]	USA; NHANES	Men and women; ≥20 years (mean 46.3 years)	CVD mortality; NDI; 827/17 938	11.9 years (median)	Interview	No Yes	1 0.53 (0.21 to 1.29)	Other leisure-time activities, age, gender, race, education, cigarette use, heavy alcohol consumption, BMI, household activity, transportation activity, and history of diabetes, arthritis, cancer, disability, and CVD	7
Patel, 2020[48]	USA; CPS-IINC	Men and women; 59-83 years (mean 70.2 years)	CVD mortality; NDI; 5770/72 462	13 years (max)	Questionnaire	0 min/week 1-59 min/week 60-119 min/week ≥120 min/week	1 0.81 (0.71 to 0.92) 0.98 (0.86 to 1.10) 1.03 (0.90 to 1.19)	Sex, age, BMI, survey type, education, self-reported overall health, smoking duration and intensity, alcohol use, marital status, work status, TV sitting time, aspirin use, and comorbidity score (reported personal history of high blood pressure, type 2 diabetes, and high cholesterol), and MVPA	6

First author, year	Country; Cohort	Participants characteristics	Outcome; Case ascertainment; Case/Participants	Follow-up	Exposure measurement	Exposure category	Effect estimates	Covariates	Quality assessment
Zhao, 2020[51]	USA; NHIS	Men and women; ≥18 years	CVD mortality; NDI; 13 509/479 856	8.75 years (median)	Interview	Neither guideline Aerobic only Strength only Both guideline	1 0.65 (0.62 to 0.69) 0.82 (0.74 to 0.92) 0.50 (0.46 to 0.56)	Sex, age, race/ethnicity, education, marital status, BMI, smoking status, alcohol intake, and chronic conditions (hypertension, heart disease, stroke, cancer, and diabetes)	5
Total cancer									
Kamada, 2017[42]	USA; WHS	Women; ≥45 years (mean 62.2 years)	Cancer mortality; Family members, postal authorities medical records, death certificates, or NDI; 748/28 879	12 years (mean)	Questionnaire	0 min/week 1-59 min/week ≥60 min/week Aerobic MVPA (<150 min/week) & No strength training Aerobic MVPA (≥150 min/week) & No strength training Aerobic MVPA (<150 min/week) & Any strength training Aerobic MVPA (≥150 min/week) & Any strength training	1 0.87 (0.73 to 1.05) 0.92 (0.68 to 1.24) 1 0.97 (0.79 to 1.19) 0.91 (0.70 to 1.18) 0.93 (0.74 to 1.17)	Age, trial randomization, race, education, postmenopausal status, hormone use, smoking status, parental history of myocardial infarction or cancer, alcohol intake, energy intake, saturated fat intake, fiber intake, fruit and vegetable intake, physical examination for screening, time per week spent in aerobic MVPA* BMI, incidence of hypertension, high cholesterol, cardiovascular diseases, diabetes mellitus, and cancer before and during follow-up. *Excluded from the joint analysis.	7
Stamatakis, 2018[20]	England and Scotland; HSE and SHS	Men and women; ≥30 years (mean 45.6 years)	Cancer mortality; National Health Service Central Register; 2089/77 195	9.2 years (mean)	Questionnaire	No Yes None <66.0 min/week (women) and <52.5 min/week (men) ≥66.0 min/week (women) and ≥52.5 min/week (men) Neither guideline Aerobic only Strength only Both guideline	1 0.69 (0.57 to 0.84) 1 0.72 (0.58 to 0.93) 0.67 (0.52 to 0.88) 1 0.99 (0.88 to 1.11) 0.66 (0.48 to 0.92) 0.70 (0.50 to 0.98) (personal communication)	Age, sex, long-standing illness, alcohol consumption, psychological distress, BMI, smoking status, educational level, and weekly volume of other physical activity *Total volume of physical activity was alternatively included in the joint analysis	6

First author, year	Country; Cohort	Participants characteristics	Outcome; Case ascertainment; Case/Participants	Follow-up	Exposure measurement	Exposure category	Effect estimates	Covariates	Quality assessment
Siahpush, 2019[47]	USA; NHIS	Men and women; ≥18 years (mean 43.5 years)	Cancer mortality; NDI; 7275/310 282	7.9 years (mean)	Interview	0 time/week 1 time/week 2 times/week 3 times/week 4 times/week ≥5 times/week	1 0.89 (0.70 to 1.12) 0.77 (0.63 to 0.95) 0.82 (0.70 to 0.95) 0.71 (0.53 to 0.95) 0.84 (0.73 to 0.96)	Minutes of moderate physical activity, minutes of vigorous physical activity, smoking status, BMI, previous cancer diagnosis, chronic condition, self-rated health, sex, age, marital status, race/ethnicity, nativity, poverty status, and education	7
Porter, 2020[49]	USA; NHANES	Men and women; ≥20 years (mean 46.3 years)	Cancer mortality; NDI; 945/17 938	11.9 years (median)	Interview	No Yes	1 0.81 (0.46 to 1.42)	Other leisure-time activities, age, gender, race, education, cigarette use, heavy alcohol consumption, BMI, household activity, transportation activity, and history of diabetes, arthritis, cancer, disability, and CVD	7
Patel, 2020[48]	USA; CPS-IINC	Men and women; 59-83 years (mean 70.2 years)	Cancer mortality; NDI; 5038/72 462	13 years (max)	Questionnaire	0 min/week 1-59 min/week 60-119 min/week ≥120 min/week	1 0.92 (0.81 to 1.04) 0.94 (0.83 to 1.06) 1.02 (0.89 to 1.17)	Sex, age, BMI, survey type, education, self-reported overall health, smoking duration and intensity, alcohol use, marital status, work status, TV sitting time, aspirin use, and comorbidity score (reported personal history of high blood pressure, type 2 diabetes, and high cholesterol), and MVPA	6
Rezende, 2020[50]	USA, HPSF	Men; 40-75 years (mean 67.5 years)	Total cancer incidence; Self-reported cancer diagnosis confirmed from medical records or NDI; 5158/33 787	24 years (max)	Questionnaire	None Any None 1-59 min/week ≥60 min/week Per 60 min/week increase	1 0.98 (0.92 to 1.05) 1 0.98 (0.91 to 1.05) 0.99 (0.90 to 1.10) 1.01 (0.97 to 1.05)	Age, race, height, family history of cancer, physical exam in past two years, history of colonoscopy or sigmoidoscopy, smoking in pack years, regular aspirin use, multivitamin use, alcohol consumption, red and processed meat intake, Alternate Healthy Eating Index, prostate-specific antigen test in past 2 years, total physical activity except for resistance training, total energy intake, and BMI	7

First author, year	Country; Cohort	Participants characteristics	Outcome; Case ascertainment; Case/Participants	Follow-up	Exposure measurement	Exposure category	Effect estimates	Covariates	Quality assessment
Zhao, 2020[51]	USA; NHIS	Men and women; ≥18 years	Cancer mortality; NDI; 14 375/479 856	8.75 years (median)	Interview	Neither guideline Aerobic only Strength only Both guideline	1 0.76 (0.73 to 0.80) 0.85 (0.77 to 0.95) 0.60 (0.56 to 0.65)	Sex, age, race/ethnicity, education, marital status, BMI, smoking status, alcohol intake, and chronic conditions (hypertension, heart disease, stroke, cancer, and diabetes)	5
Diabetes									
Grøntved, 2012[19]	USA; HPFS	Men; 40-75 years	Type 2 diabetes incidence; Self-reported diagnosis; 2278/32 002	18 years (max)	Questionnaire	0 min/week 1-59 min/week 60-149 min/week ≥150 min/week Per 60 min/week increase	1 0.92 (0.82 to 1.02) 0.82 (0.67 to 1.00) 0.71 (0.49 to 1.00) 0.87 (0.81 to 0.94)	Age, smoking, alcohol consumption, coffee intake, race, family history of diabetes, intake of total energy, trans fat, polyunsaturated fat to saturated fat ratio, cereal fiber, whole grain, glycemic load, aerobic exercise, other physical activity of at least moderate intensity, television viewing, and BMI	6
Grøntved, 2014[40]	USA; NHS&NHSII	Women; 36-81 years	Type 2 diabetes incidence; Self-reported diagnosis; 3491/99 316	8 years (max)	Questionnaire	None 1-29 min/week 30-59 min/week 60-150 min/week >150 min/week Per 60 min/week increase	1 0.83 (0.73 to 0.94) 0.96 (0.82 to 1.11) 0.82 (0.70 to 0.95) 0.74 (0.54 to 1.01) 0.95 (0.90 to 1.00)	Age, smoking, alcohol consumption, coffee intake, race, family history of diabetes, postmenopausal hormone use, intake of total energy, trans fat, polyunsaturated fat to saturated fat ratio, cereal fiber, wholegrain, glycemic load, oral contraceptive use, menopausal status, aerobic physical activity, lower intensity muscular conditioning exercises, and BMI	6
Kuwahara, 2015[41]	Japan; J-ECOH	Men and women; 30-64 years (mean 45.3 years)	Type 2 diabetes incidence; HbA1c ≥6.5%, fasting glucose ≥126 mg/dL, random plasma glucose ≥200 mg/dL, history of diabetes or current medication for diabetes; 1770/26 630	5.2 years (mean)	Questionnaire	No Yes	1 0.70 (0.51 to 0.96)	Age, sex, smoking status, alcohol consumption, sleep duration, aerobic exercise, hypertension, shift work, occupational physical activity, family history of diabetes, and BMI	6

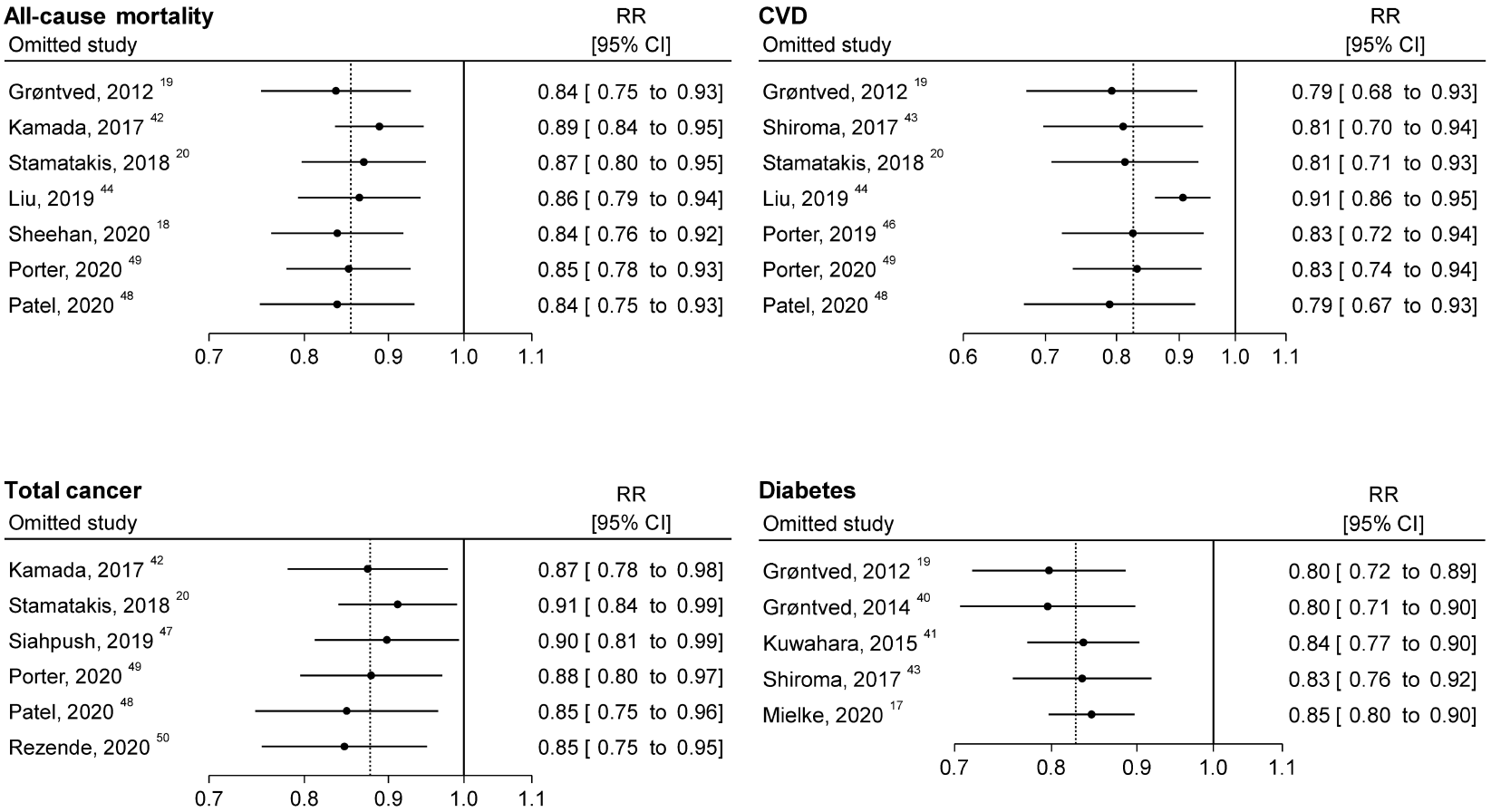
First author, year	Country; Cohort	Participants characteristics	Outcome; Case ascertainment; Case/Participants	Follow-up	Exposure measurement	Exposure category	Effect estimates	Covariates	Quality assessment
Shiroma, 2017[43]	USA, WHS	Women; 47-97.8 years (mean 62.6 years)	Type 2 diabetes incidence; Annual follow-up questionnaires confirmed from a telephone interview, supplemental questionnaire, and medical records; 2120/35 754	10.7 years (mean)	Questionnaire	0 min/week 1-19 min/week 20-59 min/week 60-119 min/week ≥120 min/week	1 0.74 (0.59 to 0.93) 0.91 (0.72 to 1.14) 0.76 (0.60 to 0.95) 0.76 (0.54 to 1.05)	Age, smoking status, dietary habits, alcohol intake, postmenopausal status, hormone use, parental history of myocardial infarction, trial randomization, time per week spent in lower-intensity activities and aerobic activities, and BMI	6
Mielke, 2020[17]	Australia; HABITAT	Men and women; 40-65 years	Type 2 diabetes incidence; Self-reported diabetes diagnosis; 267/8784	6 years (max)	Questionnaire	None <1 time/week ≥1 time/week	1 0.55 (0.32 to 0.93) 0.69 (0.45 to 1.05) (personal communication)	Sex, age, education, annual income, living arrangements, cigarette smoking status, physical activity, hypertension, and obesity	4
Colon cancer									
Mazzilli, 2019[45]	USA, NIH-AARP DHS	Men and women; 50-71 years	Colon cancer incidence; Cancer registries; 1715 /215 122	10 years (max)	Questionnaire	None Any None 5-90 min/week ≥120 min/week Low activity & No weight lifting High activity & No weight lifting Low activity & Any weight lifting High activity & Any weight lifting (Low activity: <7.5 MET-h/week) (High activity: ≥7.5 MET-h/week)	1 0.95 (0.90 to 1.00) 1 0.75 (0.66 to 0.87) 0.78 (0.61 to 0.98) 1 0.93 (0.83 to 1.03) 0.77 (0.57 to 1.03) 0.69 (0.60 to 0.80)	Age, sex, BMI, smoking status, race, education, alcohol intake, and MVPA not including weight lifting* *Excluded from the joint analysis.	6

First author, year	Country; Cohort	Participants characteristics	Outcome; Case ascertainment; Case/Participants	Follow-up	Exposure measurement	Exposure category	Effect estimates	Covariates	Quality assessment
Rezende, 2020[50]	USA, HPSF	Men; 40-75 years (mean 67.5 years)	Colon cancer incidence; Self-reported cancer diagnosis confirmed from medical records or NDI; 700/33 787	24 years (max)	Questionnaire	None Any None 1-59 min/week ≥60 min/week Per 60 min/week increase Low activity & No resistance training High activity & No resistance training Low activity & Any resistance training High activity & Any resistance training (Low activity: <16 MET-h/week) (High activity: ≥16 MET-h/week)	1 1.04 (0.87 to 1.25) 1 0.94 (0.77 to 1.16) 1.32 (1.01 to 1.72) 1.12 (1.02 to 1.22) 1 0.88 (0.73 to 1.06) 0.84 (0.57 to 1.25) 0.95 (0.77 to 1.19)	Age, race, height, family history of cancer, physical exam in past two years, history of colonoscopy or sigmoidoscopy, smoking in pack years, regular aspirin use, multivitamin use, alcohol consumption, red and processed meat intake, Alternate Healthy Eating Index, prostate-specific antigen test in past 2 years, total physical activity except for resistance training*, total energy intake, and BMI *Excluded from the joint analysis.	7
Kidney cancer									
Mazzilli, 2019[45]	USA, NIH-AARP DHS	Men and women; 50-71 years	Kidney cancer incidence; Cancer registries; 851/215 122	10 years (max)	Questionnaire	None 5-90 min/week ≥120 min/week	1 0.94 (0.78 to 1.12) 0.80 (0.59 to 1.11)	Age, sex, BMI, smoking status, race, education, alcohol intake, and MVPA not including weight lifting	6
Rezende, 2020[50]	USA, HPSF	Men; 40-75 years (mean 67.5 years)	Kidney cancer incidence; Self-reported cancer diagnosis confirmed from medical records or NDI; 212/33 787	24 years (max)	Questionnaire	None Any None 1-59 min/week ≥60 min/week Per 60 min/week increase	1 0.80 (0.58 to 1.11) 1 0.89 (0.63 to 1.26) 0.58 (0.32 to 1.04) 0.78 (0.58 to 1.04)	Age, race, height, family history of cancer, physical exam in past two years, history of colonoscopy or sigmoidoscopy, smoking in pack years, regular aspirin use, multivitamin use, alcohol consumption, red and processed meat intake, Alternate Healthy Eating Index, prostate-specific antigen test in past 2 years, total physical activity except for resistance training, total energy intake, and BMI	7

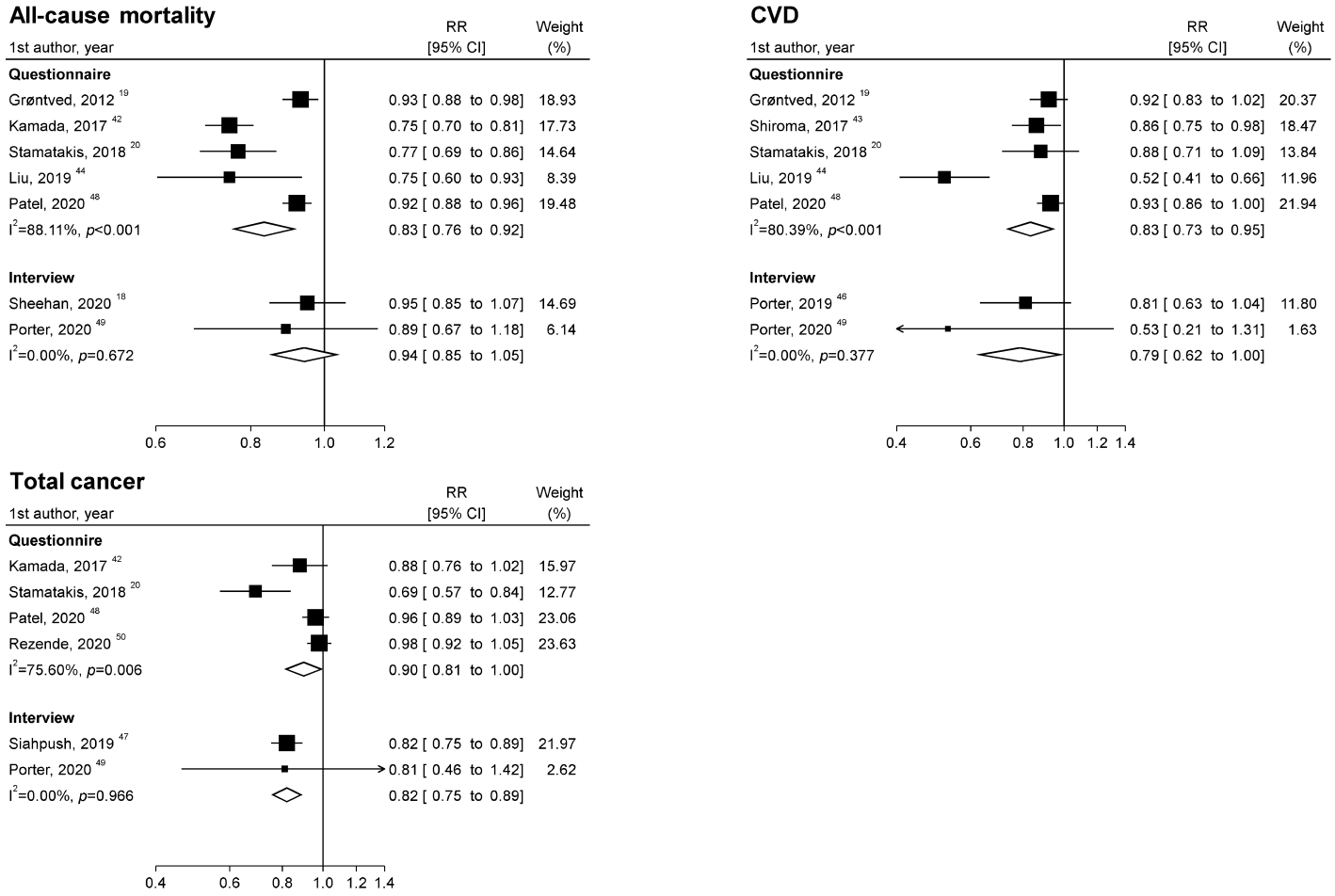
First author, year	Country; Cohort	Participants characteristics	Outcome; Case ascertainment; Case/Participants	Follow-up	Exposure measurement	Exposure category	Effect estimates	Covariates	Quality assessment
Bladder cancer									
Mazzilli, 2019[45]	USA, NIH-AARP DHS	Men and women; 50-71 years	Bladder cancer incidence; Cancer registries; 1836/215 122	10 years (max)	Questionnaire	None 5-90 min/week ≥120 min/week	1 0.97 (0.86 to 1.10) 0.98 (0.81 to 1.19)	Age, sex, BMI, smoking status, race, education, alcohol intake, and MVPA not including weight lifting	6
Rezende, 2020[50]	USA, HPSF	Men; 40-75 years (mean 67.5 years)	Bladder cancer incidence; Self-reported cancer diagnosis confirmed from medical records or NDI; 505/33 787	24 years (max)	Questionnaire	None Any None 1-59 min/week ≥60 min/week Per 60 min/week increase	1 0.85 (0.69 to 1.05) 1 0.94 (0.75 to 1.18) 0.61 (0.42 to 0.90) 0.80 (0.66 to 0.96)	Age, race, height, family history of cancer, physical exam in past two years, history of colonoscopy or sigmoidoscopy, smoking in pack years, regular aspirin use, multivitamin use, alcohol consumption, red and processed meat intake, Alternate Healthy Eating Index, prostate-specific antigen test in past 2 years, total physical activity except for resistance training, total energy intake, and BMI	7
Lung cancer									
Mazzilli, 2019[45]	USA, NIH-AARP DHS	Men and women; 50-71 years	Lung cancer incidence; Cancer registries; 3480/215 122	10 years (max)	Questionnaire	None 5-90 min/week ≥120 min/week	1 0.91 (0.82 to 1.00) 0.90 (0.81 to 1.12)	Age, sex, BMI, smoking status, race, education, alcohol intake, and MVPA not including weight lifting	6
Rezende, 2020[50]	USA, HPSF	Men; 40-75 years (mean 67.5 years)	Lung cancer incidence; Self-reported cancer diagnosis confirmed from medical records or NDI; 595/33 787	24 years (max)	Questionnaire	None Any None 1-59 min/week ≥60 min/week Per 60 min/week increase	1 0.87 (0.71 to 1.07) 1 0.86 (0.69 to 1.09) 0.90 (0.63 to 1.27) 0.93 (0.79 to 1.09)	Age, race, height, family history of cancer, physical exam in past two years, history of colonoscopy or sigmoidoscopy, smoking in pack years, regular aspirin use, multivitamin use, alcohol consumption, red and processed meat intake, Alternate Healthy Eating Index, prostate-specific antigen test in past 2 years, total physical activity except for resistance training, total energy intake, and BMI	7

First author, year	Country; Cohort	Participants characteristics	Outcome; Case ascertainment; Case/Participants	Follow-up	Exposure measurement	Exposure category	Effect estimates	Covariates	Quality assessment
Pancreas cancer									
Mazzilli, 2019[45]	USA, NIH-AARP DHS	Men and women; 50-71 years	Pancreas cancer incidence; Cancer registries; 795/215 122	10 years (max)	Questionnaire	None 5-90 min/week ≥120 min/week	1 1.15 (0.96 to 1.37) 0.98 (0.71 to 1.34)	Age, sex, BMI, smoking status, race, education, alcohol intake, and MVPA not including weight lifting	6
Rezende, 2020[50]	USA, HPSF	Men; 40-75 years (mean 67.5 years)	Pancreas cancer incidence; Self-reported cancer diagnosis confirmed from medical records or NDI; 233/33 787	24 years (max)	Questionnaire	None Any None 1-59 min/week ≥60 min/week Per 60 min/week increase	1 1.15 (0.85 to 1.56) 1 1.13 (0.81 to 1.57) 1.22 (0.76 to 1.96) 1.01 (0.84 to 1.23)	Age, race, height, family history of cancer, physical exam in past two years, history of colonoscopy or sigmoidoscopy, smoking in pack years, regular aspirin use, multivitamin use, alcohol consumption, red and processed meat intake, Alternate Healthy Eating Index, prostate-specific antigen test in past 2 years, total physical activity except for resistance training, total energy intake, and BMI	7

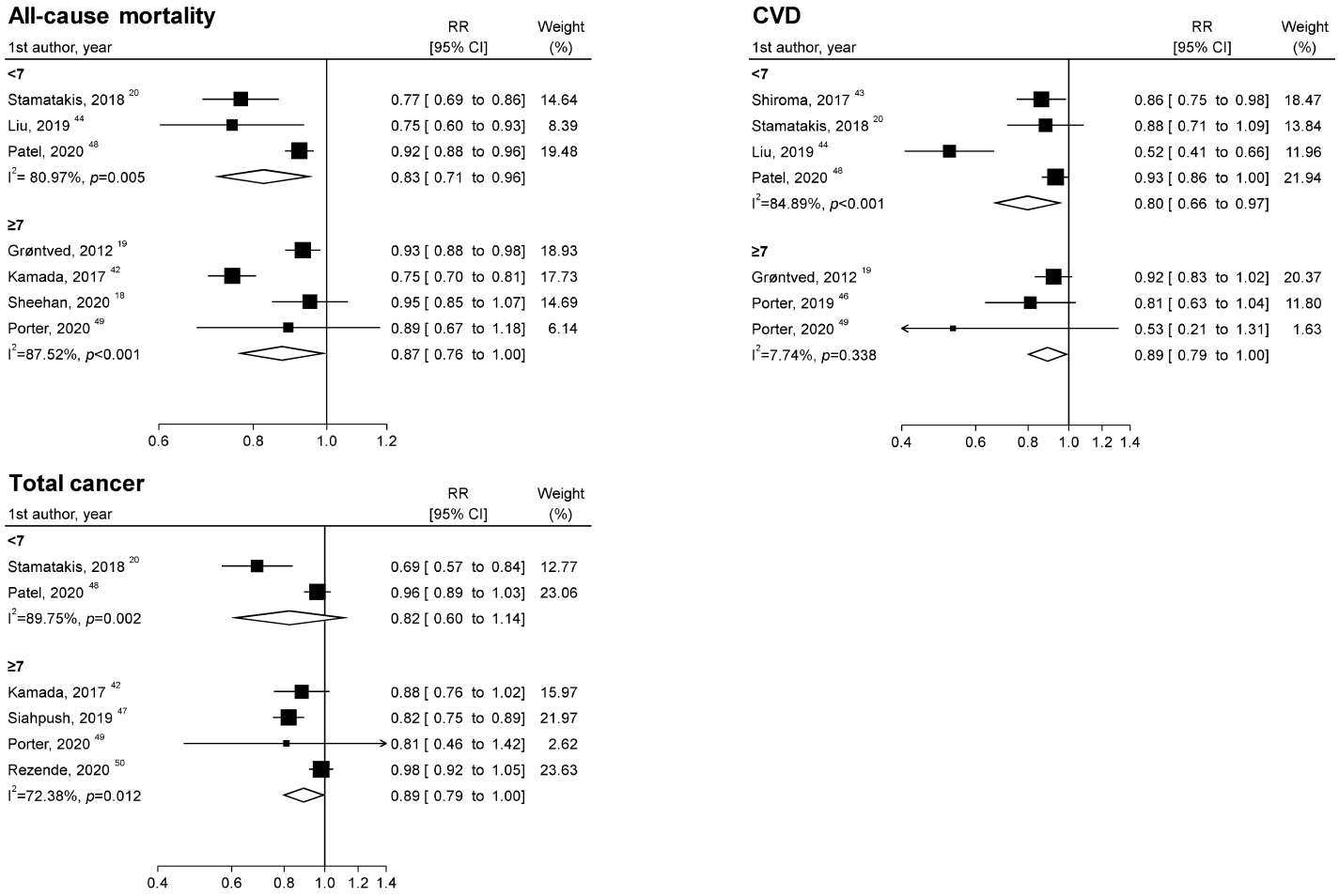
ACLS, Aerobics Center Longitudinal Study; ARICS, Atherosclerosis Risk in Communities Study; BMI, body mass index; CHD, coronary heart disease; CVD, cardiovascular disease; HABITAT, how areas in Brisbane Influence health and activity; HPFS, Health Professionals Follow-Up Study; HSE, Health Survey for England; J-ECOHS, Japan epidemiology collaboration on occupational health study; MI, myocardial infarction; MVPA, moderate-to-vigorous physical activity; NDI, national death index; NHIS, National Health Interview Survey; NHIS-LMF, National Health Interview Survey-Linked Mortality Files; NHANES, National Health and Nutrition Examination Survey; NHS, Nurses' Health Study; NHSII, Nurses' Health Study II; NIH-AARP DHS, National Institutes of Health-American Association for Retired Persons Diet and Health Study; SHS, Scottish Health Survey; TV, television; WHS, Women's Health Study



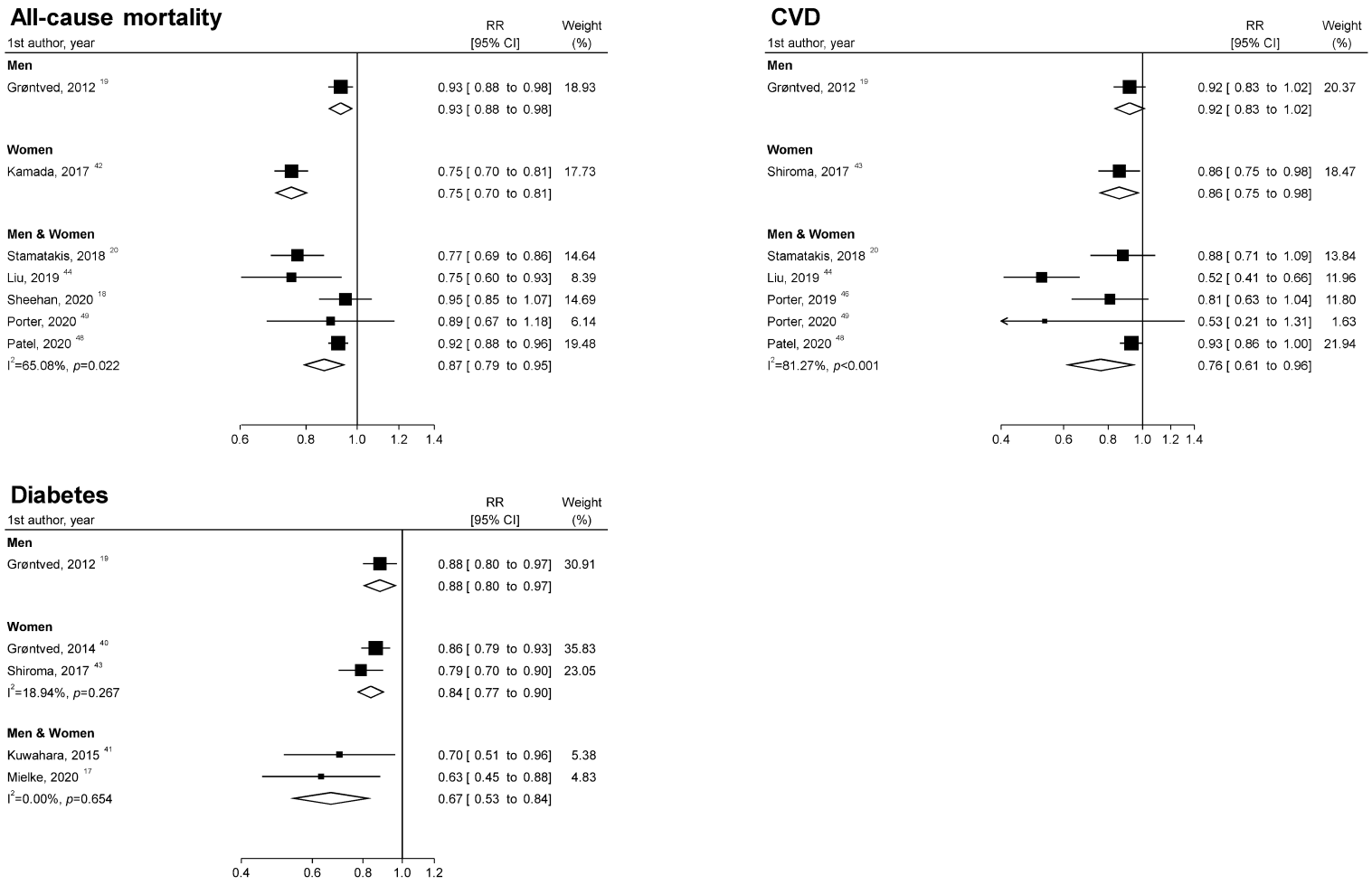
Appendix Figure 1. Leave-one-out analysis for the associations of muscle-strengthening activities (two-group analysis) with all-cause mortality, CVD, total cancer, and diabetes. For CVD, the heterogeneity disappeared (I^2=0.0%) when the study by Liu et al. was excluded (I^2=0.0%). For diabetes, when the study by Mielke et al.[17] with low quality (NOS=4) was excluded, the heterogeneity substantially reduced (I^2=9.5%). CI=confidence intervals; CVD=cardiovascular diseases; NOS=Newcastle-Ottawa Scale; RR=relative risk.



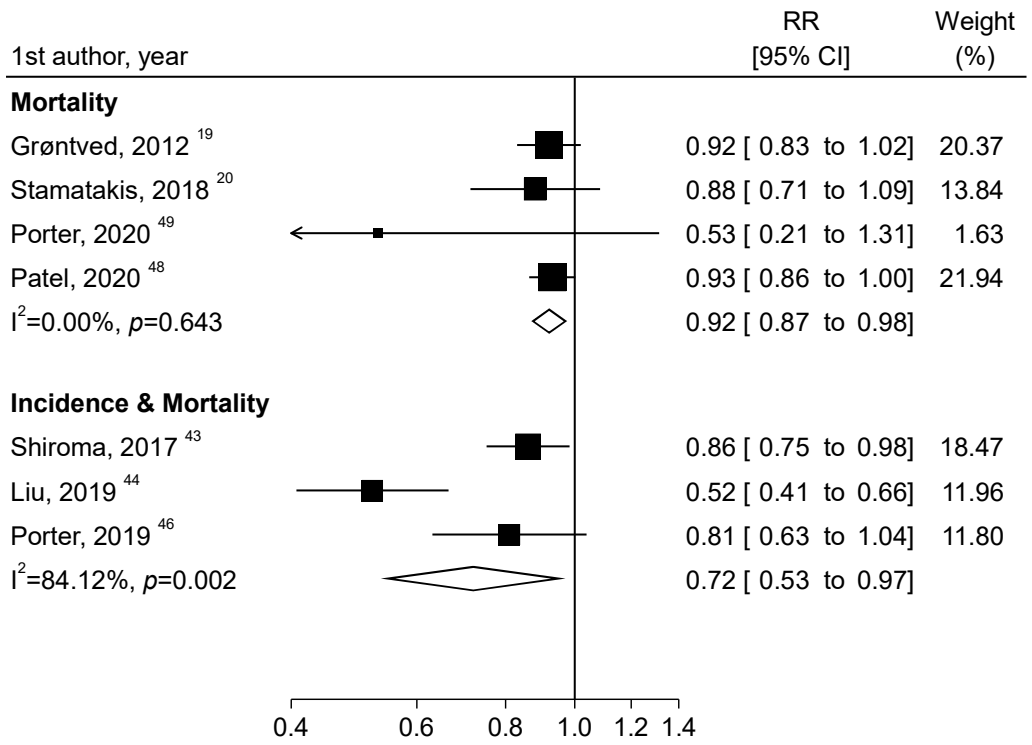
Appendix Figure 2. Forest plot of subgroup analysis by the exposure assessment (questionnaire or interview) for the association of muscle-strengthening activities (two-group analysis) with all-cause mortality, CVD, and total cancer. Diamonds indicate overall RRs with 95% CI. CI=confidence intervals; CVD=cardiovascular diseases; RR=relative risk.



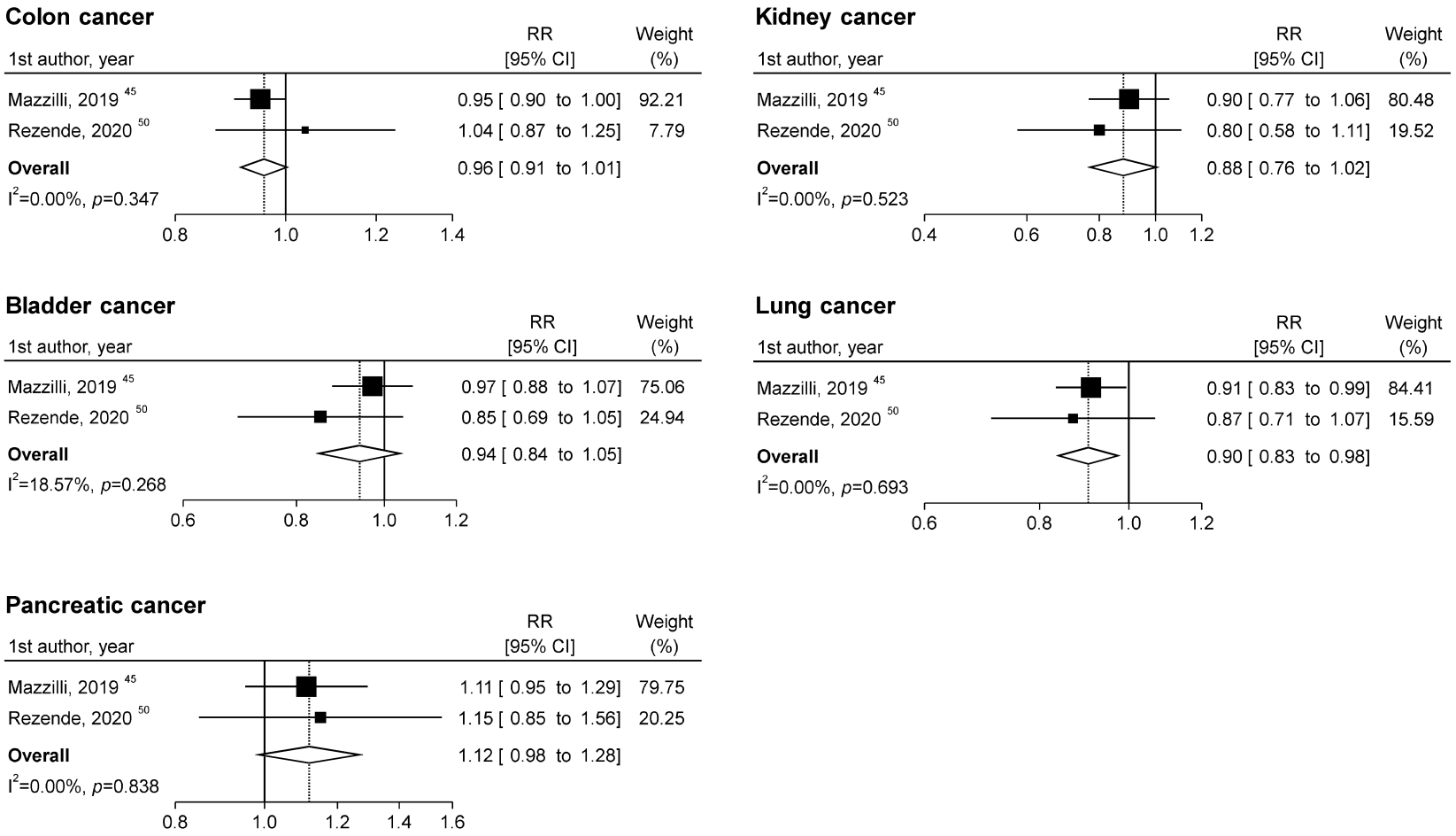
Appendix Figure 3. Forest plot of subgroup analysis by the quality score of Newcastle-Ottawa Scale (<7 or ≥7) for the association of muscle-strengthening activities (two-group analysis) with all-cause mortality, CVD, and total cancer. Diamonds indicate overall RRs with 95% CI. CI=confidence interval; CVD=cardiovascular diseases; RR=relative risk.



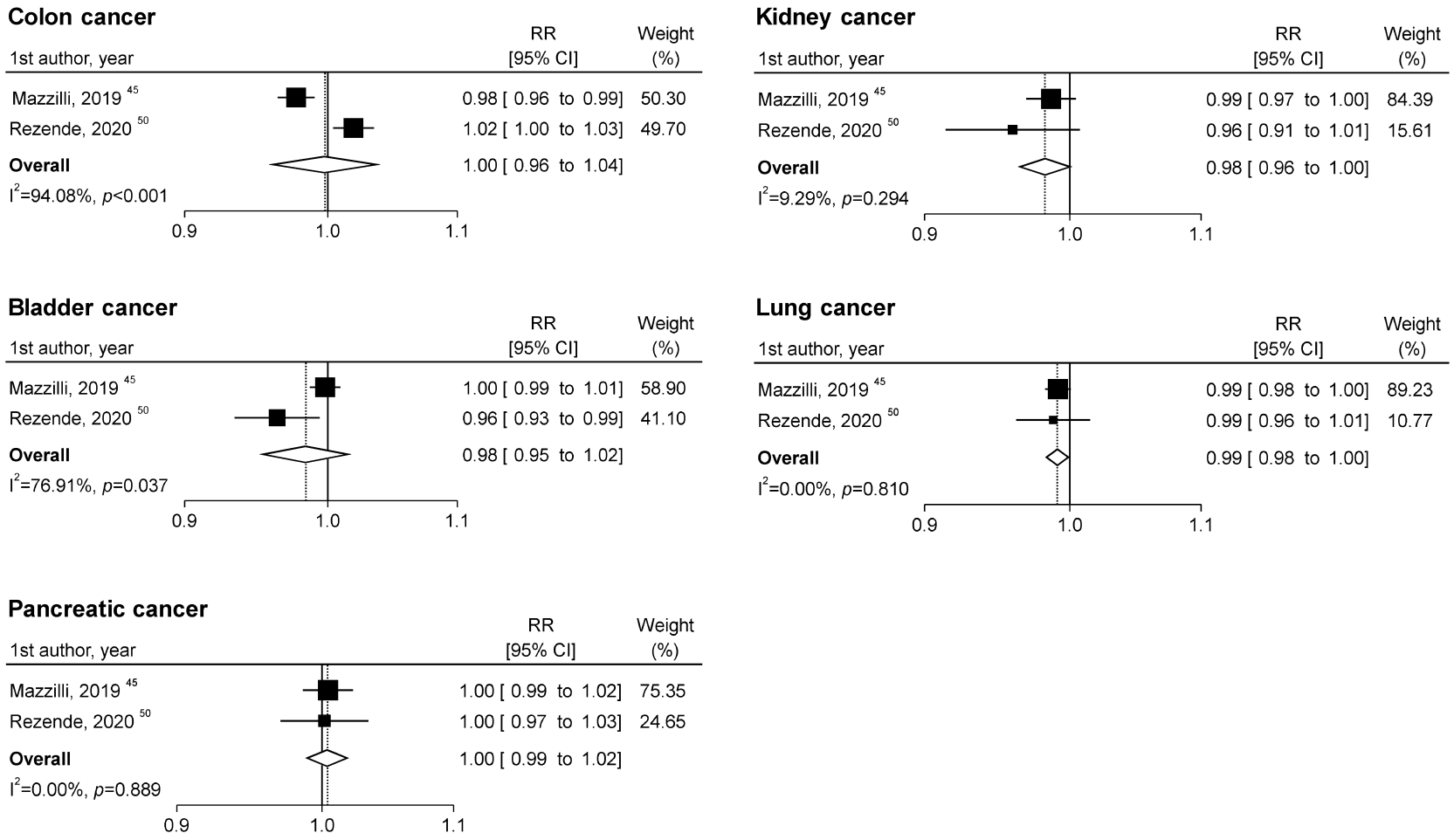
Appendix Figure 4. Forest plot of subgroup analysis by sex for the association of muscle-strengthening activities (two-group analysis) with all-cause mortality, CVD, and diabetes. Diamonds indicate overall RRs with 95% CI. CI=confidence interval; CVD=cardiovascular diseases; RR=relative risk



Appendix Figure 5. Forest plot of subgroup analysis by the type of case for the association of muscle-strengthening activities (two-group analysis) with CVD. Diamonds indicate overall RRs with 95% CI. CI=confidence interval; CVD=cardiovascular diseases; RR=relative risk.



Appendix Figure 6. Forest plot for the associations of muscle-strengthening activities (two-group analysis) with site-specific cancers incidence. Diamonds indicate overall RRs with 95% CI. CI=confidence interval; RR=relative risk.



Appendix Figure 7. Forest plot for the linear dose-response association of muscle-strengthening activities (per 10-min/week increase) with site-specific cancers incidence. Diamonds indicate overall RRs with 95% CI. CI=confidence interval; RR=relative risk.