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The association of resistance training with mortality: A systematic review and meta-analysis

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Abstract

Background: The benefits of aerobic exercise are well-studied; there is no consensus on the association between resistance training and major adverse cardiovascular outcomes. This systematic review and meta-analysis aimed to address this issue.

Design and methods: We searched for randomized trials and cohort studies that evaluated the association between resistance training and mortality and cardiovascular events. Two investigators screened the identified abstracts and full-texts independently and in duplicate. Cochrane tools were used to assess the risk of bias. We calculated hazard ratios and 95% confidence intervals using random effect models.

Results: From the 1430 studies identified, 11 (one randomized trial and 10 cohort studies) met the inclusion criteria, totaling 370,256 participants with mean follow-up of 8.85 years. The meta-analysis showed that, compared with no exercise, resistance training was associated with 21% (hazard ratio (95% confidence interval (CI)), 0.79 (0.69–0.91)) and 40% (hazard ratio (95% CI), 0.60 (0.49–0.72)) lower all-cause mortality alone and when combined with aerobic exercise, respectively. Furthermore, resistance training had a borderline association with lower cardiovascular mortality (hazard ratio (95% CI), 0.83 (0.67–1.03)). In addition, resistance training showed no significant association with cancer mortality. Risk of bias was low to intermediate in the included studies. One cohort study looked at the effect of resistance training on coronary heart disease events in men and found a 23% risk reduction (risk ratio, 0.77, CI: 0.61–0.98).

Conclusion: Resistance training is associated with lower mortality and appears to have an additive effect when combined with aerobic exercise. There are insufficient data to determine the potential beneficial effect of resistance training on non-fatal events or the effect of substituting aerobic exercise with resistance training.

Keywords

Resistance training, strength training, mortality, cardiovascular outcome, systematic review, meta-analysis

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Introduction

Sedentary lifestyle is a risk factor for a shorter lifespan, adverse cardiovascular events and many other comorbidities such as diabetes, hypertension, obesity and cancer.[1,2] A range of physical activities, from standing and walking to performing moderate-to-vigorous physical activities, reduce sedentary time and have been independently associated with longer life expectancy and improvement in quality-of-life,[3] with lower rates of multiple comorbidities and mortality.[3–5] Physical

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activity including endurance and resistance training may also improve clinical outcomes even in patients with cardiovascular or valvular heart disease.[6,7] Most of the evidence for the benefits of substituting sedentary time with physical activity has focused on testing the effect of aerobic exercise on different health measures.[8] Existing evidence overwhelmingly shows that aerobic exercise positively affects health measures including increasing lifespan, reducing rates of cardiovascular events, improving metabolic health, and preventing many comorbidities, while lowering healthcare costs.[9,10]

Another form of physical activity that can be used to reduce sedentary time is resistance training; however, whether resistance training shares the potential benefits and positive long-term effects of aerobic exercise on health in general, and on cardiovascular events in particular, is currently unclear. Resistance training normally involves lifting weights (using either machines or free weights) typically at loads greater than 65% of the one-repetition maximum, defined as the heaviest weight a person can lift with maximum effort in a single repetition.[11] Resistance training is sub-divided into dynamic resistance training, involving concentric and/or eccentric contractions of muscles with changes in length and the tension of the muscles, and static exertion or isometric resistance training, based on sustained muscle contraction against a fixed load or resistance with no change in length of the muscles.[12] Mechanistic studies have shown that relatively short periods of resistance training could lead to improvements in a number of cardiovascular risk factors including insulin resistance, glucose and lipid metabolism,[5,11] and endothelial function, with reduced sympathetic neural activation.[13] Further, a small number of epidemiologic studies suggest a possible beneficial effect on survival,[14–16] but the results have been conflicting and inconclusive.

The present study aims to systematically review the association between resistance training and multiple outcomes including all-cause mortality, cardiovascular mortality, cancer mortality, ischemic heart disease, and stroke, with a focus on comparisons between resistance training and no resistance training adjusted for aerobic exercise, and resistance training versus aerobic exercise.

Methods

We designed the protocol based on the Cochrane Handbook of Systematic Reviews of Intervention and Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement, and the Scientific Statement from the American Heart Association on systematic review and meta-analysis on cardiac prevention and treatment studies.[17]

We searched for randomized or quasi-randomized trials and cohort studies that compared resistance training with aerobic exercise or no exercise, in the general adult population in terms of major cardiovascular outcomes including all-cause mortality, cardiovascular mortality, cancer mortality, ischemic heart disease, and stroke. We did not exclude studies on the basis of the year of publication, language, or length of follow-up; but we excluded studies with different designs or outcomes.

We conducted a comprehensive search of several databases from each database's inception to 25 September 2017. The databases included Ovid MEDLINE Epub Ahead of Print, Ovid Medline In-Process & Other Non-Indexed Citations, Ovid MEDLINE, Ovid EMBASE, Ovid Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, and Scopus. The search strategy was designed and conducted by an experienced librarian (LJP) with input from the study's lead investigators. We used controlled vocabulary supplemented with keywords to search for the association between resistance training and cardiovascular outcomes in adults (detailed strategy is available in the Supplementary Material online). We renewed the search on 6 November 2018.

One investigator (FS) reviewed the references of the eligible studies to identify any additional studies that had been missed by the original search. Additionally, the authors of the eligible studies were contacted by email to identify any similar studies done by the same author or other authors that were not found in the primary search.

Having applied the search strategy and generated a list of potential studies, two investigators (FS and JRMI) conducted eligibility screening: first, by excluding any papers that did not match the criteria of interest based on the title and abstracts; and second, by reviewing their full text to evaluate their eligibility for inclusion in the final analysis. The entire screening process was performed independently and in duplicate using the systematic review software Covidence®.

Studies meeting all eligibility criteria underwent data extraction for further analysis. When the investigators disagreed on the inclusion or exclusion of a study, they would discuss the case and attempt to resolve the issue; when a third opinion was needed the senior investigator (FLJ) would independently review the study and make a final decision.

The data abstraction included the general characteristics of the study (author, year of publication, study design), characteristics of the study participants (sample size, age, gender, and basic health status in both intervention and control groups), characteristics of the intervention and comparisons (type, frequency, and intensity of resistance training) and the duration of follow-up, and outcomes data (all-cause mortality,

cardiovascular mortality, cancer mortality, ischemic heart disease, and stroke). Data were collected by two investigators (FS and JRMI) independently and in duplicate. The authors of studies were contacted when the data needed in the analysis were not accessible through the published version of the articles.

We used Cochrane tools for assessment of the risk of bias in clinical trials and observational studies at both study and outcome levels. The tool used for the clinical trials assessed the sequence generation, allocation concealment, blinding, incomplete outcome data, and selective outcome reporting, and other sources of bias. The tool for evaluation of the observational studies (ROBINS-E) assessed different domains for any possible bias.[18,19] The domains for evaluating the risk of bias are as follows: confounding bias, bias in selection of the participants into the study, bias in classification of exposures, bias due to departures from intended exposures, bias due to missing data, bias in measurement of outcomes, bias in selection of the reported result, and overall risk of bias.

Since most of the included studies were derived from National Health and Nutritional Examination Survey (NHANES) and National Health Interview Survey (NHIS) surveys, we minimized the overlap between participants of the included papers in several ways. To exclude the studies with overlap but not losing any important data, we contacted the authors of the original studies, looking for data on specific subgroup analyses. We excluded studies that were conducted in the same time frame and also those that had more than 10% overlap in their study samples. Finally, when conducting subgroup analyses we verified that no subgroups representing the same population would be included.

The outcomes-of-interest in this study were counts and rates and reported mostly as hazard ratio or risk ratio (RR) (from Cox regression model) and in one study as odds ratio (OR) (from logistic regression model); we converted OR to RR ((RR = OR/(1-prevalence of the outcome in the reference group) + (prevalence of the outcome in the reference group)) and assumed the RR equivalent to hazard ratio for the analysis. For analyses adjusted for covariates we used the most adjusted ratios, recognizing that those analyses would adjust for similar but not identical potential confounders. The majority of the multivariate analyses included for covariates age, gender, comorbidities (including hypertension, hyperlipidemia, and diabetes mellitus), body mass index, physical activities, aerobic exercise, smoking status, and diet.

To conduct a meta-analysis we used RevMan v.5.3 and generic inverse variance model. To measure the heterogeneity between the individual studies for each outcome we used I^2 statistics, deeming I^2 values more than 75% as considerable heterogeneity. Funnel plots were used and visually inspected for assessing publication bias.

We predefined different subgroup analyses based on factors believed to affect the possible association between resistance training and outcomes, such as: intensity, frequency (low: >2, moderate: 2–5 and high ≥5 sessions/week) and duration of the resistance training, gender, presence or absence of hypertension, baseline health status of the participants, and patient or population based studies. We also predefined a subgroup based on the level of adjustment of the analysis comparing resistance training with the primary outcomes, dividing studies adjusted for multiple potential confounders versus those adjusted only for age and/or gender, or not adjusted.

Results

The primary search identified 1421 records and nine more studies were found by searching the reference lists of the eligible studies. From these records, 11 studies with a total of 370,256 participants met the inclusion criteria for the systematic review and meta-analysis, from which eight were from the screening of the studies identified through the primary search and three were from those identified through hand-searching. Figure 1 is a PRISMA diagram showing the details of each stage of the screening and eligibility assessment and also the reasons for the exclusion of the studies. Reviewers were in agreement over which studies should be included ($\kappa = 0.83$).

Although the primary search included key terms for major cardiovascular outcomes, the majority of the studies included in the final analysis assessed only mortality (all-cause, cardiovascular, and cancer).

Table 1 shows the characteristics of the studies[14–16,20–27] in detail. One study was a randomized clinical trial and the other studies were cohort studies, mostly focused on the data from the NHANES and NHIS. All of the studies except one were done in the United States. All of the included studies were published in English and one of the studies was not yet published by the time of the data extraction so its data were obtained through contacting the authors.[20]

The average follow-up was 8.85 years and the age range was 18–75 years. Within-study risk of bias was low to moderate (we considered a mild risk of bias for the design of the included studies, which were mostly cohorts compared with a well-done randomized clinical trial) in all of the included studies, except one that was moderate. Table 2 shows the details of the risk of bias in different domains for each study.

The studies evaluating the association between resistance training and all-cause mortality included 341,820 participants. The results are presented in

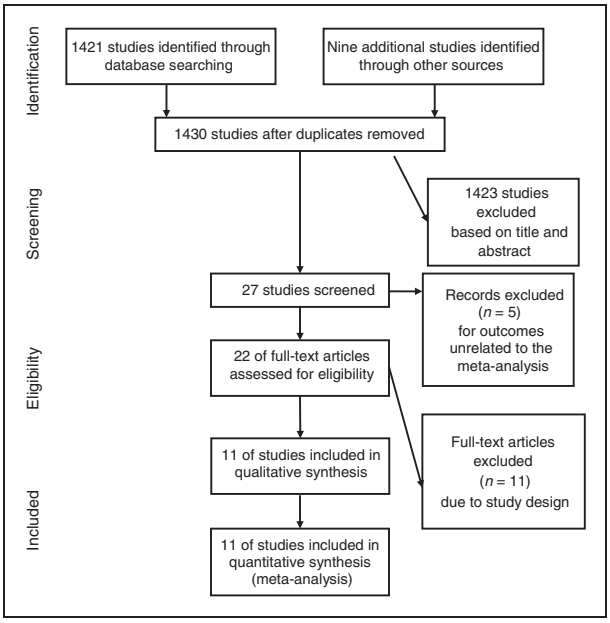

Figure 1. PRISMA flow diagram detailing the literature search, with the number of included and excluded studies and reasons for exclusion in each stage.

Figures 2–4: Figure 2(a) shows that performing any frequency of resistance training is associated with 21% lower all-cause mortality in comparison with no exercise (hazard ratio (95% confidence interval (CI)), 0.79 (0.69–0.91)). Based on the subgroup analysis, performing >0 to two sessions of resistance training per week is associated with lower all-cause mortality (0.79 (0.66–0.95)), but doing more than two sessions of resistance training is not (Figure 2(b)). These results were unchanged after performing a sensitivity analysis that restricted the analysis to population based studies (data not shown). Additionally, the results show that following the current recommendations by the American College of Sport Medicine and the American Heart Association on performing 2–3 sessions of resistance training per week is not significantly better than performing lower frequencies of resistance training in terms of all-cause mortality (1.00 (0.89–1.11)) (Figure 2(c)).

Some studies included in this analysis also compared aerobic exercise with no exercise[21–24] and, as expected, they demonstrated that aerobic exercise is associated with lower all-cause mortality (0.59 (0.45–0.76) for any aerobic exercise versus no exercise[21–24]) with a dose–response relationship (*data not shown*) (0.64 (0.56–0.74) for 1–2 sessions of aerobic exercise[22–24] and 0.56 (0.41–0.76) for ≥ 2 sessions of aerobic exercise[21–24]).

Some studies tested the association between the combination of resistance training and aerobic exercise and all-cause mortality. As Figure 2(d) shows, the combination of any frequency of resistance training with any frequency of aerobic exercise compared with no exercise is associated with a significantly lower all-cause mortality (40%, 0.60 (0.49–0.72)).

The association between resistance training and cardiovascular mortality was tested in 122,671 participants and revealed that performing resistance training had a borderline association with lower cardiovascular mortality (hazard ratio 0.83 (0.68–1.01)) (Figure 3(a)). As shown in Figure 3(b) and (c), results suggested that no frequency of resistance training has a significant association with lower cardiovascular mortality. In contrast, as Figure 3(d) shows, the combination of any frequency of resistance training with any frequency of aerobic exercise compared with no exercise is significantly associated with lower cardiovascular mortality (0.43 (0.27–0.70)).

The result of the analysis of the data from 57,557 participants testing the association between resistance training and cancer mortality shows no association between resistance training and cancer mortality (0.81 (0.54–1.20)) (Figure 4(a)), which was not affected by increasing the frequency of resistance training in a week (Figure 4(b)). Furthermore, the combination of resistance training and aerobic exercise had no significant association with cancer mortality (Figure 4(c)).

We identified only one cohort study that investigated the association between resistance training and different types of non-fatal events. The study followed 44,452 US men for two years and defined coronary events as the occurrence of fatal coronary heart disease and non-fatal myocardial infarctions (MIs). The results of the study showed a 23% (RR 0.77, CI: 0.61–0.98) risk reduction in men who trained with weights for 30 min or more per week compared with men who did not train with weights.[28] Two other cohort studies investigated the association between resistance training and all fatal and non-fatal cardiovascular outcomes under a general definition of "cardiovascular disease (CVD)" and did not meet our inclusion criteria for the final analysis although they reported an association between resistance training and lower CVD.[29]

No study specifically assessed the association between resistance training and cerebrovascular outcomes.

Discussion

This study showed that performing resistance training is associated with lower all-cause mortality while it has a borderline association with cardiovascular mortality. There is an additional lowering of risk seen among those performing resistance training along with aerobic exercise. By contrast, there is no association between resistance training and cancer mortality. Based on the

Table 1. Characteristics of the studies included in the systematic review and meta-analysis of the association between resistance training and different cardiovascular outcomes.

First author	Year of publication	Study design	*N*	Mean follow-up (years)	Setting (PICO) (patient, intervention/exposure, comparison, outcome)	Factors adjusted for	Location of the study
Courneya[21]	2014	Randomized trial	242	7.4	**Participants**: breast cancer patients (female) between 2003 and 2005 **Intervention**: resistance exercise during chemotherapy, three times per week, performing two sets of 8–12, repetitions of nine different exercises at 60%–70% of their estimated 1-repetition maximum. Resistance was increased by 10% when participants completed > 12 repetitions. **Comparison**: usual care and supervised aerobic **Outcomes**: disease-free survival, overall survival, distant disease-free survival, and recurrence-free interval **Exclusion criteria**: Women were excluded if they had incomplete axillary surgery, transabdominal rectus abdominis muscle reconstructive surgery, uncontrolled hypertension, cardiac illness, and psychiatric illness or were otherwise not cleared by their oncologist	None	Canada
Dankel[16]	2016	Cohort	8772	6.7	**Participants**: Individuals, both men and women with mean, age 46.6 in alive participants and 72.2 in dead participants at the time of follow-up from the 2003–2006 NHANES **Exposure**: muscle-strengthening activities at baseline. Individuals self-reported their involvement in muscle-strengthening activities at the initial baseline assessment by responding to two questions: "Over the past 30 days, did you do any physical activities specifically designed to strengthen your muscles, such as lifting weight, push-ups or sit-ups?"; and if so "Over the past 30 days, how many times did you do these activities designed to strengthen your muscles, such as lifting weights, push-ups or sit-ups?" as the number of self-reported sessions completed within the past 30 days **Comparison**: not meeting the guideline for muscle strengthening activities **Outcomes**: all-cause and cardiovascular mortality adjusted for age, sex, ethnicity, average level of daily physical activities, mean CRP, overweight/obesity and number of comorbidities	Age, gender, ethnicity, education, average level of daily PA, mean CRP, weight, comorbidities.	The United States

(continued)

Table 1. Continued

First author	Year of publication	Study design	*N*	Mean follow-up (years)	Setting (PICO) (patient, intervention/exposure, comparison, outcome)	Factors adjusted for	Location of the study
Dankel[20]	2017	Cohort	2773	9.7	**Participants**: Individuals ≥ 50 years, both men and women, from the 1999–2002 NHANES **Exposure**: muscle-strengthening activities at baseline. Individuals self-reported their involvement in muscle-strengthening activities at the initial baseline assessment by responding to two questions: "Over the past 30 days, did you do any physical activities specifically designed to strengthen your muscles, such as lifting weight, push-ups or sit-ups?"; and if so "Over the past 30 days, how many times did you do these activities designed to strengthen your muscles, such as lifting weights, push-ups or sit-ups?" as the number of self-reported sessions completed within the past 30 days **Comparison**: not meeting the guideline for muscle strengthening activities **Outcomes**: cancer mortality adjusted for self-reported aerobic-based PA, age, race/ethnicity, total cholesterol; mean arterial pressure, body mass index, CRP, self-reported smoking status; and the following self-reported conditions: use of ambulatory device, statin medication, arthritis, congestive heart failure, coronary artery disease, cancer, diabetes, and stroke	Self-reported aerobic-based PA, age, race/ethnicity, total cholesterol; mean arterial pressure, body mass index, CRP, self-reported smoking status; and the following self-reported conditions: use of ambulatory device, statin medication, arthritis, congestive heart failure, coronary artery disease, cancer, diabetes, and stroke.	The United States
Evenson[22]	2016	Cohort	3809	6.7	**Participants**: Individuals ≥ 40 years, both male and female, from the 2003–2006 NHANES **Exposure**: muscle-strengthening activities at baseline. Individuals self-reported their involvement in muscle-strengthening activities at the initial baseline assessment by responding to two questions: "Over the past 30 days, did you do any physical activities specifically designed to strengthen your muscles, such as lifting weight, push-ups or sit-ups?"; and if so "Over the past 30 days, how many times did you do these activities designed to strengthen your muscles, such as lifting weights, push-ups or sit-ups?" as the number of self-reported sessions completed within the past 30 days **Comparison**: not meeting the guideline for muscle strengthening activities	Age, sex, race/ethnicity, educational, married, cigarette smoking, interaction between current employment and follow-up time, need special equipment to walk, arthritis, cancer, body mass index, interaction between body mass index categories and follow-up time, hypertension prehypertension, and diabetes, prediabetes, other PA/sedentary behavior components.	The United States

(continued)

Table 1. Continued

First author	Year of publication	Study design	*N*	Mean follow-up (years)	Setting (PICO) (patient, intervention/exposure, comparison, outcome)	Factors adjusted for	Location of the study
					Outcomes: all-cause and cardiovascular mortality adjusted for age, sex, race/ethnicity, educational level, marital status, smoking status, employment, the need for special equipment to walk, arthritis, and cancer **Exclusion**: Limited the sample to participants who were 40 years of age or older and excluded persons who were not eligible for mortality linkage. Participants were asked whether a doctor or health professional ever told them that they had a history of angina, coronary heart disease, congestive heart failure, myocardial infarction, or stroke. Participants were classified as having prevalent CVD if they answered "yes" to any of these five questions and were further excluded, although in sensitivity analyses these participants were incorporated. To account for prevalent conditions that might affect PA levels and sedentary behavior, they excluded participants who died in the first two years of follow-up. They also excluded those who either did not wear the accelerometer or whose accelerometer was found to not be in calibration upon return or was faulty. Further limited the cohort by excluding persons who did not provide adherent data. Lastly, excluded those who were missing data on self-reported PA or any potential confounder left in the final models.		
Grøntved[25]	2012	Cohort	32,002	18	**Participants**: men from the Health Professionals Follow-up Study **Exposure**: muscle-strengthening activities at baseline. The participants reported their average weekly amount of weight training, other physical activities **Comparison**: not meeting the guideline for muscle strengthening activities **Outcomes**: risk of type 2 diabetes, all-cause and cardiovascular mortality adjusted for 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, wholegrain, and glycemic load, aerobic exercise, other PA of at least moderate intensity, and TV viewing	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, wholegrain, and glycemic load, aerobic exercise, other PA of at least moderate intensity, and TV viewing, body mass index	The United States

(continued)

Table 1. Continued

First author	Year of publication	Study design	*N*	Mean follow-up (years)	Setting (PICO) (patient, intervention/exposure, comparison, outcome)	Factors adjusted for	Location of the study
					Exclusion: excluded those men who reported a history of diabetes, cancer, myocardial infarction angina, coronary artery bypass graft, other heart conditions, stroke, or pulmonary embolism on the baseline questionnaire (1986) and in 1988, and 1990.		
Hardee[26]	2014	Cohort	2863	7.3	**Participants**: cancer survivors aged 18–81 years, both male and female, who received a preventive medical examination while enrolled in the Aerobics Center Longitudinal Study in Dallas, Texas **Exposure**: $\geq$ 1 session of muscle-strengthening activities at baseline which was assessed by self-report on the medical history questionnaire. Participants were asked to provide yes/no answers to the following questions: 1). "Are you currently involved in a muscle-strengthening program?" 2). "Can you specify the muscle-strengthening activity as 'Calisthenics', 'Free Weights', 'Weight Training Machines', or 'Other'?" 3). "How many days per week do you do these exercises?" Those that responded "Yes" to free weights or weight training and had exercised at least one day per week were classified as positive for muscle-strengthening activity **Comparison**: no muscle strengthening activities in the past 30 days **Outcomes**: all-cause and cardiovascular mortality adjusted by age, gender, body mass index, current smoking, heavy drinking, hypertension, diabetes, hypercholesterolemia, and parental history of cancer **Exclusion**: Participants were excluded from the final analysis if they were underweight (body mass index $<$ 18.5); reported myocardial infarction or stroke; died during first year of follow-up; or had missing data on resistance exercise or PA	Age, gender, examination year, body mass index, current smoking, heavy drinking, hypertension, diabetes, hypercholesterolemia, and parental history of cancer, leisure-time aerobic physical activity, resistance exercise	The United States

(continued)

Table 1. Continued

First author	Year of publication	Study design	*N*	Mean follow-up (years)	Setting (PICO) (patient, intervention/exposure, comparison, outcome)	Factors adjusted for	Location of the study
Kamada[23]	2017	Cohort	28,879	12	**Participants**: participants of Women's Health Study (female) who were free of cardiovascular disease, diabetes mellitus, and cancer with average baseline age of 62.2 years **Exposure**: muscle-strengthening activities at baseline. A strength training questionnaire was included: "During the past month, what was your approximate time per week spent at each of the following recreational activities? Weight lifting/strength training." **Comparison**: no muscle strengthening activities in the past 30 days **Outcomes**: all-cause, cardiovascular, and cancer mortality adjusted for age and 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, and time per week spent in aerobic moderate to vigorous PA (for strength training and vice versa), body mass index and incidence of hypertension, high cholesterol, cardiovascular diseases, diabetes mellitus, and cancer before and during follow-up **Exclusion**: we excluded women with missing information on PA then, and women diagnosed as having CVD (myocardial infarction, stroke, percutaneous transluminal coronary angioplasty, or coronary artery bypass grafting), cancer, or diabetes mellitus before the 96-month questionnaire	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 moderate to vigorous PA, body mass index, incidence of hypertension, high cholesterol, cardiovascular diseases, diabetes mellitus, and cancer before and during follow-up	
Kraschnewski[27]	2016	Cohort	25,663	15	**Participants**: individuals $\geq$ 65 years, both men and women, from the 1997–2001 NHIS **Exposure**: muscle-strengthening activities at baseline that was assessed using the following question: "How often do you do leisure-time physical activities specifically designed to strengthen your muscles, such as lifting weight or doing calisthenics?" Participant responses included both the number of times strength training was performed and the unit of time (i.e. "per week," "per month").	Age, gender, race/ethnicity, educational status, marital status, body mass index, PA, alcohol use, smoking, diabetes mellitus, hypertension, coronary heart disease, non-skin cancer	The United States

(continued)

Table 1. Continued

First author	Year of publication	Study design	*N*	Mean follow-up (years)	Setting (PICO) (patient, intervention/exposure, comparison, outcome)	Factors adjusted for	Location of the study
					Comparison: not meeting the guideline for muscle strengthening activities **Outcomes**: all-cause mortality adjusted for age, gender, ethnicity, educational status, marital status, body mass index, PA, alcohol use, smoking status, diabetes, hypertension, coronary heart disease, non-skin cancers		
Loprinzi[14]	2015	Cohort	12,321	4.8	**Participants**: individuals with mean age of 45.0 years, both men and women, from the 1999–2004 NHANES **Exposure**: muscle-strengthening activities at baseline. Individuals self-reported their involvement in muscle-strengthening activities at the initial baseline assessment by responding to two questions: "Over the past 30 days, did you do any physical activities specifically designed to strengthen your muscles, such as lifting weight, push-ups or sit-ups?"; and if so "Over the past 30 days, how many times did you do these activities designed to strengthen your muscles, such as lifting weights, push-ups or sit-ups?" as the number of self-reported sessions completed within the past 30 days **Comparison**: not having muscle strengthening activities in the past 30 days **Outcomes**: all-cause mortality and cardiovascular mortality adjusted for age, gender, race–ethnicity, body mass index, and CRP **Exclusion**: excluding participants with missing data on the movement based behaviors, those with missing covariate data, those with missing mortality status or duration to follow-up	Age, gender, race–ethnicity, body mass index, and CRP	The United States
Schoenborn[15]	2011	Cohort	242,397	~7	**Participants**: individuals aged ≥ 18 years, both men and women, from the 1997–2004 NHIS **Exposure**: muscle-strengthening activities at baseline as the number of self-reported sessions completed within the past 30 days by asking: How often do you do LEISURE-TIME physical activities specifically designed to STRENGTHEN your muscles such as lifting weights or doing calisthenics? **Comparison**: not meeting the guideline for muscle strengthening activities	Gender, continuous age, race/ethnicity, education, poverty status, health insurance status, body mass index, smoking, and consumption of alcohol and were stratified by the presence/absence of selected chronic health conditions.	The United States

(continued)

Table 1. Continued

First author	Year of publication	Study design	*N*	Mean follow-up (years)	Setting (PICO) (patient, intervention/exposure, comparison, outcome)	Factors adjusted for	Location of the study
					Outcomes: all-cause mortality adjusted for gender, continuous age, race/ethnicity, education, poverty status, health insurance status, body mass index, smoking, consumption of alcohol, and chronic health condition **Exclusion**: excluding cases whose functional limitations may be the result of their closeness to death		
Zhao[24]	2013	Cohort	10,535	4.8	**Participants**: individuals aged $\geq$ 20 years, both men and women, from the 1999 to 2004 NHANES **Exposure**: muscle-strengthening activities at baseline. Individuals self-reported their involvement in muscle-strengthening activities at the initial baseline assessment by responding to two questions: "Over the past 30 days, did you do any physical activities specifically designed to strengthen your muscles, such as lifting weight, push-ups or sit-ups?"; and if so "Over the past 30 days, how many times did you do these activities designed to strengthen your muscles, such as lifting weights, push-ups or sit-ups?" as the number of self-reported sessions completed within the past 30 days **Comparison**: not meeting the guideline for muscle strengthening activities **Outcomes**: all-cause and cardiovascular mortality adjusted for sex, race/ethnicity, education, body weight status, smoking, heavy alcohol drinking, serum concentrations of total cholesterol and high-density lipoprotein cholesterol, elevated CRP, eGFR, pre-existing chronic conditions (hypertension, diabetes mellitus, cardiovascular disease, asthma, arthritis, disability, and cancer) and type of PA (aerobic and resistance) **Exclusion**: excluded women who reported being pregnant, adults who had missing responses to the questions on leisure-time PA or muscle-strengthening activity and adults with unascertained survival status and those with missing values for study covariates	Age, sex, race/ethnicity, education, body weight status, smoking, heavy alcohol drinking, serum concentrations of total cholesterol and high-density lipoprotein cholesterol, elevated CRP, eGFR, pre-existing chronic conditions (hypertension, diabetes mellitus, cardiovascular disease, asthma, arthritis, disability, and cancer), aerobic PA	The United States

CRP: C-reactive protein; CVD: cardiovascular disease; eGFR: estimated glomerular filtration rate; NHANES: National Health and Nutritional Examination Survey; NHIS: National Health Interview Survey; PA: physical activity

Table 2. Risk of bias in different domains[a] and overall risk of bias in different studies that were included in the systematic review and meta-analysis of the association between resistance training and mortality (all-cause, cardiovascular, and cancer).

First author	Sequence allocation	Allocation concealment	Blinding	Incomplete outcome data	Selective outcome reporting	Other sources of bias	Overall risk of bias	
Courneya[21]								
	Confounding	Participants	Classification of interventions	Deviations from intended interventions	Missing data	Measurement of the outcome	Selection of the reported result	Overall risk[b] of bias
Dankel 2016[16]								
Dankel 2017[20]								
Evenson[22]								
Grøntved[25]								
Hardee[26]								
Kamada[23]								
Kraschnewski[27]								
Loprinzi[14]								
Schoenborn[15]								
Zhao[24]								

[a]Different colors show different amount of risk of bias within different domains: green represents a low risk of bias, yellow represents an unclear risk of bias or not enough information is provided in the study to make a judgment and red represents serious-to-critical risk of bias within each domain.
[b]Shows the overall risk of bias in different studies in the range of low to critical (low, moderate, serious, and critical risk of bias). Green shows a low risk of bias and yellow shows a moderate risk of bias.

results of the study, only one cohort study looked at the association between resistance training and each non-fatal cardiovascular events also showing a lower risk of MI among those performing resistance training.

The associations between resistance training and all-cause and also borderline association with cardiovascular mortality could be explained by the multiple beneficial changes that occur with resistance training, related to changes in body composition and glucose metabolism and to the neuro-humoral system: resistance training decreases abdominal fat and specifically visceral fat, decreases the android-to-gynoid fat ratio, increases lean mass, prevents the development of sarcopenic obesity and slows muscle loss.[5,11,30] This is key because total body fat, and abdominal fat in particular, plays a pivotal role in facilitating the development of multiple kinds of chronic diseases such as obesity, type 2 diabetes mellitus (T2DM) and cardiovascular conditions;[8,11] all major contributors to a lower lifespan. On the other hand, obesity itself is associated with dysregulation of fatty acid metabolism resulting in accumulation of lipid in the skeletal muscle cells, which increases insulin resistance.[5] Resistance training also decreases inflammatory products, likely as a reflection of changes in body composition.[5,31] Because inflammatory mediators increase the risk of CVD, metabolic syndrome, and T2DM, the effect of resistance training on reducing these mediators would at

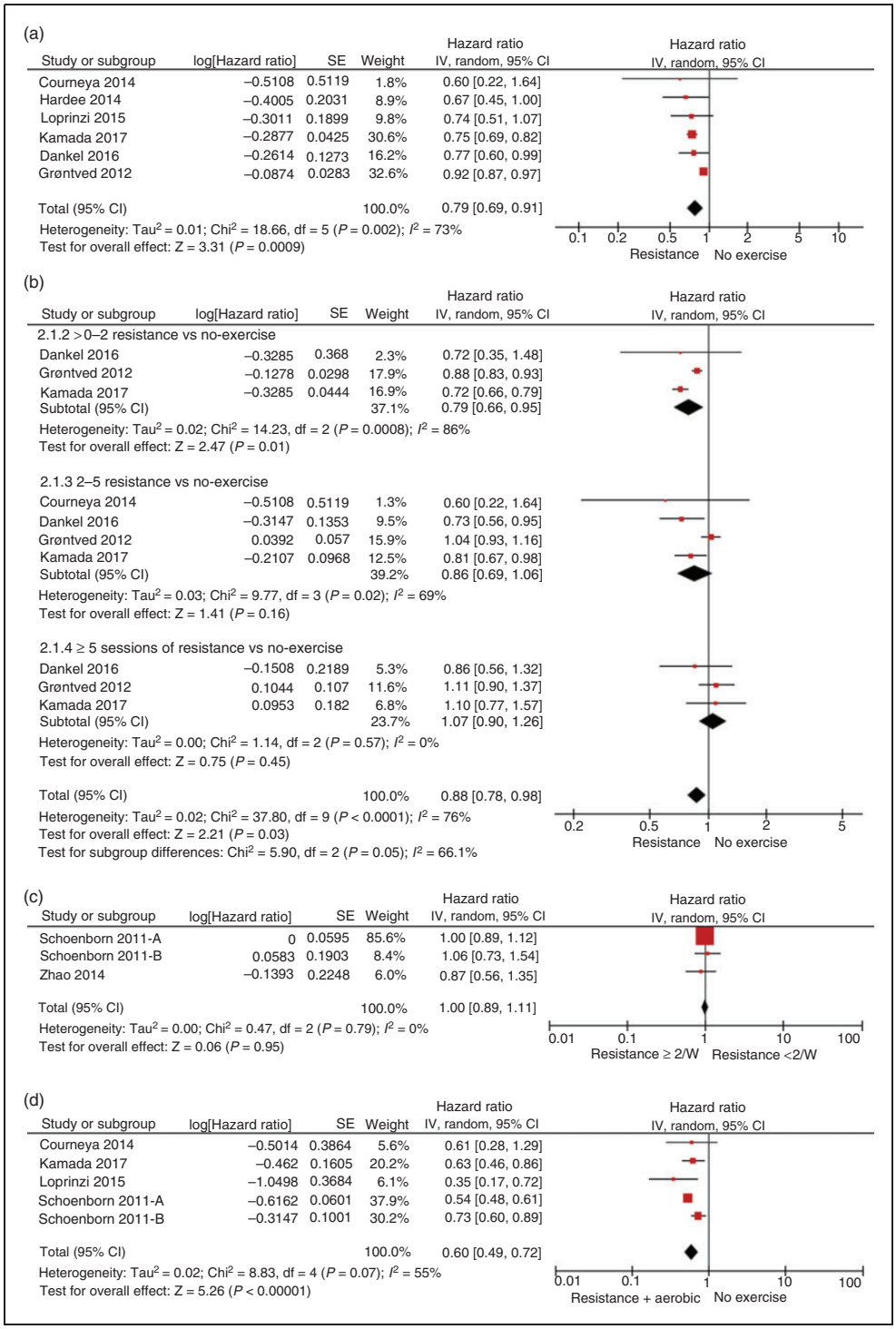

Figure 2. Meta-analysis of the association between resistance training and all-cause mortality. (a) The association between ≥ 1 sessions of resistance training in the last 30 days versus performing no exercise and all-cause mortality. (b) Subgroup analysis based on the association between different doses of resistance training and all-cause mortality. (c) Difference between the association of ≥2 and <2 sessions of resistance training per week with all-cause mortality. (d) The association of the combination of resistance training and aerobic exercise versus no-exercise with all-cause mortality. Squares show the weight given to each study in the analysis; larger squares represent bigger weights. Diamonds denote pooled effect size. Vertical lines represent no effect.
SE: standard error; IV: inverse variance; CI: confidence interval

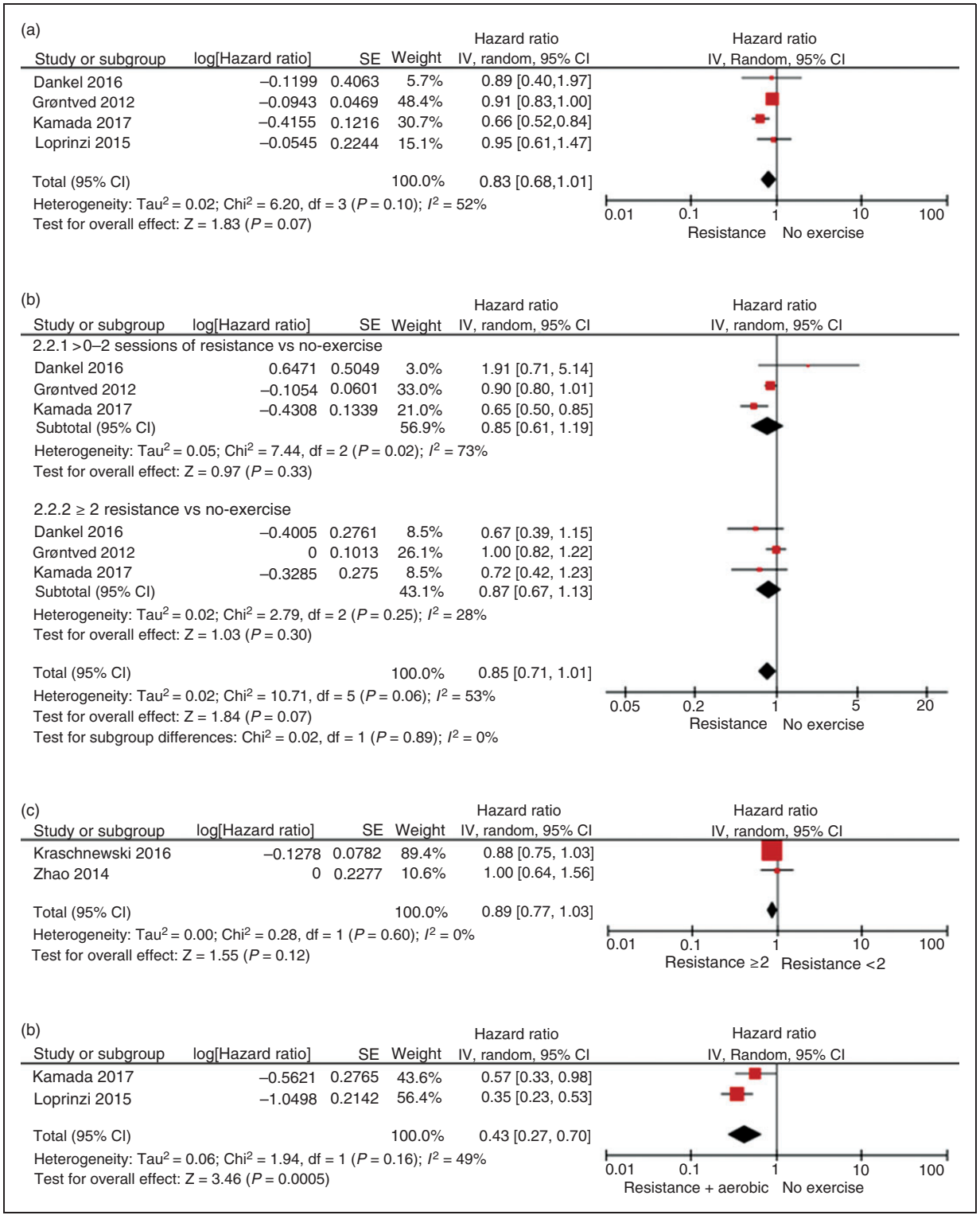

Figure 3. Meta-analysis of the association between resistance training and cardiovascular mortality. (a) The association between ≥ 1 sessions of resistance training in the last 30 days versus performing no exercise and cardiovascular mortality. (b) Subgroup analysis based on the association between different doses of resistance training and cardiovascular mortality. (c) Difference between the association of ≥2 and <2 sessions of resistance training per week with cardiovascular mortality. (d) The association of the combination of resistance training and aerobic exercise versus no exercise with cardiovascular mortality. Squares show the weight given to each study in the analysis; larger squares represent bigger weights. Diamonds denote pooled effect size. Vertical lines represent no effect.

SE: standard error; IV: inverse variance; CI: confidence interval

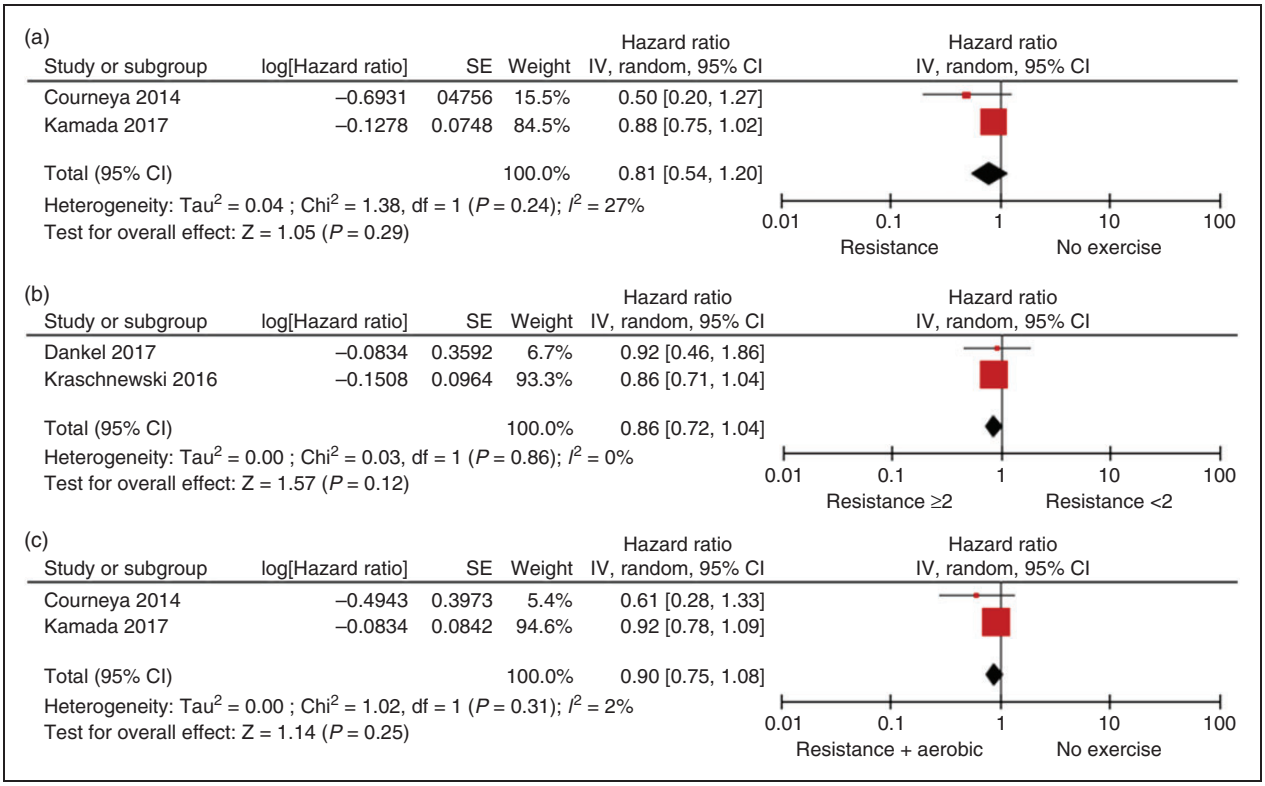

Figure 4. Meta-analysis of the association between resistance training and cancer mortality. (a) The association between ≥ 1 sessions of resistance training per week versus performing no exercise and cancer mortality. (b) Difference between the association of ≥2 and <2 sessions of resistance training per week with cancer mortality. (c) The association of the combination of resistance training and aerobic exercise versus no-exercise with cancer mortality. Squares show the weight given to each study in the analysis; larger squares represent bigger weights. Diamonds denote pooled effect size. Vertical lines represent no effect.
SE: standard error; IV: inverse variance; CI: confidence interval

least partially explain the lower mortality in people performing resistance training. In addition, resistance training increases clearance of very low-density lipoprotein-triglycerides from plasma as well as lipoprotein lipase gene expression and activity on the muscle cell membranes, thereby increasing the catabolism and hydrolysis of very low-density lipoprotein-triglycerides.[5] Lastly, resistance training improves mitochondrial function in skeletal muscles and increases the expression of glucose transporter type 4, the translocator of glucose in the skeletal muscle, thus ultimately increasing glucose uptake and glycogen synthesis in this tissue. The overall outcome is decreased blood glucose and reduced cellular content of lipids, leading to improved control of T2DM.[5] The simultaneous increase in lean mass due to resistance training also increases basal metabolic rate,[32] potentially contributing to the prevention of obesity.

Evidence shows that performing four months of resistance training or aerobic exercise leads to comparable decreases in hepatic fat content, body fat mass, HBA1c levels, T2DM and non-alcoholic fatty liver disease, while also increasing insulin sensitivity.[33] In addition, a meta-analysis revealed that resistance training (dynamic or isometric) may significantly lower systolic and diastolic blood pressure.[4] Also another meta-analysis showed that resistance training increases the lower and upper body strength and aerobic fitness to a similar degree of aerobic exercise in patients with coronary artery disease.[7] All these physiologic adaptations resulting from resistance training may likely explain the inverse association between resistance training and mortality. On the other hand, Werner et al. found that, in contrast to endurance training, resistance training was not associated with telomerase activity and length, suggesting that resistance training had no anti-aging effect.[34] This may explain why the potentially beneficial effects of resistance training in survival were modest when compared with endurance training.

In contrast to the improvements in overall mortality and possible reduction in cardiovascular mortality, this analysis showed no significant association between resistance training and cancer mortality. Regardless of

its association with mortality, resistance training is likely to be particularly important for cancer patients, as it helps to improve their muscle strength and specifically retains lean body mass.[35,36] This may help to protect patients from the adverse musculoskeletal effects of cancer treatments such as chemotherapy, as well as increasing quality of life and functional capacity compared with patients that do not participate in resistance training.[21,37,38]

Besides the overall association between resistance training and cardiovascular outcomes, a key question in the association between resistance training and cardiovascular outcomes is how much resistance training is associated with maximal health benefits. The results of this study suggested a ''U-shape'' dose–response relationship between resistance training and all-cause and cardiovascular mortality, which reflects the results of some of the included studies.[16,23] Similarly, studies testing the association of resistance training with glycemic control in T2DM patients showed a non-linear relationship between repetition and intensity of resistance training and HbA1c levels.[39,40] One potential explanation for the non-linear association between resistance training and mortality could be related to the possible adverse effects of high-intensity resistance training, which may significantly affect heart rate, increase blood pressure and lead to adverse events.[41,42] Also high-intensity resistance training has been associated with increased arterial stiffness via increasing sympathetic nervous system activity which contributes to chronic restraint on the arterial wall.[43] The accentuated Valsalva maneuver occurring during resistance training may result in some changes to heart rhythm such as bradycardia or atrial ectopy: a rapid fall in blood pressure after maximum workload can cause syncope even in healthy adults.[44] Finally, people performing a high volume of resistance training may be more likely to use anabolic–androgenic steroids or supplements with substances that could adversely affect their health.[45] Some of our analysis suggest that the optimal health benefits of resistance training are most likely obtained by 1–2 sessions per week and avoiding high-intensity low-repetition type activities. However, it is important to recognize that the current evidence is not enough to conclude that the relationship between resistance training and survival has a U-shape curve.

As expected, the association between the combination of the resistance and aerobic training with all-cause and cardiovascular mortality was greater than the association of each kind of exercises alone with all-cause mortality. This confirms the results of the individual studies in this regard.[14,15,21,23]

To the best of our knowledge, this is the first systematic review and meta-analysis assessing the association between resistance training and total mortality and major cardiovascular outcomes, with over 370,000 participants and around nine years of follow-up. Additionally, the included studies evaluated the association exclusively between resistance training and mortality, adjusting for different types of exercise and for cardiovascular risk factors, thereby increasing the validity of the results. This study also pooled data on the association between the combination of resistance training and aerobic exercise with mortality from different causes; although the direction of the result was not surprising, it can be used as objective evidence supporting current guidelines.[46]

This study had several limitations. Most of the included studies were observational studies and the only included randomized clinical trial was on patients with breast cancer. The observational nature of most of the studies is a major limitation, a limitation shared with the level of evidence testing the effect of aerobic exercise on major cardiovascular outcomes and mortality. This raises concerns about potential confounders not accounted for in the multivariate analyses of each study. It is possible that unaccounted confounders such diet, medical conditions, use of medications or anabolic steroids may have affected the results. Most participants in the primary studies represented the general population and therefore the generalizability of the results to cardiac patients could be questionable. Studies performed in cardiac patients are needed to prove the safety and benefit of resistance training among those with cardiovascular diseases. The definition of resistance training between studies was heterogeneous, underscoring the complexity of measuring resistance training dose according to type of resistance training, repetition, intensity, resting time and whether machines, free weights or no equipment were used. The exposure to resistance training was self-reported and measured using questionnaires. Resistance training was assessed at a single time, with no information about initiation or changes in frequency or duration of resistance training over time, limiting the validity of the data. Furthermore, heterogeneity was high in some analyses, likely reflecting differences in the type of resistance training or in the populations studied. Unfortunately, the differences in type and dose of resistance training across studies could not be accurately determined, preventing a subgroup analysis to prove this hypothesis. There was no study that directly compared resistance training with aerobic exercise and their association with mortality from different causes, limiting our ability to make conclusions about the benefit of performing resistance training instead of aerobic exercise. The results also highlight the limited data assessing the association between resistance training and non-fatal cardiovascular outcomes such as MI, sudden death, and stroke. It also remains unclear how

resistance training and aerobic exercise compare, and what is the optimal dose of resistance training, alone and in combination with aerobic exercise, for health benefits in both the general population and specific patient groups. The limited number of eligible studies was also a limitation, although the number of the study participants was considerably large. Further studies testing the association between resistance training and major cardiovascular outcomes will help to elucidate the role of resistance training in cardiovascular disease prevention as well as the optimal dose and modality of resistance training to yield any benefit.

Conclusion

There is a significant association between resistance training and lower all-cause mortality and a borderline association with cardiovascular mortality. There are insufficient data to determine the potential beneficial effect of resistance training on non-fatal events or the effect of substituting aerobic exercise with resistance training.

Author contribution

FS, JRMI, CPW, TPO, VKS, ARB, LJP, MV and FLJ contributed to the conception or design of the work. FS and FLJ contributed to the acquisition, analysis, and interpretation of data, JRMI contributed to the acquisition and analysis, CPW, TPO, VKS and ARB contributed to the interpretation and LJP contributed to the acquisition of the data for the work. FS, JRMI, CPW, TPO, VKS, ARB, LJP, MV and FLJ drafted the manuscript. FS, JRMI, CPW, TPO, VKS, ARB, LJP, MV and FLJ critically revised the manuscript. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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