‘Weight-ing to Live’: investigating the association between resistance training and all-cause mortality, cardiovascular disease mortality and cancer mortality

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List of Abbreviations

Acronym	Definition
ABS	Australian Bureau of Statistics
AIHW	Australian Institute of Health and Welfare
CI	Confidence Interval
CVD	Cardiovascular disease
g	grams
HR	Hazards Ratio
I^2	Degree of heterogeneity
kg	kilograms
m	metres
MET-hrs	Metabolic equivalent hours
mins	minutes
MVPA	Moderate to Vigorous physical activity
n	number of
NIH-AARP	National Institutes of Health-American Association of Retired Persons
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	Prospective Register of Systematic Reviews
RR	Risk ratio
RT	Resistance training
SEER	Surveillance epidemiology end result
WHO	World Health Organization
WT	Weight training

Summary

Resistance training, also called weight training, strength training and muscle strengthening activity, is aimed at improving muscular strength, endurance, balance, and power. This thesis will continue to refer to the exposure as ‘resistance training’, except in Chapter 3 where the exposure will specifically be called ‘weight training’. While previous research indicates resistance training is associated with a range of cardiometabolic, musculoskeletal and mental health benefits, less is known about the benefits of resistance training for reducing mortality risk.

As outlined in Chapter 1, the overall aim of the research program described in this thesis was to extend the current understanding of the relationship between resistance training and mortality risk. The specific objectives of the research program related to the following research questions:

(1) Is resistance training associated with the risk of all-cause, cancer-specific and/or cardiovascular disease (CVD)-specific mortality?

(2) What is the dose-response relationship between resistance training and mortality risk?

(3) Does performing both resistance training and MVPA reduce mortality risk more than performing either of these activities alone?

The first study (Chapter 2) is a systematic review and meta-analysis that investigated current research on the relationship between resistance training and mortality. The inclusion criteria was met by eleven cohort studies. The results of the meta-analyses showed that, compared with doing none, engaging in any amount of resistance training decreased the risk of all-cause mortality by 15%, the risk of CVD mortality by 13% and the risk of cancer mortality by 14%. A dose-response meta-analysis of four studies found a maximum all-cause mortality risk reduction of 27% at 60 minutes per week of resistance training, but no further mortality benefits beyond that volume. The results also indicated ~~also~~ that engaging in both resistance training and MVPA provided greater mortality benefits than engaging in either alone.

The second study (Chapter 3) was an original study on the association between weight training and mortality risk and used data from the NIH-AARP Diet and Health cohort (n=221,857 participants). After adjusting for confounders, engaging in any amount of weight

training reduced the risk of all-cause mortality by 9%, the risk of CVD mortality by 10% and the risk of cancer mortality by 9%, compared to doing none. In a dose-response analysis the maximum risk reduction for all three mortality outcomes were observed at 2-3 hours of weight training per week and higher durations were associated with smaller or no mortality benefits. Engaging in both resistance training and MVPA provided greater mortality benefits than engaging in either alone, as was also observed in the systematic review.

In conclusion, the results of this research program indicate that engaging in resistance training may have mortality benefits. These findings support the inclusion of muscle-strengthening activities in physical activity guidelines. The results of the research program are summarised in the final section of the thesis (Chapter 4), along with the public health implications of the findings and directions for future research on resistance training and mortality.

Declaration

This thesis presents studies that were carried out by myself and does not incorporate any material that has not been properly acknowledged or any material that has been previously submitted for a degree or diploma in any university, to the best of my knowledge. It does not contain previously published material or material written by another person except where due reference is made in the text.



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Chapter 1: Introduction

1.1 Background

Cardiovascular disease (CVD) and cancer are the two leading causes of death in Australia (AIHW 2018). In 2017, 30.5% of all deaths in Australia were due to CVD. Coronary heart disease accounted for 44% of CVD-related deaths, while 18% were due to stroke and 10% were due to heart failure or cardiomyopathy (AIHW 2018). There were 45,200 deaths due to cancer in 2017 in Australia, accounting for 28% of total deaths (ABS 2019). The leading causes of cancer mortality in Australia were lung cancer, bowel cancer, prostate cancer, and breast cancer (ABS 2019). CVD and cancer share many modifiable and non-modifiable risk factors. Non-modifiable risk factors include age, sex, ethnicity and family history (Ligibel 2012). Modifiable energy-balance factors, such as diet and body weight, have been identified as having a strong association with the risk of developing and dying from CVD and several cancers (Odegaard *et al*. 2011). Other modifiable lifestyle factors, such as alcohol and tobacco consumption, have also been strongly linked with developing CVD and some cancers (Ligibel 2012).

Physical activity is another modifiable exposure that has been shown to reduce the risk of developing CVD and several types of cancer, as well as both CVD ~~mortality~~ and cancer mortality (Samitz, Egger & Zwahlen, 2011). ~~Physical activity can be broadly classified into two different types: aerobic (e.g., walking, jogging, and biking) and anaerobic exercises (e.g. resistance training, also termed strength training or weight training).~~ Moderate to vigorous physical activity (MVPA) has been associated with the prevention of non-communicable diseases such as CVD, type-2 diabetes and some cancers (Lee *et al.* 2012). Resistance training activities are performed to increase muscle resistance, endurance and power, by specifically targeting the musculoskeletal system (Peterson & Serra-Rexach 2012). MVPA in particular has been strongly associated with a reduction in the risk of chronic disease and premature mortality (Samitz, Egger & Zwahlen, 2011), and based on this strong evidence the Australian Physical Activity Guidelines and the World Health Organisation (WHO) guidelines recommend that adults take part in 150 to 300 minutes of moderate intensity physical activity or 75 to 150 minutes of vigorous physical activity per week (Department of Health 2014; Bull et al., 2020). The Guidelines also recommended that adults participate in muscle-strengthening activities such as resistance training at least two days per week (Department of Health 2014). This recommendation is based on evidence that resistance training reduces age-related muscle and bone density loss and improves general

health, especially in older adults (Nelson *et al*. 2007). Some research also indicates resistance training may reduce the risk of mortality and some chronic diseases (Saeidifard *et al*. 2019); however, there is very limited research on this topic compared to the myriad of research on the benefits of MVPA and reduced mortality and risk of chronic disease (Fogelholm 2010).

1.2 Resistance Training and Mortality

Resistance training refers to several forms of exercises intended to overload the body (Kraemer & Ratamess 2004). Resistance training elicits physiological adaptations by applying the force of resistance (including body weight or resistance external to the body) in an attempt to move one or more joints through a range of motion or to prevent the motion (Behm & Colado 2012). Common resistance training activities include lifting weights and body weight movements such as squats, lunges and push-ups, and are commonly prescribed in repetitions (reps) and sets (Kraemer & Ratamess 2004). Following regular resistance training activities, metabolic, neural, muscular, connective tissue, endocrine and cardiovascular changes occur and give rise to increases in muscular strength, power, speed, endurance, muscle-hypertrophy, motor performance, balance and coordination (Kraemer & Ratamess 2004). Systematic reviews and meta-analyses of controlled studies found that engaging in resistance training is independently associated with a range of health benefits, such as cardio-metabolic (Ashton et al., 2020; MacDonald et al., 2016) musculo-skeletal (Martyn-St James and Carroll, 2009; Zhao et al., 2015) and mental health benefits (Gordon et al., 2017; Gordon et al., 2018). Systematic reviews of randomised controlled trials also indicate that the combination of resistance training and aerobic training leads to greater improvements in anthropometric outcomes (Morze et al., 2021), metabolic syndrome factors and cardiovascular risk markers (Minyu et al., 2021) than performing either of those activities alone. Less is known about the impact that resistance training has on the risk of chronic disease and mortality. While some studies have found that resistance training is associated with a lower risk of CVD, some cancers, type 2 diabetes and all-cause mortality, more research is needed to confirm the emerging evidence from a limited number of studies (Bennie et al., 2020).

While the results of the limited number of studies to date concerning resistance training and the risk of all-cause mortality suggest an inverse association, there remains critical gaps in the literature. One reason for the limited research on RT and health outcomes such as mortality is that historically the vast majority of cohort and case-control studies did not ask participants about RT specifically, or if they did it was included as a type of MVPA rather than a distinct form of physical activity. Of the six studies which have examined the relationship between resistance training and all-cause mortality, five (Dankel et al. 2016; Kamada et al. 2017; Kraschnewski et al. 2016; Siapush et al. 2019; Stamatakis et al. 2018) have found a significant association between resistance training and mortality, while the study conducted by Zhao et al. (2014) failed to find an association. However, the studies listed did not specify whether the association differs between males and females and only a few studies have investigated the association between performing both resistance training and MVPA (as recommended by physical activity guidelines) on all three mortality outcomes. There is also limited research on the "dose-response" association between resistance training and all-cause mortality risk (Kamada et al., 2017; Stamatakis et al., 2018; Liu et al., 2019; Patel et al., 2020). All four studies measured the exposure as the number of minutes/hours per week that participants engaged in "weight-training/resistance exercises" (Patel et al., 2020) and "weight-lifting/strength training" (Kamada et al., 2017). However, the results did not present a clear picture on how much and how often people should undertake resistance training to get the maximum mortality benefits.

A range of different terms for resistance training have been used in various epidemiological studies, including, but not limited to, 'weight-training', 'strength-training' and 'muscle-strengthening activity'. These terms used are not clearly defined, which limits the exact definition and type of physical activity that was measured. This makes it more difficult to draw any strong conclusions from the literature. I will use the term 'resistance training' throughout my thesis, except in Chapter 3 and when referring to the results of Chapter 3, where I will use 'weight-training', as that was the exact term used in the questionnaire and measured in the study.

1.3 Aims and Objectives

Given the limited evidence base around the association between resistance training and all-cause mortality, the overall aim of the research program described in this thesis was to extend

the current understanding of the relationship between resistance training and risk of all-cause mortality, cancer-specific mortality, and CVD-specific mortality. The specific objectives of the research program related to the following research questions:

1) Is resistance training associated with the risk of all-cause, cancer-specific and/or CVD-specific mortality?
2) What is the dose-response relationship between resistance training and mortality risk?
3) Does performing both resistance training and MVPA reduce mortality risk more than performing either of these activities alone?

The aim and objective of this research program were achieved by conducting two studies. The first study systematically reviewed the current research regarding the association between resistance training and mortality (Chapter Two). The second study involved analysing data from the National Institutes of Health-American Association of Retired Persons (NIH-AARP) Diet and Health Cohort Study. This dataset consisted of mid-to-older adults and was used to investigate the relationship between weight training and cardiovascular mortality, cancer mortality and all-cause mortality (Chapter Three).

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Chapter 2: The association between resistance training and all-cause mortality, cardiovascular disease mortality and cancer mortality: A systematic review and meta-analysis

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This systematic review was recently submitted to the American Journal of Preventive Medicine (AJPM) and it is currently under review thus is formatted as per the journal specifications. AJPM is a peer-reviewed journal that publishes research in the areas of preventive research, practice, and policy.

Abstract

Objective: Systematically review and meta-analyse the relationship between resistance training and all-cause, cardiovascular disease (CVD), and cancer mortality.

Design: Systematic review and meta-analysis following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (PROSPERO Registration No. CRD42019136654).

Data Sources: MEDLINE (OVID), Embase, Emcare, SPORTDiscus, The Cochrane Library, and SCOPUS were searched from inception to 6 June 2021.

Eligibility criteria for selecting studies: Included studies reported resistance training as the exposure and CVD-specific mortality, cancer-specific mortality, and/or all-cause mortality as outcome/s. Only studies conducted among non-clinical adult populations (18 years or older) and written in English were included.

Results: Eleven studies were included in the meta-analyses. Compared to no resistance training, undertaking any amount of resistance training reduced the risk of all-cause mortality by 15% (Relative Risk (RR)=0.85; 95% Confidence Interval (CI) [0.77; 0.93]), CVD mortality by 13% (RR=0.87; 95% CI [0.77; 0.99]) and cancer mortality by 14% (RR=0.86; 95% CI [0.78; 0.95]). A dose-response meta-analysis of four studies suggested a non-linear relationship between resistance training and risk of all-cause mortality. A maximum risk reduction of 27% was observed at around 60 minutes per week of resistance training (RR= 0.73; 95% CI= 0.63; 0.85). Mortality risk reductions diminished at higher volumes.

Conclusion: This systematic review and meta-analysis provides strong evidence that resistance training is associated with reduced risk of all-cause, CVD, and cancer-specific mortality. More research is needed to determine if any potential mortality benefits gained from resistance training diminish at higher volumes.

2.1 Introduction

Cardiovascular diseases (CVDs) and cancers are the leading cause of death globally, accounting for an estimated 32% and 17% of all reported deaths in 2019, respectively (WHO, 2020). Physical inactivity is an important modifiable risk factor for the prevention and management of CVD and cancer (WHO, 2020; Physical Activities Committee, 2018). At present, the majority of epidemiological evidence on physical activity and health is based on studies assessing the health benefits of moderate-to-vigorous intensity physical activity (MVPA; walking, cycling, running etc.). In brief, regular engagement in MVPA is recognized as a strong protective factor against a wide range of health outcomes, including the risk of CVD (Sattelmair et al., 2011) and some cancers (Moore et al., 2016) as well as the risk of CVD mortality, cancer-mortality, and all-cause mortality (WHO, 2020).
For optimal health and wellbeing, the 2020 World Health Organisation (WHO) physical activity guidelines recommend adults take part in 150 to 300 minutes of moderate-intensity physical activity or 75 to 150 minutes of vigorous physical activity per week (Bull et al., 2020). The WHO physical activity guidelines also recommended that adults participate in muscle-strengthening activity at least two days per week (Bull et al., 2020). Resistance training also referred to as strength- or weight-training or muscle-strengthening activity, is a common activity/exercise mode that is performed with the purpose of increasing muscle strength, endurance, and power by specifically targeting the musculoskeletal system (Peterson and Serra-Rexach, 2012). Systematic reviews and meta-analyses of controlled exercise studies have shown that resistance training is independently associated with a range of cardiometabolic, (Ashton et al., 2020; MacDonald et al., 2016) musculoskeletal, (Martyn-St James and Carroll, 2009; Zhao et al., 2015) and mental health benefits (Gordon et al., 2017; Gordon et al., 2018). However, less is known about the benefits of resistance training for reducing the risk of all-cause mortality, CVD mortality, and cancer mortality, particularly compared to the large body of epidemiological evidence on the benefits of MVPA for these outcomes (Bennie et al., 2020).

A systematic review of studies published up to 2018 by Saeidifard et al. (2019) found that doing any amount of resistance training was associated with 21% lower all-cause mortality compared with doing none (n=six studies). Saeidifard et al. (2019) also found a 40% risk reduction in all-cause mortality among those doing resistance training in conjunction with MVPA compared with those not performing either of these activities, and this risk reduction

was greater than was observed for performing either of these activities alone. The results of the review also provided some evidence that resistance training may be associated with risk reductions for CVD-mortality and cancer-mortality, although the summary estimates were limited as these were only based on four and two studies, respectively (Saeidifard et al., 2019).

Since the review by Saeidifard et al. (2019) several additional studies have reported on the relationships between resistance training and all-cause, CVD, and cancer mortality (Porter et al., 2020; Stamatakis et al., 2018; Zhao et al., 2020). As such, there is a need for an updated systematic review to consolidate the growing body of research on the association between resistance training and mortality, particularly the evidence for CVD-mortality and cancer-mortality, and to better understand the dose-response relationship between resistance training and mortality. Updated research on the associations between resistance training and mortality outcomes will provide information critical to the development of future physical activity guidelines, especially regarding the nature of the dose-response relationship.
The aim of this systematic review and meta-analysis was to examine the relationships between resistance training and the risk of all-cause mortality, CVD mortality and cancer mortality among the general adult population. This review also examined the dose-response relationship between resistance training and mortality outcomes, and whether the joint association of resistance training and MVPA confers greater mortality-related benefit compared to either MVPA or resistance training alone.

2.2 Methods

2.2.1 Protocol and Search Strategy

This systematic review follows the preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (Moher et al., 2009) and was registered with the International Prospective Register of Systematic Reviews (PROSPERO) database (Registration number CRD42019136654). Initially, we planned to include cancer risk outcomes in addition to mortality outcomes in this review. However, studies on cancer risk outcomes were excluded after the data extraction phase due to the publication of a review on those outcomes (Nascimento et al., 2021).

With the aid of an academic librarian, a systematic search for peer-reviewed articles published up to 6 June 2021 was conducted using an amalgamation of keywords and Medical Subject Headings (MeSH) controlled vocabulary in the following databases: MEDLINE (OVID), Embase, Emcare, SPORTDiscus, The Cochrane Library and SCOPUS (Supplementary Table 2, Appendix A), The reference lists of relevant systematic reviews and all included studies were also screened. In addition, Google Scholar was used to conduct a forward citation search of relevant systematic reviews and all included studies. Studies were considered eligible for inclusion if they investigated and reported on exposure to resistance training and mortality within a healthy adult population of those aged ≥18 years and were either an RCT or a cohort study. The studies which included exposure to MVPA in combination with resistance training were included in the joint association analysis. Studies that were conducted in clinical populations (e.g., cancer survivors), nonhuman studies, studies not published in English, editorials, reviews, commentaries, conference abstracts, and letters were excluded.

2.2.2 Study selection

All studies identified by the search were imported into Covidence^{TM}, where duplicates were removed before screening. Three investigators (PS, TB, and KL) conducted the title and abstract screening independently against the eligibility criteria. Any conflicts were resolved by consensus between two investigators (PS and TB). Two investigators (PS and TB) then reviewed the full text of eligible studies against the eligibility criteria. Disagreements were resolved by discussion and consensus between the same two investigators. Where more than one published article had used the same or overlapping data to investigate the same outcome, we only included the study with the largest sample size.

2.2.3 Risk of Bias

The 'Tool to Assess Risk of Bias in Cohort Studies' was used to assess the risk of bias of the cohort studies and was developed by the CLARITY Group at McMaster University 2013. (Tools to assess risk of bias in cohort studies). The risk of bias tool was used to assess the study selection, measurement of the exposure, matching, and assessment of the prognostic variables (i.e., consideration and adjustment of confounders), confidence in the outcome, adequate follow-up, and the similarity between the intervention and non-intervention groups (Tools to assess risk of bias in cohort studies). Researchers select from the range of response options provided for each question, including, "1 - Definitely yes (low risk of bias)", "2-

Probably yes", "3- Probably no", and "4- Definitely no (high risk of bias)". The appraisal was completed independently by two reviewers (PS and TB) and any differences were resolved by consensus.

2.2.4 Data Extraction

Data extraction was performed for all studies that met the inclusion criteria, using a pre-determined data extraction proforma in Microsoft Excel (version 1811, © Microsoft Cooperation 2018) by one investigator (PS). The extraction template was trialled on one study by one investigator (PS); the other three investigators (TB, KB and KL) revised the template, and all four investigators came to an agreement over the template used.
The accuracy of the extracted data extracted was independently reviewed by a second investigator (TB), and any disagreements or discrepancies were resolved by consensus.
The following general variables were extracted: author, year of publication, country, dataset, and study population characteristics such as sample size, age, and gender**.** Details on exposure characteristics included details on date, type, duration, intensity and/or frequency of resistance training and MVPA at baseline (and any follow-ups if applicable). The outcome measures included the date of the end of follow-up, mean or median follow-up time, total person-years of follow-up in different categories of the exposure, all effect sizes (e.g., hazard ratios, odds ratios), and associated 95% confidence intervals related to the association between resistance training and the risk of mortality (all-cause, CVD, cancer) and all effect sizes and associated 95% CIs related to the joint association between resistance training and MVPA with mortality risk.

2.2.5 Meta-Analysis

For all-cause, CVD and cancer mortality outcomes with risk estimates from three or more studies available, random-effects meta-analyses were conducted to estimate the association between: (1) performing any amount of resistance training compared with performing no resistance training; and (2) the highest levels of resistance training compared with the lowest levels of resistance training reported (highest versus lowest) and the outcome. Statistical heterogeneity between studies was tested using the Cochrane's Q test and quantified by the I^2 statistic. Forest plots were used to visually display the summary effect size and individual results of the studies included in each meta-analysis. A narrative synthesis of results was undertaken for all outcomes with fewer than three studies.

A one-stage random-effects dose-response meta-analysis using restricted cubic splines (with knots placed at 0, 1, and 180 minutes) was performed to estimate the relationship between volume of resistance training (i.e., minutes per week) and all-cause mortality and to investigate if the dose-response relationship was non-linear. Where applicable, the midpoint of each category of resistance training was used as the dose. If person-years were not reported for each category of resistance training it was estimated by multiplying the number of persons in a specific exposure group and the mean follow-up years of the total study population. Stata (version 16; StataCorp, College Station TX) was used for all analyses.

2.3 Results

The initial search identified 6,702 studies. After removal of duplicates (n=3,137) and initial title and abstract screening, 47 studies were included for full-text screening. Of these 47 studies, we excluded nine that were conducted on clinical populations, eight that did not have resistance training as an exposure, seven that did not include any of the outcomes of interest, and four articles that were a review, editorial, or letter. Eight further studies were excluded due to overlapping samples (Dankel et al., 2016; Dankel et al., 2018; Evenson et al., 2016; Loprinzi and Davis, 2015; Loprinzi and Loenneke, 2016; Schoenborn and Stommel, 2011; Zhao et al., 2014,). A total of 11 studies met the eligibility criteria for inclusion (Figure 2.1).

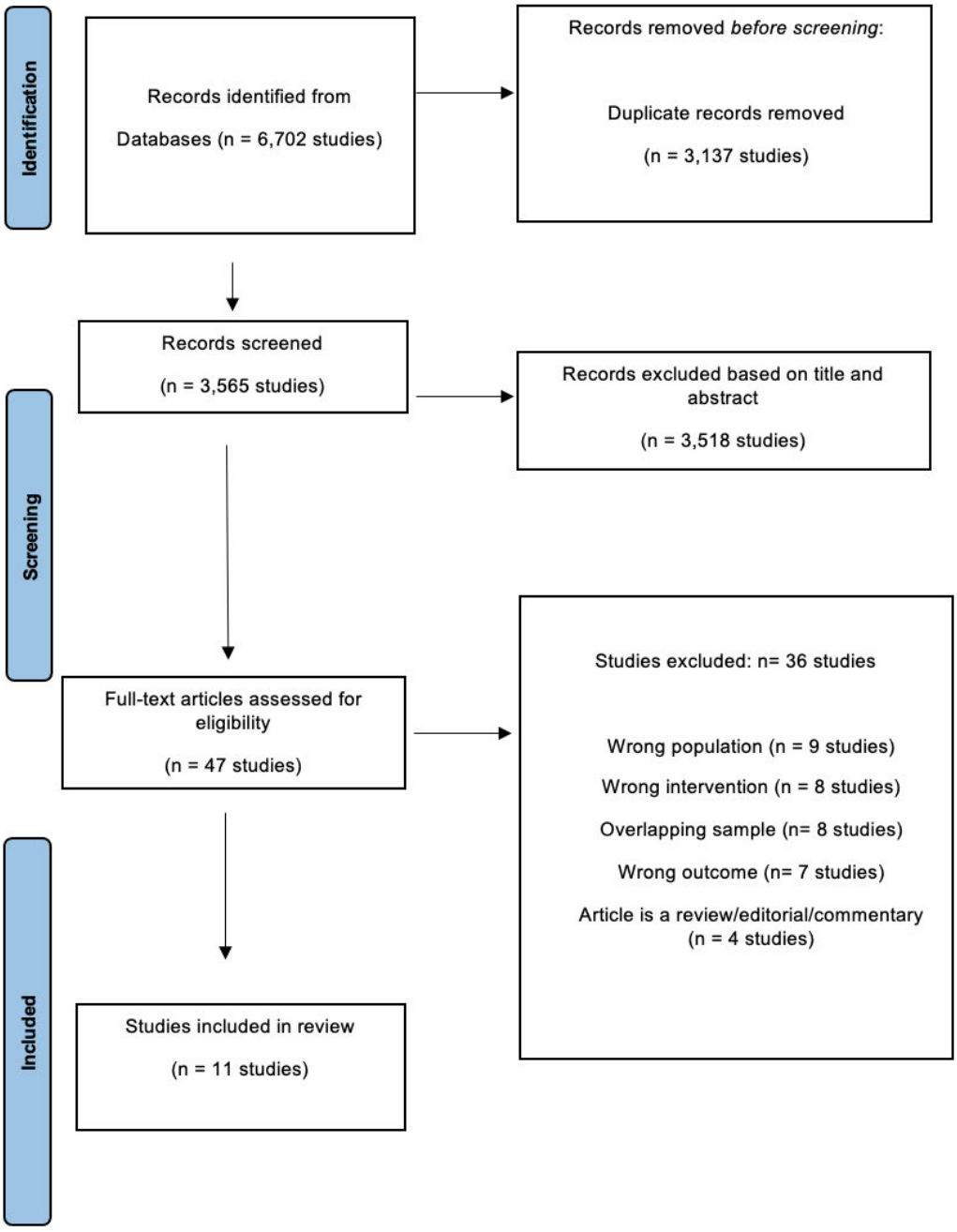

Figure 2.1. PRISMA flow diagram with details about the literature search, with the number of included and excluded studies at each stage, with reasons for exclusion

2.3.1 Risk of Bias results

All 11 included studies were found to have a higher risk of bias in the way the exposure (resistance training) was measured, as it was self-reported, measured at only a single point in time, and/or did not report on the validity or reliability of the question used to assess resistance training (Supplementary Table 1, Appendix A). One of the studies was found to

have a very high risk of bias on the assessment of the exposure (Hsu et al., 2018). All other items on the risk of bias assessments were rated as having 'very low' or 'low' risk of bias.

2.3.2 Study characteristics

The characteristics of the included studies are shown in Table 2.1. Length of follow-up ranged from 4.3 years to 17 years in the studies assessing the risk of mortality, and the age range of the total participants was 18-85 years. The majority (nine) of the studies included males and females in their study population, while one study only included females (Kamada et al., 2017) and one study only included males (Hsu et al., 2018).

Table 2.1. Descriptive characteristics of the studies included in the systematic review

A. Studies with Mortality outcomes								
Author	*Study design*	*Sample size (n)*	*Follow-up*	*Participants*	*Question used to measure Resistance training and Baseline date*	*Exposure categories used in analyses (Resistance training)*	*Outcome/s used in this review / Mortality end date*	*Confounders*
Kamada et al 2017	Cohort	28,879	12 years (Mean)	Healthy female participants of the Women's Health Study (1992-2004) conducted in the U.S. with an average age of 62.2 years	"During the past month, what was your approximate time per week spent at each of the following recreational activities? Weightlifting/strength training."	5 categories: 0 (Reference), 1-19 mins/wk 20-59 mins/wk, 60-149 mins/wk and ≥150 mins/wk	All-cause, cardiovascular disease (CVD) and cancer mortality 31, December 2015	Age, trial randomization, menopausal status, hormone use, smoking status, parental history of MI or cancer, alcohol intake, energy intake, saturated fat intake, fibre intake, fruit & vegetable intake, MVPA, BMI, hypertension, high

								cholesterol, CVD, diabetes, cancer.
Stamatakis 2017	Cohort	All-cause: 72,459 CVD: 73,937 Cancer: (77,195 individuals)	9.2 years	≥30 Years old individuals (males and females) who took part in the Health Survey for England (1994-2008) and Scottish Health Survey (1995-2003)	Self-reported questionnaire on Own body weight strength exercise; gym-based strength exercise; All strength exercise & Adherence to strength exercise guidelines	3 categories: None, Low, High - mins/wk based on median values: (Women: 66 mins/wk) (Men: 52.5 mins/wk)	All-cause, CVD and cancer mortality December 31, 2009 (Scottish Health Survey) March 31, 2011 (Health Survey for England)	Age and sex, long-standing illness, alcohol intake, psychological distress, BMI, smoking status, education level, and weekly physical activity volume excluding strength-promoting activity.
Kraschewski 2016	Cohort	29,975	N/A	Healthy participants (males and females) ≥65 years of age who took part in the National Health Interview Survey	"How often do you do leisure-time physical activities specifically designed to strengthen	2 categories: <2 times/week and ≥2 times/week	All-cause, CVD and cancer mortality 2011	Age, gender, race, education level and marital status. Health behaviours, BMI, smoking, alcohol intake, physical activity

				(NHIS) (1997-2001) in the U.S.	your muscles, such as lifting weight or doing calisthenics?"			and comorbid conditions (hypertension, diabetes, heart disease, nonskin cancer).
Hsu 2018	Cohort	1,705	7 years (median)	Male participants≥70 years of age, who took part in the Concord Health and Aging in Men Project (CHAMP) in the years 2005-2007, in Australia	The frequency and time spent in the past 7 days that they walked outside for any purposes and participated in light, moderate, or strenuous sports and in muscle strengthening exercise.	2 categories: No engagement in muscle-strengthening activity and Yes, any engagement in muscle-strengthening activity	All-cause, CVD and cancer mortality	Age, comorbidity, smoking status, alcohol intake, BMI, race, education level, cardiovascular disease, diabetes, self-rated health, ADL disability, depression and PASE score (based on walking, muscle and sport exercise)
Liu 2019	Cohort	12,591	10.5 years	Male and female participants	Resistance training using	5 categories: 0 sessions/wk, 1	All-cause mortality	Age, sex, smoking status, alcohol intake,

				between the ages of 18-89 years, who took part in the Aerobics Center Longitudinal Study, during (1987-2006), in the U.S.	either free weights or weight training machine was evaluated. Weekly frequency x average mins per sessions was calculated. Used the long-term RE and AE levels, measured by average frequency or average minutes per week during the follow-ups.	sessions/wk, 2 sessions/wk, 3 sessions/wk, ≥4 sessions/wk) 4 categories: 0 mins/wk, 1-59 mins/wk, 60-119 mins/wk, ≥120 mins/wk	December 31, 2003	parental history of CVD, BMI, AE (average PA ≥500 MET min/wk or not), hypertension, diabetes, and hypercholesterolemia.
Siahpush 2019	Cohort	310,282	7.9 years	Male and Female participants who were 18 years or older, who took part in the	"How often do you do leisure time physical activities specifically	6 categories: 0 times/wk; 1 time/wk; 2 times/wk; 3 times/week; 4 times/week and ≥5	Cancer mortality 31 December 2011	Age, sex, race, marital status, MVPA, smoking status, BMI, previous cancer diagnosis, chronic

				National Health Interview Survey (NHIS) between (1998-2009), in the U.S.	designed to strengthen your muscles such as lifting weights or doing calisthenics?"	times/wk of MSA frequency 2 categories: Yes (met the physical activity guidelines) and No (did not meet the physical activity guidelines)		condition, self-rated health, poverty status and education level.
Sheehan 2020	Cohort	26,727	17 years	Male and female participants aged between 18-84 years, who were part of the NHIS (1998) data set, in the U.S.	"How many times in the past 2 weeks did you weight-lift for exercise?" for 15 different types of exercises including resistance and aerobics	2 categories: No (did not engage in any resistance training activity) and Yes (engaged in any resistance training activity) 3 categories: Weight-lifting: None (0 MET-hrs/wk), Low (≤4.50 MET-	All-cause mortality 31 December 2015	Total volume of all physical activities, demographic information, socioeconomic measures, health behaviours and status including (smoking status, alcohol intake, BMI, self-reported health status, physical handicap, and

						hrs/wk) and High (≥4.50 MET-hrs/wk)		health condition).
Zhao 2020	Cohort	479,856	8.75 years (Median)	Male and female participants ≥18 years of age, who were part of the NHIS dataset between (1997-2014), in the U.S.	"How often do you do LEISURE-TIME physical activities specifically designed to STRENGTHEN your muscles such as lifting weights or doing calisthenics?"	2 categories: No, did not adhere to the physical activity guidelines (<2 times per week); Yes, adhered to physical activity guidelines (≥2 times per week)	All-cause, CVD and cancer mortality 31 December 2015	Age, sex, race, education, marital status, BMI, smoking status, and alcohol intake and chronic conditions.
Porter 2020	Cohort	17,938	11.9 years	Healthy male and female participants, 20 years and older, who were part of	"Over the past 30 days, did you do any physical activities specifically	2 categories: (<2 times per week); (≥2 times per week)	All-cause, CVD and cancer mortality 31 December 2015	Adjusted for leisure-time MET mins/week minus the MET mins/week spent in the specific activity

				the NHANES (1999-2006), in the U.S.	designed to strengthen your muscles such as lifting weights, push-ups or sit-ups?" And "…how many times did you do these	3 categories: None; <60 mins/wk, and ≥60 mins/wk		under study. Further adjusted age, sex, race, education status, smoking status, alcohol intake, BMI, household, and transportation MET mins/wk, and of pre-existing conditions including diabetes, arthritis, cancer, disability, and CVD.
Patel 2020	Cohort	72,462	NR	Healthy male and female participants, 50-74 years old who were part of the Cancer Prevention Study-II Nutrition	"During the past year, what was the average time per week you spent at the following kinds of activities: ...weight	4 categories: None, 0 to < 1 hrs/ week, 1-<2 hrs/week, ≥ 2 hrs/week	All-cause, CVD and cancer mortality 31 December 2014	Adjusted for sex and age, race, BMI, survey type (long/short), education status, self-reported health status, smoking status, alcohol intake, marital status, work status, TV sitting time,

				Cohort (1982-2014) in the U.S.	training/resistance exercises?"			aspirin use, comorbidity score and MVPA
Nie 2021	Cohort	89,962	7.48 years (Median)	Healthy male and female participants, 65 years and older who were part of the National Health Interview Survey (NHIS) (1997-2013), in the U.S.	"How often do you do leisure-time physical activities specifically designed to strengthen your muscles such as lifting weights or doing calisthenics?"	2 categories: <2 times/week and ≥2 times/week	All-cause, CVD and cancer mortality 31 December 2015	Adjusted for age, sex, race/ ethnicity, education status, MVPA, income, smoking status, alcohol intake, BMI, hypertension, diabetes, CHD, stroke, and cancer
B. Studies that analysed the Joint Association between Resistance training and Mortality								
Author	*Study design*	*n*	*Follow-up*	*Participants*	*Exposure (measurement)*	*Exposure categories (MVPA + Resistance training)*	*Outcome/s Mortality end date*	*Confounders*
Kamada et al. 2017	Cohort	28,879	12 years (Mean)	Healthy female participants of the Women's Health	"During the past month, what was your approximate	5 categories: (Total physical activity: RT + MVPA): 0	All-cause, CVD and cancer mortality	Age, trial randomization, menopausal status,

				Study (1992-2004) conducted in the U.S. with an average age of 62.2 years	time per week spent at each of the following recreational activities? Weightlifting/strength training."	(Reference), 1-19 mins/wk, 20-59 mins/wk, 60-149 mins/wk and ≥150 mins/wk	31 December 2015	hormone use, smoking status, parental history of MI or cancer, alcohol intake, energy intake, saturated fat intake, fibre intake, fruit & vegetable intake, MVPA, BMI, hypertension, high cholesterol, CVD, diabetes, cancer.
Stamatakis et al. 2017	Cohort	All-cause: 72,459 CVD: 73,937 Cancer: (77,195 individuals)	9.2 years	≥30 Years old individuals (males and females) who took part in the Health Survey for England (1994-2008) and Scottish Health Survey (1995-2003)	Self-reported questionnaire on Own body weight strength exercise; gym-based strength exercise; All strength exercise & Adherence to	2 categories: No, did not adhere to the physical activity. Yes, adhered to the physical activity guidelines for both aerobic and resistance training	All-cause, CVD and cancer mortality December 31, 2009 (Scottish Health Survey) March 31, 2011 (Health Survey for England)	Age and sex, long-standing illness, alcohol intake, psychological distress, BMI, smoking status, education level, and weekly physical activity volume excluding strength-promoting activity.

					strength exercise guidelines			
Zhao et al. 2020	Cohort	479,856	8.75 years (Median)	Male and female participants ≥18 years of age, who were part of the NHIS dataset between (1997-2014), in the U.S.	"How often do you do LEISURE-TIME physical activities specifically designed to STRENGTHEN your muscles such as lifting weights or doing calisthenics?"	2 categories: No, did not adhere to the physical activity. Yes, adhered to the physical activity guidelines for both aerobic and resistance training.	All-cause, CVD and cancer mortality 31 December 2015	Age, sex, race, education, marital status, BMI, smoking status, and alcohol intake and chronic conditions.

Abbreviations: BMI, body mass index; MVPA, moderate-to-vigorous intensity physical activity; CVD, Cardiovascular disease; PSA test, Prostate Specific Antigen test; A1 B1 A2 B2,; MET-hrs, Metabolic Equivalent of Task hours; mins/wk; minutes per week; TV, Television; CHD, Coronary Heart Disease; ADL, difficulties in performing activities of daily living; PASE, Physical Activity Scale for the Elderly; AE, Aerobic Activity; PA, Physical Activity; MI, Myocardial Infraction; NR, Not Reported

All studies were conducted in the United States, except one study from the United Kingdom (Stamatakis et al., 2018) and one study from Australia (Hsu et al., 2018). All studies used a cohort design.

Seven out of the 11 studies conducted one or more sensitivity analyses. Five of the seven studies that conducted sensitivity analyses, excluded participants that died 12-24 months after follow-up (Kamada et al., 2017; Patel et al., 2020; Siahpush et al., 2019; Zhao et al., 2020). Four of the seven studies ran sensitivity analyses by excluding those with prior cases of CVD events (Liu et al., 2019; Porter et al., 2020) or early cancer diagnoses (Porter et al., 2020; Siahpush et al., 2019) or chronic conditions (Zhao et al., 2020). They all reported that the results from these sensitivity analyses were similar to the results from their main analyses.

2.3.3 Assessment of resistance training

Resistance training was measured with self-reported questionnaires in all of the included studies. There was large heterogeneity in the way the exposure variable was defined; for example, the term "resistance training" was used in one study (Liu et al., 2019), "weight-lifting" in three studies (Kamada et al., 2017; Porter et al., 2020; Sheehan and Li, 2020), "strength exercises" in one study Stamatakis et al. (2018) and "muscle strengthening activities" or "exercises to strengthen the muscles" in six studies(Hsu et al., 2018, Kraschnewski et al., 2015, Nie et al., 2021; Patel et al., 2020; Siahpush et al., 2019; Zhao et al., 2020).

Five of the 11 included studies categorized resistance training of either minutes/hours per week of resistance training (Kamada et al., 2017; Liu et al., 2019; Patel et al., 2020; Porter et al., 2020; Stamatakis et al., 2018) or Metabolic Equivalent of Task hours (MET-hrs) per week of resistance training (Sheehan and Li, 2020). Resistance training was also categorized as none or some in two studies (Hsu et al., 2018; Sheehan and Li, 2020) while three studies categorized participants as meeting or not meeting physical activity guidelines if they performed two or more sessions per week of resistance training (Porter et al., 2020; Sheehan and Li, 2020; Zhao et al., 2020).

2.3.4 All-cause mortality

Doing any amount of resistance training versus doing no resistance training lowered the risk of all-cause mortality by 15% (Summary RR of six studies = 0.85; 95% CI=0.77, 0.93; I^2 =

79.9%; Table 2.2; Figure 2.2). This association was attenuated and not statistically significant when comparing the highest level of resistance training with the lowest level of resistance training (RR of seven studies=0.92; 95% CI= 0.83, 1.01; I^2 =57.6%; Table 2.2; Figure 2.3). Four studies reported the required information to include in the dose-response meta-analysis of the association between minutes per week of resistance training and all-cause mortality (Kamada et al., 2017; Stamatakis et al., 2018; Liu et al., 2019; Patel et al., 2020). A non-linear, U-shaped relationship was observed in the analysis with the risk of mortality decreasing and a maximum risk reduction of 27% observed at around 60 minutes per week of resistance training (RR= 0.73; 95% CI= 0.63; 0.85; Figure 2.3). Mortality risk reductions diminished at higher volumes than 60 minutes per week of resistance training.

The joint effect of both resistance training and MVPA was analysed among three studies (Kamada et al., 2017; Stamatakis et al., 2018; Zhao et al., 2020). When compared to doing neither resistance training nor MVPA, all-cause mortality was reduced by 18% (RR=0.82; 95% CI=0.72, 0.93; I^2=73.4% ; Table 2.2; Figure 2.5) among those only performing resistance training, by 25% (RR=0.75; 95% CI=0.67, 0.84; I^2=88%) among those only performing MVPA, and by 40% (RR=0.60; 95% CI=0.54, 0.66; I^2= 57.5%) among those performing both resistance training and MVPA.

Table 2.2: Summary of results from meta-analysis of resistance training and mortality

	All-cause Mortality			CVD- Mortality			Cancer-Mortality		
	n	**I^2**	**Summary RR (95% CI)**	**n**	**I^2**	**Summary RR (95% CI)**	**n**	**I^2**	**Summary RR (95% CI)**
Resistance Training									
Some vs None	6	79.9%	0.85 (0.77; 0.93)	5	44.0%	0.87 (0.77; 0.99)	5	62.8%	0.86 (0.78; 0.95)
Highest vs Lowest	7	57.6%	0.92 (0.83; 1.01)	6	35.2%	0.90 (0.79; 1.02)	6	55.7%	0.87 (0.77; 0.99)
Joint Association of RT and MVPA									
No RT & no MVPA	3	-	1.00 (Ref)	3	-	1.00 (Ref)	3	-	1.00 (Ref)
RT only	3	73.4%	0.82 (0.72; 0.93)	3	0%	0.82 (0.74;0.91)	3	11.1%	0.84 (0.75; 0.94)
MVPA only	3	88.0%	0.75 (0.67; 0.84)	3	65.2%	0.71 (0.61; 0.81)	3	90.3%	0.89 (0.72; 1.10)
RT & MVPA	3	57.5%	0.60 (0.54; 0.66)	3	61.0%	0.54 (0.41; 0.70)	3	84.8%	0.72 (0.53; 0.98)

Abbreviations: RR, Relative Risk; CI, Confidence Interval; RT, Resistance Training; MVPA, Moderate-to-Vigorous Physical Activity; n, number of studies; I^2, degree of heterogeneity

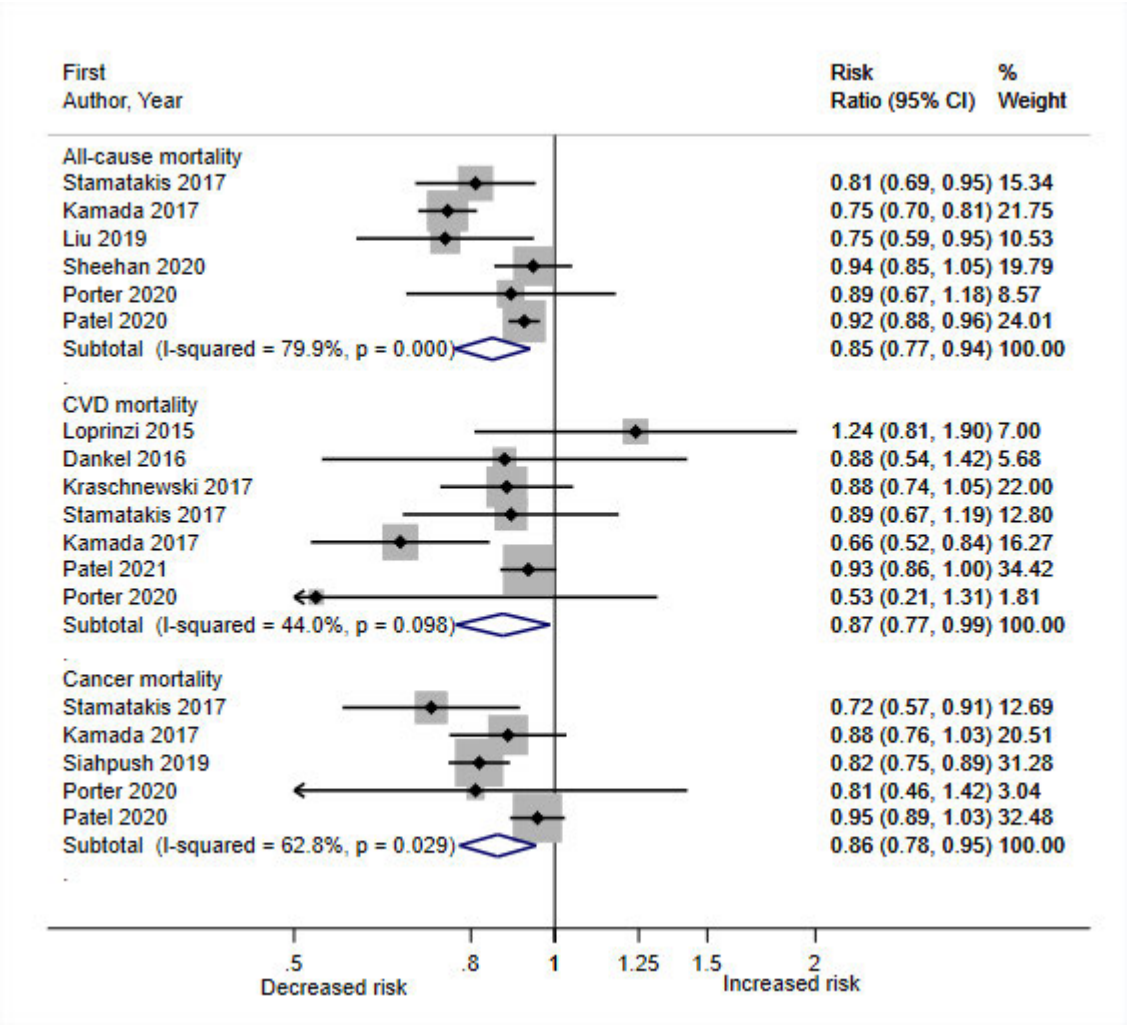

Figure 2.2. Meta-analysis of the association between engaging in any resistance training vs no resistance training and the risk of three mortality outcomes

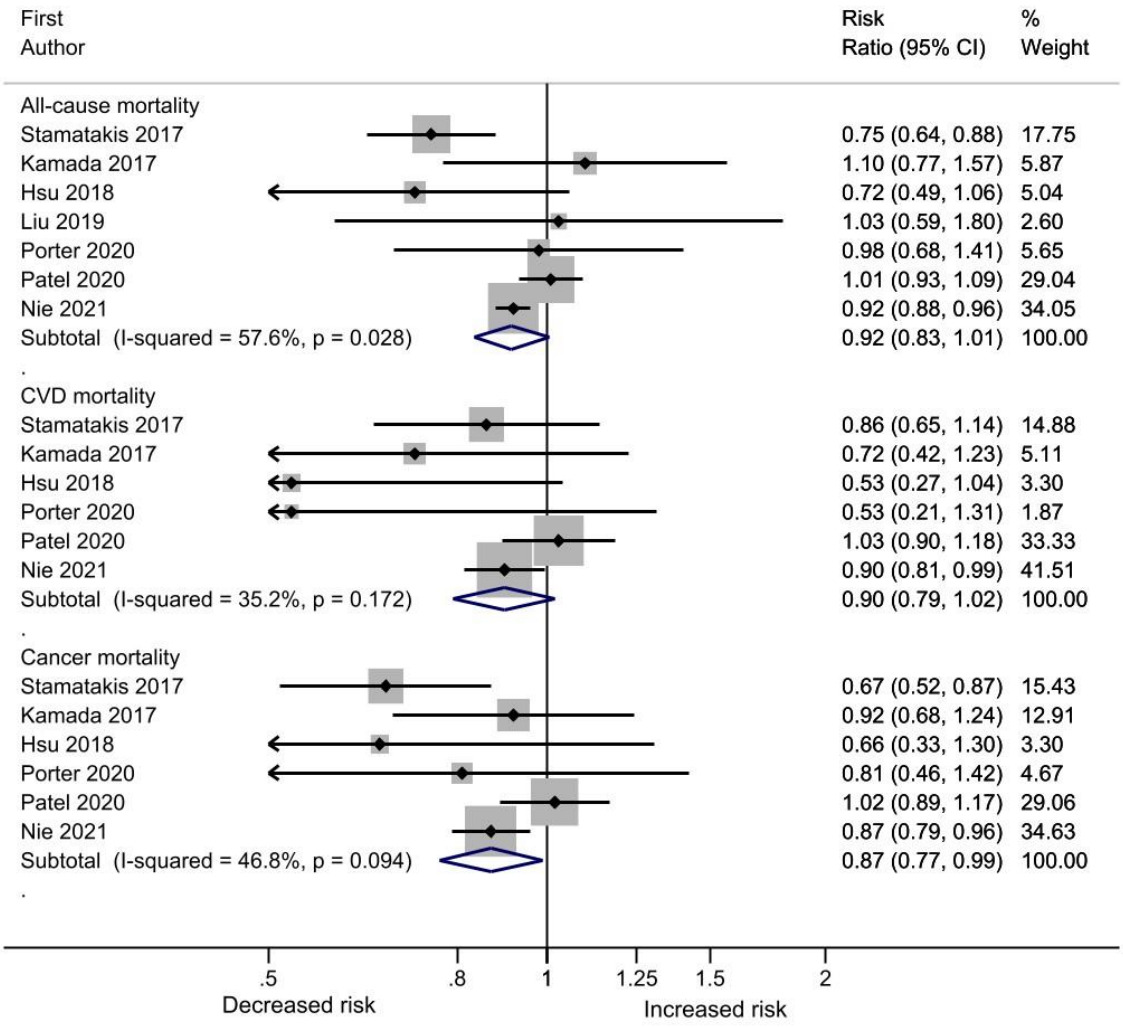

Figure 2.3. Meta-analysis of the association between high and low levels of resistance training and three mortality outcomes

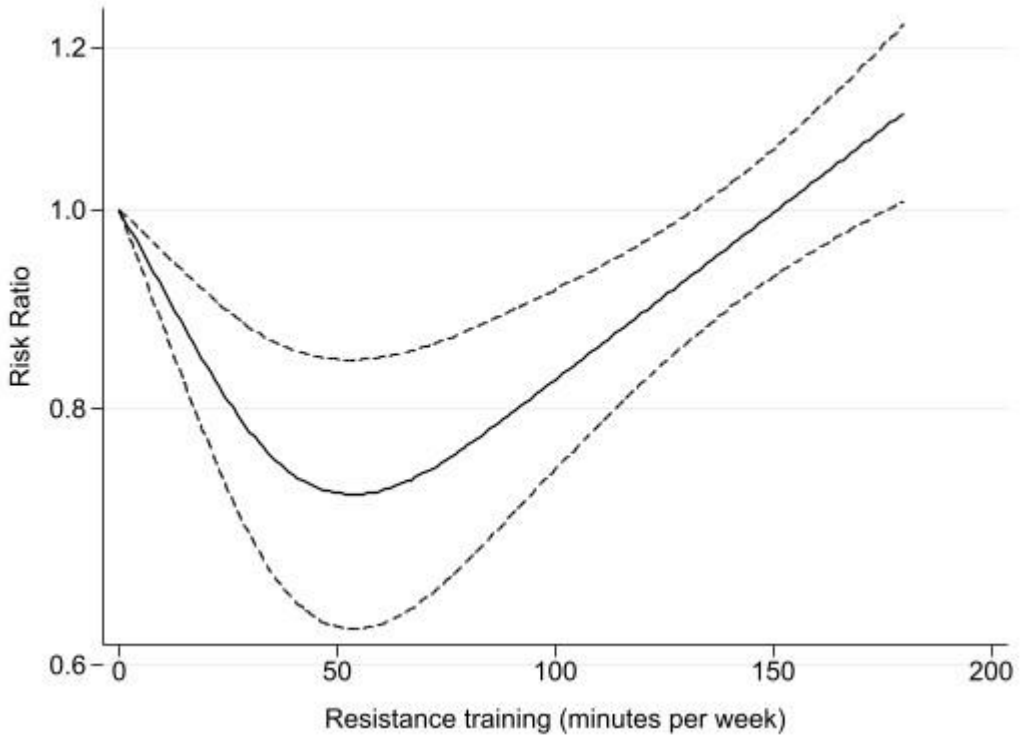

Figure 2.4. Figure showing the dose response association between the duration of resistance training performed in minutes per week and all-cause mortality (n=4)

2.3.5 CVD mortality

Doing any amount of resistance training versus doing no resistance training lowered the risk of CVD mortality by 13% (Summary RR of five studies=0.87; 95% CI=0.77, 0.99; I^2= 44.0%; Table 2.2; Figure 2.2). As for all-cause mortality, this association was attenuated and not statistically significant when comparing the highest level of resistance training to the lowest level of resistance training (RR of six studies=0.90; 95% CI=0.79, 1.02; I^2=35.2%; Table 2.2; Figure 2.3).

The joint effect of resistance training and MVPA on CVD mortality was analysed among three studies (Kamada et al., 2017; Stamatakis et al., 2018; Zhao et al., 2020). When compared to doing neither resistance training nor MVPA, the risk of CVD mortality was reduced by 18% by performing resistance training only (RR=0.82; 95% CI=0.74, 0.91; I^2=0%; Table 2.2), by 29% by performing MVPA only (RR= 0.71; 95% CI=0.61, 0.81; I^2=65.2%), and by 46% among those performing both resistance training and MVPA (RR=0.54; 95% CI=0.41, 0.70; I^2=61.0%; Table 2.2).

2.3.6 Cancer mortality

Doing any amount of resistance training versus doing no resistance training lowered the risk of cancer mortality by 14% (Summary RR of five studies=0.86; 95% CI=0.78, 0.95; I^2 = 62.8%; Table 2.2; Figure 2.2). Similarly, performing the highest level of resistance training compared to the lowest level of resistance training lowered the risk of cancer mortality by 13% (RR of six studies=0.87; 95% CI=0.77, 0.99; I^2=55.7%; Table 2.2; Figure 2.3).
The joint effect of resistance training and MVPA on cancer mortality was analysed among three studies (Kamada et al., 2017; Stamatakis et al., 2018; Zhao et al., 2020). When compared to doing neither resistance training nor MVPA, the risk of cancer mortality was reduced by 16% by performing resistance training only (RR of three studies=0.84; 95% CI=0.75, 0.94; I^2=11.1%; Table 2.2), no reduction in the risk of cancer mortality was observed by performing MVPA only (RR of three studies=0.89; 95% CI=0.72, 1.10; I^2=90.3%; Table 2.2). However, cancer mortality risk reduced by 28% among those performing both resistance training and MVPA (RR=0.72; 95% CI=0.53, 0.98; I^2=84.8%; Table 2.2).

2.4 Discussion

In this systematic review and meta-analysis of 11 studies, resistance training was associated with a lower risk of all-cause mortality, cancer mortality, and CVD mortality. Compared to doing no resistance training, doing any resistance training lowered risk of all-cause mortality by 15%, CVD mortality by 13%, and cancer mortality by 14%. The results of our dose-response meta-analysis suggested a possible U-shaped relationship between duration of resistance training and risk of all-cause mortality, however since this analysis only included four studies this finding should be viewed with caution. Our results also indicate that performing both resistance training and MVPA was associated with the greatest reduction in the risk of all-cause, cancer, and CVD mortality, when compared to performing either physical activity mode alone.

Consistent with the previous systematic review on this topic (Saeidifard et al., 2019), our results indicate that resistance training is associated with a reduced risk of all-cause mortality. By including nine new studies (Hsu et al., 2018; Liu et al., 2019; Nie et al., 2021; Patel et al.,

2020; Porter et al., 2020; Sheehan and Li, 2020; Siahpush et al., 2019; Stamatakis et al., 2018; Zhao et al., 2020) our review builds on previous research (Saeidifard et al., 2019) and provides the strongest evidence to date that resistance training is also associated with a reduced risk of CVD-mortality and cancer-specific mortality. Our results for cancer mortality are also consistent with a more recently published review, (Nascimento et al., 2021) which indicates that resistance training is associated with a reduced risk of cancer mortality.

Several different physiological mechanisms could explain why resistance training is a protective factor against mortality. Clinical exercise studies have shown that resistance training has favourable associations with glucose and lipid metabolism, (Ashton et al., 2020) regulating insulin sensitivity (Ismail et al., 2019) and blood pressure (Cornelissen et al., 2011). Randomized control trials have found that resistance training was associated with a 15% increase in insulin sensitivity and MVPA was associated with a 30% increase insulin sensitivity after a 4-month intervention period (Bacchi et al., 2012). Resistance training is also associated with improving lean muscle mass and strength (Grgic et al., 2018) and the reduction of visceral fat, (Khalafi et al., 2021) all of which are associated with lower risk of mortality (Jayedi et al., 2020; Srikanthan et al., 2015).

A novel finding was that the results of our dose-response meta-analysis showed a possible U-shaped relationship between duration of resistance training and risk of all-cause mortality. In particular, the largest mortality risk reduction (33%) was observed at 60 minutes of resistance training per week, and greater volumes than 60 minutes per week were associated with smaller or no mortality risk reductions. Given the small number of studies included we urge caution in interpreting this finding. However, the results of the studies to date indicate that any potential mortality benefits gained by performing resistance training may diminish at higher volumes of resistance training. Previous clinical studies have shown that high volumes and intensity resistance training may also result in adverse effects on blood pressure, heart rate and arterial compliance (Lamotte et al., 2005; Miyachi et al., 2004). More research is needed to better understand the dose-response relationship between resistance training and mortality.

Data from public health surveillance have shown that almost 60% of U.S. adults report not engaging in any resistance training activity at all, however only 25% of the adults report not engaging in any MVPA physical activity (Bennie et al., 2018). The discrepancy between the

higher prevalence of MVPA activity compared to the prevalence of resistance training suggests that more emphasis could be placed on the health benefits of resistance training. Some of the key challenges faced when starting resistance training could be that, unlike MVPA, resistance training requires basic training and information, such as the correct form when doing squats, the muscles targeted by certain resistance training exercises, etc. (Rhodes et al., 2017) Another key factor for the low prevalence of resistance training could be the lack of resources or access to equipment (e.g. free weights, resistance bands, gym membership, etc.) (Rhodes et al., 2017). To address some of these challenges, the public health strategies will need to focus on a multi-disciplinary approach, this may include easy and affordable access to physical health/fitness instructors and affordable access to well-equipped spaces to perform any resistance training activity (e.g. community gymnasium/ fitness centre, etc.) (Bennie et al., 2018).

One of the key limitations of the literature on resistance training and risk of mortality is the measurement of resistance training. Resistance training was self-reported in all the included studies, all bar two studies had information about resistance training at a single point in time only, and no studies report on the validity or reliability of the item(s) used to measure resistance training specifically. It is currently not clear how accurately people can recall the time they spend performing resistance training levels, or if they report time at the gym rather than the exact duration of time spent engaged in resistance training activities. The studies included in this review also measured and reported the amount of resistance training in numerous different ways; some studies looked at resistance training in hours/week' (Kamada et al., 2017; Liu et al., 2019) while others measured resistance training in the frequency or number of sessions/weeks.(Liu et al., 2019; Siahpush et al., 2019) This meant that only four studies were included in the dose-response meta-analysis for all-cause mortality and limited our ability to conduct dose-response analyses for cancer mortality and CVD mortality. The heterogeneity in measurement of resistance training in the included studies is consistent with a recent review that examined the way resistance training exercise has been measured in public health surveillance studies (Shakespear-Druery et al., 2021). More research is needed to identify the best/most valid method to measure resistance training to comprehensively understand the dose-response association between resistance training and mortality/other chronic disease outcomes. Since few studies have stratified by age and sex, it is also not clear if the association between resistance training and mortality risk may differ depending on these important demographic factors.

In conclusion, this systematic review and meta-analysis suggests a strong association between resistance training and a reduced risk of all-cause mortality, CVD-mortality, and cancer-specific mortality. These results, combined with the low prevalence of resistance training in the general population (Bennie et al., 2019), indicate that more emphasis could be placed on resistance training in health promotion campaigns aimed at increasing physical activity levels.

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Chapter 3: Weight training and risk of all-cause, cardiovascular and cancer mortality: A cohort study

Abstract

Aim: While there is strong evidence that moderate-to-vigorous physical activity reduces the risk of premature mortality, little is known about the association between other physical activity modes such as weight-training and mortality risk. The aim of this study was to investigate the overall and dose-response associations between weight-training and the risk of all-cause, cardiovascular disease (CVD) and cancer mortality.

Methods: This cohort study used data from the United States National Institutes of Health-American Association of Retired Persons (NIH-AARP) Diet and Health Study. After exclusions, the final analytic cohort consisted of 221,857 participants. Information about weight-training was collected via self-report in 2004-2005, and participants were followed up to the end of 2019. Cox proportional-hazards regression was used to estimate the hazard ratios (HR) and associated 95% confidence intervals (CI) for the overall and dose-response relationships between weight-training and all-cause, CVD and cancer mortality, after adjusting for confounders.

Results: Participants were aged between 50 and 71 years of age, and 24% reported engaging in weight-training. Compared with doing none, engaging in any amount of weight-training reduced the risk of all-cause mortality by 9% (HR = 0.91, 95% CI = (0.90; 0.93)), CVD mortality by 10% (HR = 0.90, 95% CI = (0.88; 0.92)) and cancer mortality by 9% (HR = 0.91, 95% CI = (0.89; 0.94)). In dose-response analyses the greatest mortality risk reduction were observed at around 2.5 hours per week of weight-training, and risk reductions diminished at higher volumes.

Conclusion: Performing any amount of weight-training was significantly associated with a lower risk of all-cause, CVD and cancer mortality.

3.1 Introduction

National and global physical activity guidelines recommend that, in addition to performing moderate-to-vigorous intensity physical activity (MVPA), adults engage in muscle-strengthening activities two or more days per week (Bull et al., 2020). Muscle-strengthening exercises, sometimes referred to as resistance training, strength training or weight training, involve using weight machines, resistance bands, free weights or body weight to strengthen the musculoskeletal system (Bennie et al., 2020). Muscle-strengthening exercises have been shown to improve sensitivity to insulin and weight loss and are associated with a lower risk of developing type-2 diabetes (Yang et al., 2013), cardiovascular disease (CVD) and obesity (Schroeder et al., 2019). Less is known about the association between muscle-strengthening exercises and mortality however, and while there are numerous studies suggesting MVPA reduces the risk of premature mortality (King et al., 2019) there is limited research on resistance training and mortality risk. A randomised controlled trial compared the health benefits of resistance training versus MVPA and concluded that both resistance training and MVPA increased sensitivity to insulin independent of each other (Bacchi et al., 2012).

The limited research to date on resistance training and mortality risk has generally found that resistance training reduces the risk of all-cause mortality, with our systematic review and meta-analysis (Chapter 2) of eleven studies finding that engaging in resistance training reduced the risk of all-cause mortality by 15% compared with doing none. The dose-response relationship between resistance training and mortality is also unclear; while some studies have observed a linear relationship (Stamatakis et al., 2018), others have found diminishing or no mortality benefits at higher volumes of resistance training (Kamada et al., 2017, Liu et al., 2019, Patel et al., 2020). The systematic review (Chapter 2) found a non-linear dose-response relationship; however, this was only based on four studies. There are also other aspects of the association between resistance training and mortality which remain unclear, such as whether the association differs between males and females. Finally, few studies have investigated the association between performing both resistance training and MVPA (as recommended by physical activity guidelines) on mortality (Kamada et al., 2017, Stamatakis et al., 2018, Zhao et al., 2020).

The aim of this cohort study was to investigate the associations between weight training and all-cause mortality, CVD-mortality, and cancer-mortality overall and among males and females. In addition, this study aimed to investigate the dose-response relationship between weight training and all three mortality outcomes, as well as the joint effects of weight training and MVPA on the three mortality outcomes.

3.2 Methods

This study used data from the National Institutes of Health-American Association of Retired Persons (NIH-AARP) Diet and Health Study (Mazzilli et al., 2019). The NIH-AARP was a cohort of 566,398 AARP members aged 50-71 years who completed a mailed baseline questionnaire regrading demographics, medical history, and dietary behaviours in 1995-96. Individuals who were residing in six U.S. states (California, Louisiana, Florida, New Jersey, North Carolina, and Pennsylvania) and in two metropolitan areas (Atlanta, Georgia and Detroit, Michigan) were invited to participate. Participants who completed the baseline questionnaire were subsequently invited to complete follow-up questionnaires in 1996-97 and in 2004-05. The 2004-05 questionnaire collected detailed information on lifestyle and physical activity (including weight training) and was completed by 313,363 participants, who form the basis of the dataset used in this analysis. Of those 313,363 participants, exclusion criteria were as follows: those who filled the follow-up questionnaire using a proxy; participants who reported that they were not able to walk; those who did not complete the weight training question; and those who had missing information for any of the confounders adjusted for in the analyses (sex, age, BMI, education level, smoking status, MVPA, health status, alcohol and healthy eating index).

3.2.1 Measurement of Weight Training and Physical Activity

In the 2004-2005 questionnaire, participants were asked to report the amount of time per week performing a number of physical activities, including weight training. Weight training was defined as “weight training or lifting (include free weights and machines).” Participants could choose from 10 different durations: none, 5 minutes, 15 minutes, 30 minutes, 1 hour, 1 hour 30 minutes, 2–3 hours, 4–6 hours, 7–10 hours, >10 hours. These data were converted to a continuous ‘hours per week’ measure, with the mid-point used when the response option was a range. In addition, two categorical measures of weight training duration were also

calculated, including: a) none (0 hours/week) and some (5 minutes or greater), and b) none, low (5 mins to 1.5 hrs/week) and high (2 hrs to 10+ hrs/week).
We also calculated metabolic-hours (MET-hours) per week of leisure-time MVPA, based on time spent per week in each of the following activities: jogging, tennis, golf, swimming, cycling, walking for exercise, and other aerobic activity. Leisure-time MVPA was then categorised as "Low MVPA" (<7.5 MET-hrs/wk) and "High MVPA" (>=7.5 MET-hrs/week). These categories were created based on the distribution of the data, and to be consistent with a previous study of the same cohort (Mazzilli et al., 2019).

3.2.2 Ascertainment of Outcome

Mortality data to the end of 2019 from the Social Security Administration Death Master File and the National Data Index Plus was used to ascertain the mortality status of the participants. We used Surveillance, Epidemiology, End Result (SEER) codes for underlying and contributing causes of death to identity CVD deaths (SEER codes 50060 to 50110) and cancer deaths (SEER codes 20010 to 37000). Follow-up time began at the time of the follow-up questionnaire (2004-05) and ended at death, loss to follow-up or the time of the last available mortality extract (December 31, 2019), whichever occurred first.

3.2.3 Statistical Analysis

Participant characteristics were described using descriptive statistics (number of participants (n), participant percentage (%), mean (standard deviation)). Cox proportional-hazards regression was used to estimate the hazard ratios (HRs) and associated 95% confidence intervals (CIs) for the associations between weight training and all-cause mortality, cardiovascular disease (CVD) mortality and cancer mortality, after adjusting for potential confounders. We used a directed acyclic graph (DAG) (Supplementary Figure 1, Appendix D) to identify a minimal, sufficient set of confounders to include as covariates in statistical models, based on the possible determinants of weight training and mortality risk factors. All factors that have been previously associated with performing muscle-strengthening exercises (Bennie et al., 2020) were included in the DAG. Based on the directed acyclic graph, the following were included as confounders, from the entry questionnaire, in all models: age, sex, education, race, body mass index, alcohol consumption, healthy eating index (Arem et al., 2013) self-reported health status. To ensure appropriate temporality in the confounder-exposure relationship, where possible the variables used as confounders were extracted from the cohort entry questionnaire rather than the follow-up questionnaire. The other confounders

included were moderate-to-vigorous physical activity and cigarette smoking, which were taken from the answers to the follow-up questionnaire. Two sensitivity analyses were performed to decrease any risk of bias associated with reverse causation: 1) excluding participants who reported they had ever been diagnosed with cancer or CVD prior to completion of the follow-up questionnaire, and 2) censoring deaths within the first two years of follow-up. Interaction terms were added to the models to test whether the associations between weight training and mortality risk differed by sex.

We investigated the dose-response relationship (magnitude, direction and shape) between weight training and mortality risk by creating restricted cubic splines from a continuous measure of weight training, with three knots placed at 0.25, 1 and 5 hours per week.
We also investigated the joint associations of weight training and MVPA by creating joint categories of weight training and MVPA, i.e., 1) no weight training and low MVPA; 2) no weight training and high MVPA; 3) any weight training and low MVPA; 4) any weight training and high MVPA, and examining associations with all-cause, cancer and CVD mortality. All statistical analyses were conducted using Stata version, 15.1, statistical software (StataCorp LP, College Station, Texas).

3.3 Results

Of the 313,363 participants who completed the 2004-05 questionnaire, the following participants were excluded from the current analysis: those who filled the follow-up questionnaire using a proxy (n= 14,150); participants who reported that they were not able to walk (n= 5,482); those who failed to answer the hours per week of weight training question (n= 13,737); and those who had missing information for any of the confounders adjusted for in the analyses (sex, age, BMI, education level, smoking status, MVPA, health status, alcohol and healthy eating index) (n= 58,565). The final analytic cohort sample consisted of 221,857 participants (128,898 men and 92,959 women). The mean age of the participants was 61.3 years and there was a higher proportion of males (58%) compared to females (42%). The study population consisted primarily of white participants (94%), and 45% of the study population were college graduates. A total of 82,229 (37%) died during the 15-year follow-up period (median follow-up time = 15 years). Of all deaths, 55% were due to CVD and 32% were due to cancer.

Approximately 24% of participants reported doing some level of weight training (Table 3.1). Weight training was more prevalent among younger participants, males, participants with a BMI in the normal range, participants with higher levels of MVPA, participants with higher levels of education, and participants who self-reported their health as excellent.

Table 3.1. Characteristics of the participants in the NIH-AARP Diet and Health study who returned the follow-up questionnaire, by level of weight training (n=221,857)

	Weight training		
	None (0 mins/week) (n= 168 362)	**Low** (15 mins to 1.5 hrs per week) (n= 40 687)	**High** (2 or more hrs per week) (n= 12 808)
Age			
<65 years	31 607 (18.8%)	9 032 (22.2%)	3 089 (21.1%)
≥65 years	136 755 (81.2%)	31 655 (77.8%)	9 719 (75.9%)
Mean Age (SD), years	62.5 (5.35)	62.8 (5.35)	63.3 (5.23)
Sex			
Males	95 481 (56.7%)	24 978 (61.4%)	8 439 (65.9%)
Females	72 881 (43.3%)	15 709 (38.6%)	4369 (34.1%)
Race			
White	158 133 (94%)	38 412 (94.4%)	12 051 (94.1%)
Black	5 336 (3.2%)	1 028 (2.5%)	320 (2.5%)
Hispanic	2 516 (1.5%)	601 (1.5%)	252 (2.0%)
Other	2 347 (1.4%)	646 (1.6%)	185 (1.4%)
BMI (kg/m^2)			
Underweight (<18.5)	1 510 (0.9%)	422 (1.0%)	127 (1.0%)
Normal (18.5–24.9)	56 014 (33.3%)	17 506 (43.0%)	5 638 (44.0%)
Overweight (25–29.9)	71 999 (42.8%)	16 749 (41.2%)	5 308 (41.4%)
Obese (30-34.9)	27 600 (16.4%)	4 631 (11.4%)	1 343 (10.5%)
Morbidly obese (35+)	11 239 (6.7%)	1 379 (3.4%)	392 (3.1%)
Smoke more than 100 cigarettes in their lifetime?			
No	67 526 (40.1%)	16 403 (40.3%)	4 877 (38.1%)
Yes	100 836 (59.9%)	24 284 (59.7%)	7 931 (61.9%)
Education level			
<12 years	7 418 (4.4%)	702 (1.7%)	250 (2%)
12 years / completed high school	33 813 (20.1%)	4 346 (10.7%)	1 392 (10.9%)
Post high-school training	17 594 (10.5%)	3 081 (7.6%)	952 (7.4%)
Some college	40 629 (24.1%)	8 795 (21.6%)	2 814 (22%)

College graduate	68 908 (40.9%)	23 763 (58.4%)	7 400 (57.8%)
Alcohol Intake per day			
None	75 585 (44.9%)	16 022 (39.4%)	5 145 (40.2%)
<5g/day	69 546 (41.3%)	18 978 (46.6%)	5 787 (45.2%)
≥5g/day to <10g/day	3 141 (1.87%)	748 (1.8%)	259 (2.02%)
≥10g/day to <20g/day	9 259 (5.5%)	2 481 (6.1%)	820 (6.4%)
≥20g/day to <30g/day	3 469 (2.1%)	816 (2.0%)	299 (2.3%)
≥30g/day	7,362 (4.4%)	1 642 (4.0%)	498 (3.89%)
Mean Healthy Eating Index score (SD)	68.4 (9.49)	72.5 (8.72)	73.8 (8.73)
MVPA levels			
Low MVPA <7.5 MET-hrs/week	73 790 (43.8%)	5 539 (13.6%)	716 (5.6%)
High MVPA >=7.5 MET-hrs/week	94 572 (56.2%)	35 148 (86.4%)	12 092 (94.4%)
Self-reported health			
Excellent	27 244 (16.2%)	10 162 (25.0%)	4 062 (31.7%)
Very Good	62 787 (37.3%)	16 711 (41.1%)	5 215 (40.7%)
Good	60 877 (63.2%)	11 519 (28.3%)	2 975 (23.2%)
Fair	15 755 (9.4%)	2 108 (5.2%)	519 (4.1%)
Poor	1 699 (1.0%)	187 (0.5%)	37 (0.3%)
Cancer mortality			
No	148 198 (88.0%)	36 532 (89.8%)	11 533 (90.1%)
Yes	20 164 (12.0%)	4 155 (10.2%)	1 275 (10.0%)
CVD mortality			
No	130 687 (77.6%)	33 578 (82.5%)	10 813 (84.4%)
Yes	37 675 (22.4%)	7 109 (17.5%)	1 995 (15.6%)
All-cause mortality			
Alive at the end of follow-up	102 650 (61.0%)	27 836 (68.4%)	9 142 (31.4%)
Deceased at the end of follow up	65 712 (39%)	12 851 (31.6%)	3 666 (28.6%)

Abbreviations: BMI: Body Mass Index; CVD: Cardiovascular diseases; METs: Metabolic Equivalent of Tasks; MVPA: Moderate-to-Vigorous Physical Activity; SD: Standard Deviation

3.3.1 All-cause mortality

Compared with participants who did not perform any resistance training, participants who performed any weight training had a 9% reduced risk of all-cause mortality (HR=0.91; 95% CI= 0.90, 0.93) and cancer mortality (HR= 0.91; 95% CI= 0.89; 0.94) and a 10% reduced risk of CVD mortality (HR=0.90; 95% CI= 0.88, 0.92). Similar risk reductions were observed for all three mortality outcomes among those who performed low levels or high levels of weight training (Table 3.2). The results of the two sensitivity analyses (1) excluding participants who had died less than 730 days after baseline, and 2) excluding participants who had been diagnosed with a CVD or Cancer prior to baseline) were not meaningfully different to the original analyses (Supplementary Table 1 & 2, Appendix C).

The association between resistance training and mortality risk appeared to differ between males and females (P-interaction <0.01), with stronger inverse associations observed among females (Table 3.2). Compared to doing none, among females doing any weight training was associated with a 16% decreased risk of all-cause mortality (HR=0.84; 95% CI= 0.81; 0.87), a 19% decreased risk of CVD-mortality (HR=0.81; 95% CI= 0.78; 0.85) and a 13% decreased risk of cancer mortality (HR=0.87; 95% CI= 0.82; 0.92), while among males doing any weight training was associated with a 5% decreased risk of all-cause mortality (HR=0.95; 95% CI=0.93; 0.97), a 6% decreased risk of CVD-mortality (HR=0.94; 95% CI=0.91; 0.96) and a 7% decreased risk of cancer mortality (HR=0.93; 95%CI= 0.90; 0.97).

Table 3.2. Association between weight training and mortality (NIH-AARP (n= 221, 857))

	All-Cause Mortality			CVD Mortality			Cancer Mortality		
Weight training	Deaths	Person-Years	HR (95% CI)*	Deaths	Person-Years	HR (95% CI)*	Deaths	Person-Years	HR (95% CI)*
ALL PARTICIPANTS									
No weight training	65 712	2 102 856	1.00 (Reference)	37 675	2 102 856	1.00 (Reference)	20 164	2 102 856	1.00 (Reference)
Some weight training	16 517	705 240	0.91 (0.90; 0.93)	9104	705 240	0.90 (0.88; 0.92)	5430	705 240	0.91 (0.89; 0.94)
Categories									
None (0 mins/wk)	65 712	2 102 856	1.00 (Reference)	37 675	2 102 855	1.00 (Reference)	20 164	2 102 855	1.00 (Reference)
Low (5 mins-1.5 hrs/wk)	12 851	534 207	0.91 (0.89; 0.93)	7109	534 207	0.90 (0.87; 0.92)	4155	534 207	0.91 (0.88; 0.94)
High (2 hrs - 10+ hrs/wk)	3666	171 033	0.92 (0.89; 0.95)	1995	171 033	0.91 (0.86; 0.95)	12 75	171 033	0.93 (0.88; 0.99)
Continuous									
Per 1 hr/wk increase in WT	82 229	2 808 096	0.99 (0.99; 1.00)	46 779	2 808 096	0.99 (0.98; 1.00)	25 594	2 808 096	0.99 (0.98; 1.00)
MALES									
No weight training	40 738	1 164 280	1.00 (Reference)	23 828	1 164 280	1.00 (Reference)	12 841	1 164 280	1.00 (Reference)
Some weight training	11 796	430 291	0.95 (0.93; 0.97)	6689	430 291	0.94 (0.91; 0.96)	3840	430 291	0.93 (0.90; 0.97)
Categories									
Low (5 mins-1.5 hrs/wk)	9059	319 754	0.94 (0.92; 0.97)	5144	319 754	0.93 (0.90; 0.96)	2912	319 754	0.93 (0.90; 0.97)
High (2 hrs - 10+ hrs/wk)	2737	110 537	0.95 (0.91; 0.99)	1545	110 537	0.95 (0.90; 1.00)	928	110 537	0.93 (0.87; 1.00)
Continuous									
Per 1 hr/wk increase in WT	52 534	1 594 572	1.00 (0.99 1.00)	30 517	1 594 572	1.00 (0.99; 1.01)	16 681	1 594 572	0.99 (0.97; 1.00)
FEMALES									
No weight training	24 971	938 576	1.00 (Reference)	13 845	938 576	1.00 (Reference)	7323	938 576	1.00 (Reference)
Some weight training	4721	274 948	0.84 (0.81; 0.87)	2415	274 948	0.81 (0.78; 0.85)	1590	274 948	0.87 (0.82; 0.92)
Categories									
Low (5 mins-1.5 hrs/wk)	3792	214453	0.84 (0.81; 0.87)	1965	214 453	0.82 (0.78; 0.86)	1243	214 453	0.85 (0.80; 0.91)
High (2 hrs - 10+ hrs/wk)	929	60495	0.85 (0.79; 0.91)	450	60 495	0.79 (0.71; 0.87)	347	60 495	0.93 (0.83; 1.04)
Continuous									
Per 1 hr/wk increase in WT	29 692	1 213 524	0.98 (0.97; 1.00)	16 260	1 213 524	0.96 (0.94; 0.98)	8913	1 213 524	0.99 (0.96; 1.00)

HR: Hazard's Ratio; CVD: Cardiovascular disease; hrs: hours; wk: week; WT: Weight training

* Adjusted for the following confounders: age, sex, education, race, body mass index, moderate-to-vigorous physical activity, cigarette smoking, alcohol consumption, health eating index, self-reported health status

3.3.2 Dose-response relationship between weight training and mortality

In the dose-response analyses we observed J-shaped associations between weight training and the risk of all-cause, CVD and cancer mortality (Figure 3.1). The risk of all three mortality outcomes initially decreased with increasing amounts of weight training, with the largest risk reductions observed at around in 2.5 hrs/week of weight training (risk of all-cause mortality was reduced by 12% (HR for all-cause mortality=0.88, 95% CI= 0.85; 0.90; HR for CVD mortality=0.86, 95% CI= 0.83; 0.90; HR for cancer mortality=0.89, 95% CI=0.84; 0.93). No further mortality benefit was observed at greater durations of weight training, and HRs above one were observed at six to eight or more hours of weight training.

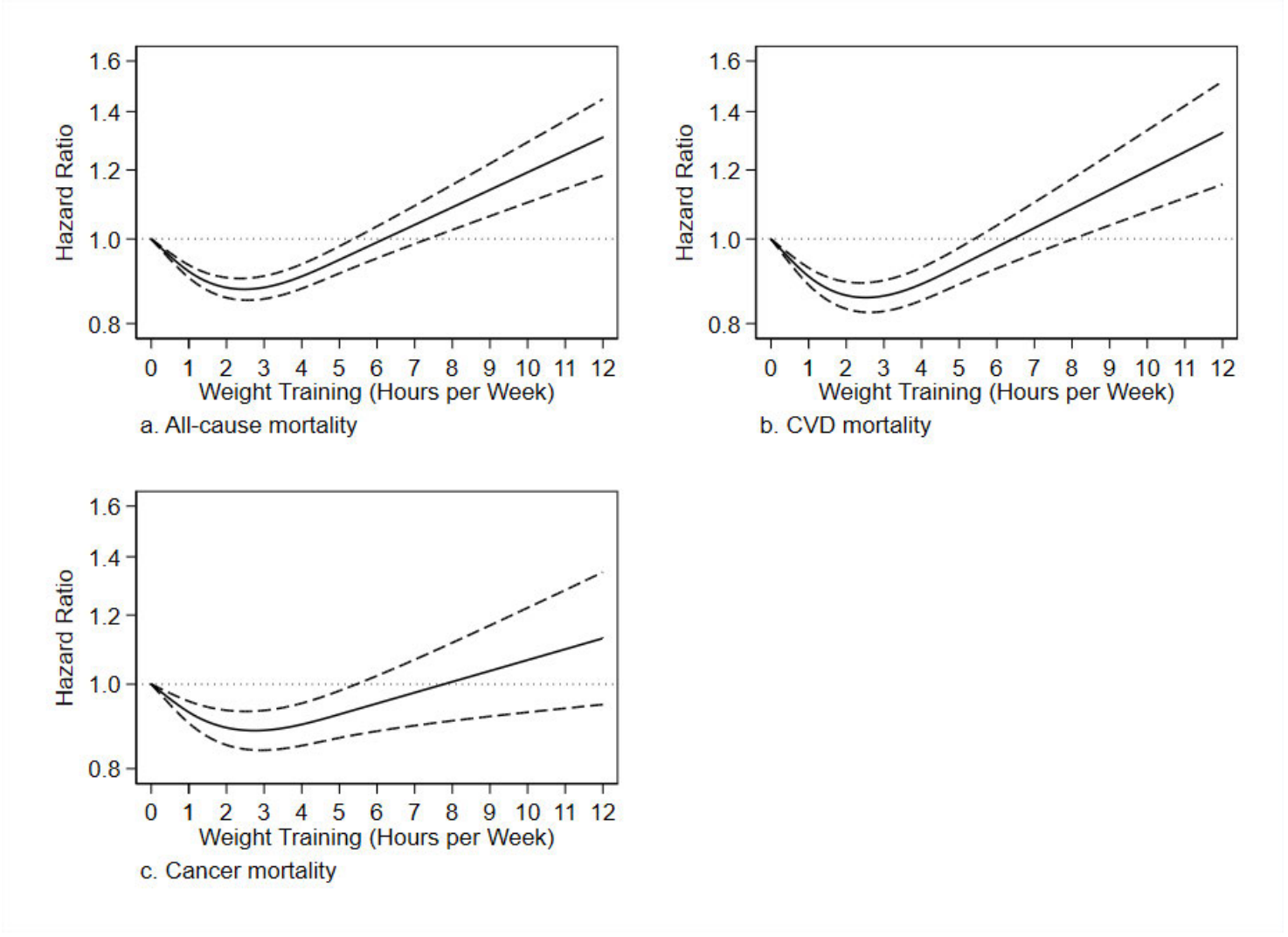

Figure 3.1. a. Dose-response association examining the duration of weight training and the risk of (a) all-cause mortality, (b) CVD mortality, and (c) cancer mortality (n=221, 857). Displaying the hazard ratio with a solid line and the upper and lower confidence intervals using dashed lines

3.3.3 Joint effects of weight training and MVPA on mortality

Engaging in high levels of MVPA and no weight training compared to engaging in neither MVPA nor weight training led to a 17% reduction in all-cause mortality (HR=0.83; 95% CI=0.82; 0.84). Engaging only in weight training with no or low levels of MVPA compared to neither MVPA nor weight training, reduced the risk of all-cause mortality by 7% (HR=0.93; 95% CI=0.89; 0.97). Engaging in both weight training and high MVPA compared to engaging in neither weight training nor MVPA, saw an all-cause mortality reduction of 22% (HR=0.78; 95% CI= 0.76; 0.80) (Table 3.3). Similar results were observed for CVD and cancer mortality.

Table 3.3. Joint association between weight training (WT) and moderate to vigorous physical activity (MVPA) and mortality **(n= 221,857)**

	HR (95% CI)		
Joint Association	**All-cause**	**CVD**	**Cancer**
No WT + Low MVPA	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Yes WT + Low MVPA	0.93 (0.89; 0.97)	0.90 (0.85; 0.95)	0.92 (0.85; 0.99)
No WT + High MVPA	0.83 (0.82; 0.84)	0.82 (0.80; 0.84)	0.88 (0.86; 0.91)
Yes WT + High MVPA	0.78 (0.76; 0.80)	0.76 (0.74; 0.79)	0.82 (0.79; 0.86)

WT: Weight training; MVPA: Moderate-to-Vigorous Physical Activity; HR: Hazard's Ratio

Adjusted for the following confounders: age, sex, education, race, body mass index, moderate-to-vigorous physical activity, cigarette smoking, alcohol consumption, healthy eating index, self-reported health status

3.4 Discussion

In this cohort study we found that participants who engaged in any amount of weight training reduced their risk of all-cause mortality by 9%, CVD mortality by 10% and cancer mortality by 9%, compared to those who did none. The association appeared to be stronger among females than males. The dose-response analyses found that engaging in two to three hours of weight training per week was associated with the greatest mortality benefits, reducing all-cause mortality by 12%, CVD mortality by 14% and cancer mortality by 11%, and no further mortality benefits were observed beyond this volume of weight training. Engaging in both weight training and high levels of MVPA reduced mortality risk more than performing either of these activities alone.

The results of this study, in which we found that doing any weight training compared to none reduced the risk of all-cause mortality by 9%, is consistent with the results of our systematic review (Chapter Two), as well as previous systematic reviews on this topic. A systematic review by (Saeidifard et al., 2019) of six studies published up to 2018 found that engaging in any resistance training reduced all-cause mortality by 21%. Three subsequent studies (Patel et al., 2020, Sheehan and Li, 2020, Zhao et al., 2020) have also found that resistance training reduces the risk for all-cause mortality, with risk reductions ranging from 10% to 15%. The results of previous research and the current study indicate that engaging in resistance is associated with lowered risk of all-cause mortality. Given only 10% of adults meet the muscle-strengthening activity guidelines (Bennie et al., 2019), this suggests that a greater emphasis could be placed on promoting resistance training to the general population.

This study also found that doing any amount of resistance training compared to doing none reduced the risk of CVD mortality by 10% and cancer mortality by 9%. Few studies have examined weight training and CVD and/or cancer outcomes compared to all-cause mortality outcomes. The systematic review by Saeidifard et al. 2019 found only a borderline association between weight training and CVD mortality (n= four studies, HR= 0.83; 95% CI= 0.68; 1.01) and found no association between weight training and cancer mortality (n= 2 studies). However, four subsequent studies published after the review (Siahpush et al., 2019, Nie et al., 2021, Patel et al., 2020, Zhao et al., 2020) have found that resistance training reduced the risk of cancer mortality, with the risk reduction ranging from 8% to 19%. Furthermore, findings of this study was consistent with a recently published systematic review by Nascimento et al., 2021a, which looked at the association between resistance training and cancer incidence/mortality, found that engaging in resistance training < 2 times/week reduced the risk of cancer mortality by 19% (n= four studies, HR= 0.81; 95% CI= 0.74; 0.87).

Few studies have examined the association between the volume of resistance training and the risk of mortality. The dose-response relationships between weight training and three mortality outcomes were examined in this study and a non-linear, J-shaped association was found. Mortality risk reductions peaked at around to 2-3.5 hours per week of weight training, with diminishing or no mortality benefits observed at greater durations of weight training. These results are similar to a study conducted by Patel et al. (2020), which found that engaging in

>0 to <2 hours per week of muscle-strengthening activity (MSA) resulted in a 10-12% reduction in the risk of all-cause mortality and concluded that engaging in more than two hours per week of MSA did not result in a lowered mortality risk. Studies conducted by (Dankel et al., 2016; Kamada et al., 2017) found that individuals who took part in two to three resistance training exercise sessions per week observed 26% and 31% lowered all-cause mortality respectively; however, both studies found that engaging in more than three resistance training sessions per week was not associated with increase in mortality benefits. In contrast, the study by Stamatakis et al. (2018) concluded that the higher the volume of resistance training sessions, the greater the reduction in all-cause and cancer mortality. While the benefits of resistance training have been acknowledged, there has also been evidence of increased levels of high- resistance training causing an increase in arterial stiffness and thereby increasing the risk of developing CVD (Miyachi, 2013).

This study found that performing both weight training and MVPA provided the greatest benefits in all three mortality outcomes, compared to doing only weight training or only MVPA. The joint effects of both weight training and MVPA, reduced the risk of all-cause mortality by 22%, CVD-mortality by 23% and cancer mortality by 18%. This was consistent with other studies that have examined the joint effects of both resistance training and MVPA on mortality, which also found that engaging in both types of physical activity provided the greatest benefits (Kamada et al., 2017; Schoenborn and Stommel, 2011; Siahpush et al., 2019, Stamatakis et al., 2018; Zhao et al., 2014). These results support the recommendations of physical activity guidelines to perform muscle-strengthening exercises in addition to MVPA (Bull et al., 2020). However, I acknowledge that there are some limitations of using a threshold of >=7.5 MET-hrs/week when categorising participants as having engaged in MVPA. Further research is needed to examine the weight training and MVPA in greater detail to investigate whether the association of weight training and mortality is different between people of different levels of MVPA.

In this study the association between weight training and mortality was found to be stronger among females than males. We found that among female participants, engaging in any weight training reduced the risk of all-cause mortality by 16%, CVD mortality by 19% and cancer mortality by 13%, whereas among males, resistance training reduced the risk of all-cause mortality by 5%, CVD mortality by 6% and cancer mortality by 7%. This finding requires confirmation in future studies however, as the only other study that examined the association

between resistance training and mortality among males and females separately found no significant difference between the sexes (Nie et al., 2021). In this study, only 34-39% of those who engaged in any weight training were females. The benefit of 16 weeks of resistance training on strength endurance was conducted among untrained males and females and it was found that females achieved an increase in improvement at the end of the study (Ribeiro et al., 2014). This difference in sexes could be attributed to the fact that the initial muscular strength recorded among females was lower than their male counterparts (Ribeiro et al., 2014) and it was found that initial muscular strength levels affected the way the body adapts to improvements in resistance training (Cormie et al., 2010).

Strengths of this study include its prospective design, large sample size, and having information about a range of potential confounders. Having information about duration of weight training meant that we were also able to look at the dose-response relationship with mortality in more detail than most previous studies on this topic, as they have only had information about frequency of resistance training (e.g., sessions per week). The limitations of this study included the use of self-reported weight training data, which is susceptible to measurement error. The validity and reliability of self-reported weight training is unknown, and it is possible that participants may have reported time spent at the gym rather the amount of time engaged in weight training activity. We also did not have data on the weight, number of repetitions or intensity of weight training, only had information about weight training at a single point in time, and we did not have information about other forms of muscle-strengthening activities such as exercises that use resistance machines, resistance bands, body-weight resistance exercises such as squats, push-ups, etc. Finally, our dataset consisted primarily of white participants, aged 60-70 years of age from the United States, and it is not known if the observed results are generalisable to populations with different demographic characteristics.

In conclusion, the results of this and previous studies indicate that engaging in muscle-strengthening activities may have mortality benefits. These findings support the inclusion of muscle-strengthening activities in physical activity guidelines. Given the low prevalence in the general population (Bennie et al., 2019), further emphasis could be placed on the benefits of muscle-strengthening activities in addition to MVPA for overall health in public health programs.

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Chapter 4: Thesis Discussion

The aim of this program of research was to examine the association between resistance training (e.g., weight training) and the risk of all-cause mortality, CVD mortality and cancer mortality. First, a systematic review and meta-analysis (Chapter 2) was conducted to evaluate the limited research on the topic (Chapter 2). Then, data from a large cohort study was analysed to further investigate the association between resistance training and the three mortality outcomes (Chapter 3). Similar findings were observed in the review and the cohort study, with the results of both indicating that resistance training is associated with the risk of risk of all-cause mortality, CVD mortality and cancer mortality.

4.1 Summary of Main Findings

Research question 1: Is resistance training associated with the risk of all-cause, cancer-specific and/or CVD-specific mortality?

The results of the systematic review and meta-analyses (Chapter Two) showed that engaging in any amount of resistance training decreased the risk of all-cause mortality by 15%, the risk of CVD mortality by 13% and the risk of cancer mortality by 14%, compared with doing none. Similarly, the results of the cohort study (Chapter Three) showed that engaging in any amount of weight training, compared to none, reduced the risk of all-cause mortality by 9%, the risk of CVD mortality by 10% and the risk of cancer mortality by 9%.

Research question 2: What is the dose-response relationship between resistance training and mortality risk?

The dose-response relationship between resistance training and mortality was examined in the systematic review and the cohort study, and a non-linear association was observed in both. The systematic review found that engaging in resistance training for 60 minutes/ week conferred the great all-cause mortality benefit, while in the cohort study 2 to 3 hours/week of resistance training was associated with the greatest reduction in the risk of all-cause mortality by 12%. Higher durations of resistance training than those amounts were associated with smaller or no mortality benefits. However, both our studies (Chapter Two and Chapter Three) strongly indicate a non-linear association between resistance training and mortality, with the greatest reduction in the risk of all-cause mortality observed when participants engaged in resistance training for one to three hours per week. However, a limitation of the research to

date on the association between resistance training and mortality risk has been the inconsistency with which resistance training has been measured, with some studies asking about ‘sessions per week’ and others about ‘minutes or hours per week’. This inconsistency makes it hard to quantify the dose-response relationship. As such, an area for future research could be to further examine the dose-response relationship between resistance training and mortality, and this could help to form better, more detailed recommendations for muscle-strengthening exercise in physical activity guidelines.

Research question 3: Does performing both resistance training and MVPA reduce mortality risk more than performing either of these activities alone?

Both the systematic review and the cohort study found that engaging in both resistance training and MVPA provided greater mortality benefits than engaging in either alone. The results of the systematic review showed that engaging in both resistance training and MVPA decreased the risk of all-cause mortality by 40%, compared to doing neither, and similarly the cohort study results showed that engaging in both decreased the risk of all-cause mortality by 22%. Similar results were observed for CVD-mortality and cancer mortality in both studies. These results are consistent with observational evidence indicating that performing both resistance training and MVPA reduces the risks of CVD, type 2 diabetes and colon cancer more than performing either of those alone (Giovanucci et al., 2021), as well as the results of systematic reviews of RCTs which have concluded that the combination of resistance training and aerobic training leads to greater improvements in anthropometric outcomes (Morze et al., 2021), metabolic syndrome and cardiovascular risk parameters (Minyu et al., 2021).

Based on the results of this research program and previous research, with reasonable confidence we can conclude that resistance training decreases the risk of all-cause mortality, and that performing both resistance training and MVPA is optimal. The dose-response relationship remains unclear, but it seems that higher volumes of resistance training does not equal greater mortality benefits.

4.2 Health Promotion implications

Both studies support the physical activity recommendations on engaging in both MVPA and resistance training and that it is associated with a decreased mortality risk. Previous research indicates engaging in resistance training also has a range of other health benefits, and physical activity guidelines recommend engaging in resistance training sessions on at least two days per week (Bull et al., 2020). However, the prevalence of resistance training remains low in the general population. Only 10% of adults in the United States adhered to the resistance training physically activity guidelines, compared to more 30% of adults who met the recommended MVPA guidelines (Bennie et al., 2019). This suggests that more promotion of resistance training in addition to MVPA is needed in health promotion/public health messages and campaigns.

It is important to identify the barriers and enablers of resistance training participation to form effective health promotion. Successful health promotion campaigns also need to understand the determinants of the health behaviour they are targeting, as well as the context in which that health behaviour occurs. As such, it is important to consider multiple levels of determinants of engaging in resistance training, rather than focusing only on individual-level factors.

Two reviews have taken a socio-ecological approach to explore the demographic, behavioural, intrapersonal, interpersonal, and environmental factors associated with participation in resistance training (Rhodes et al., 2017; Nakamura and Harada, 2015). Level of education, self-reported health status and quality of life were identified as being positively associated with engaging in resistance training, suggesting that those who with higher educational levels and those who perceived themselves to be healthy were more likely to engage in resistance training (Rhodes et al., 2017). Furthermore, they found that affordability, enjoyment, self-efficacy, social support, programme leadership, enjoyment, and behaviours of self-regulation were some of the other factors that played a role in resistance training participation (Rhodes et al., 2017, Nakamura and Harada, 2015). Similar themes arose in a qualitative study on participation in resistance training conducted in Western Australia among older adults and relevant stakeholders (e.g., resistance training instructors, policy representative, physical activity centre manager) (Pettigrew et al., 2019).

Self-regulation behaviour, especially planning and self-monitoring, was found to have the greatest association with participation in resistance training (Rhodes et al., 2017). Self-efficacy was also identified as strong contributor of resistance training participation, with the participants' perceived self-capability to perform resistance training and their perceived capability to overcome any internal or external barriers to resistance training (Pettigrew et al., 2019; Rhodes et al., 2017). It is also important for people to feel confident and capable that they can participate in resistance training (Rhodes et al., 2017).
The findings of the studies mentioned above suggest that, when designing health promotion campaigns aimed at increasing the prevalence of resistance training, and/or when designing and implementing resistance training programs, it is important to make sure resistance training is promoted as being affordable, enjoyable, accessible, and beneficial to all.

4.3 Considerations for future research

While the evidence to date indicates that engaging in resistance training decreases the risk of mortality, there are several aspects of the association that remain unclear. These aspects include the stronger association between resistance training and mortality among females compared to males, the joint effects of resistance training and MVPA on mortality, the diverse range of terms used in describing resistance training activity which makes it harder to quantify the results and whether different types of resistance training provide different levels of mortality benefits.

More research is needed to further investigate the sex/age differences in the association between resistance training and mortality, given the interesting but exploratory findings of the cohort study in which a greater inverse association between resistance training and mortality was observed among females compared to among males. The one previous study that examined the association between resistance training and mortality among males and females separately found no significant difference between the sexes (Nie et al., 2021). The difference in sexes observed in our study could be attributed to the fact that the initial muscular strength recorded among females was lower than their male counterparts (Ribeiro et al., 2014) and it was found that initial muscular strength levels affected the way the body adapts to improvements in resistance training (Cormie et al., 2010).

While the research to date suggests that performing both resistance training and MVPA reduces mortality risk more than performing either of these activities alone, it is not clear if resistance training provides mortality benefits among people who perform a high volume of MVPA. Future research should investigate the joint effects of muscle-strengthening activities and moderate-to-vigorous intensity physical activity in greater detail, as this will shed more light on whether the association between muscle-strengthening activities and mortality risk differs by volume of MVPA.

Resistance training is an umbrella term, under which fits a multitude of exercises which engage the muscles (e.g., body weight exercises such as yoga or Pilates, weightlifting, resistance training machines, etc.). More research is needed to determine whether the different types of resistance training, with different levels of intensity (e.g., body weight exercises vs exercises using external weights) provide different levels of mortality benefits.

However, to the best of my knowledge, no other studies have compared different types of resistance training and their associated health/mortality benefits. Further, resistance training is referred to using a range of terms in the epidemiological literature, such as ‘weight-training’, ‘muscle-strengthening activity’ and ‘strength-training’. These terms are often not clearly defined, which makes it difficult to define the exact type of activity that was measured. Future research on resistance training and mortality should ensure that the specific exposure being assessed is clearly defined and use consistent terminology where possible.

4.4 Conclusion

The results of this research program indicate that engaging in resistance training is associated with a lower risk of all-cause mortality, CVD-mortality and cancer-mortality. The greatest reduction in the risk of mortality was observed when resistance training was combined with MVPA, which supports the recommendations in the physical activity guidelines. Given the numerous health benefits associated with resistance training, more research is needed to increase the levels of participation in resistance training among the general population.

4.5 References

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APPENDICES

Appendix A

Chapter 2: Systematic review (Supplementary tables)

Supplementary Table 1. Risk of Bias assessment of the studies that examined the association between resistance training and the risk of mortality

Author, year	Same population	Exposure assessment	Outcome not present at the start of study	Variables associated with outcome adjusted	Presence/absence of prognostic factors	Confidence in the outcome	Adequate follow-up	Similar co-interventions
Kamada 2017	1	3	1	1	2	1	1	1
Kraschnewski 2016	1	3	1	1	2	1	1	1
Stamatakis 2018	1	4	1	1	2	1	1	1
Hsu 2018	1	2	1	1	2	2	2	1
Liu 2019	1	3	1	1	2	1	1	1
Siahpush 2019	1	3	1	1	2	1	1	1
Nie 2021	1	3	1	1	2	1	1	1
Patel 2020	1	3	1	1	2	1	1	1
Sheehan 2020	1	3	1	1	2	1	1	1
Zhao 2020	1	3	1	1	2	1	1	1
Porter 2020	1	3	1	1	2	1	1	1

Note: 1 - Definitely yes (low risk of bias), 2- Probably yes, 3- Probably no and 4- Definitely no (high risk of bias). To be assessed a low risk of bias for the items related to confounding, the study had to consider or include at least the following variables in the analysis: age, gender, body mass index (BMI), MVPA, education (if applicable) and smokin

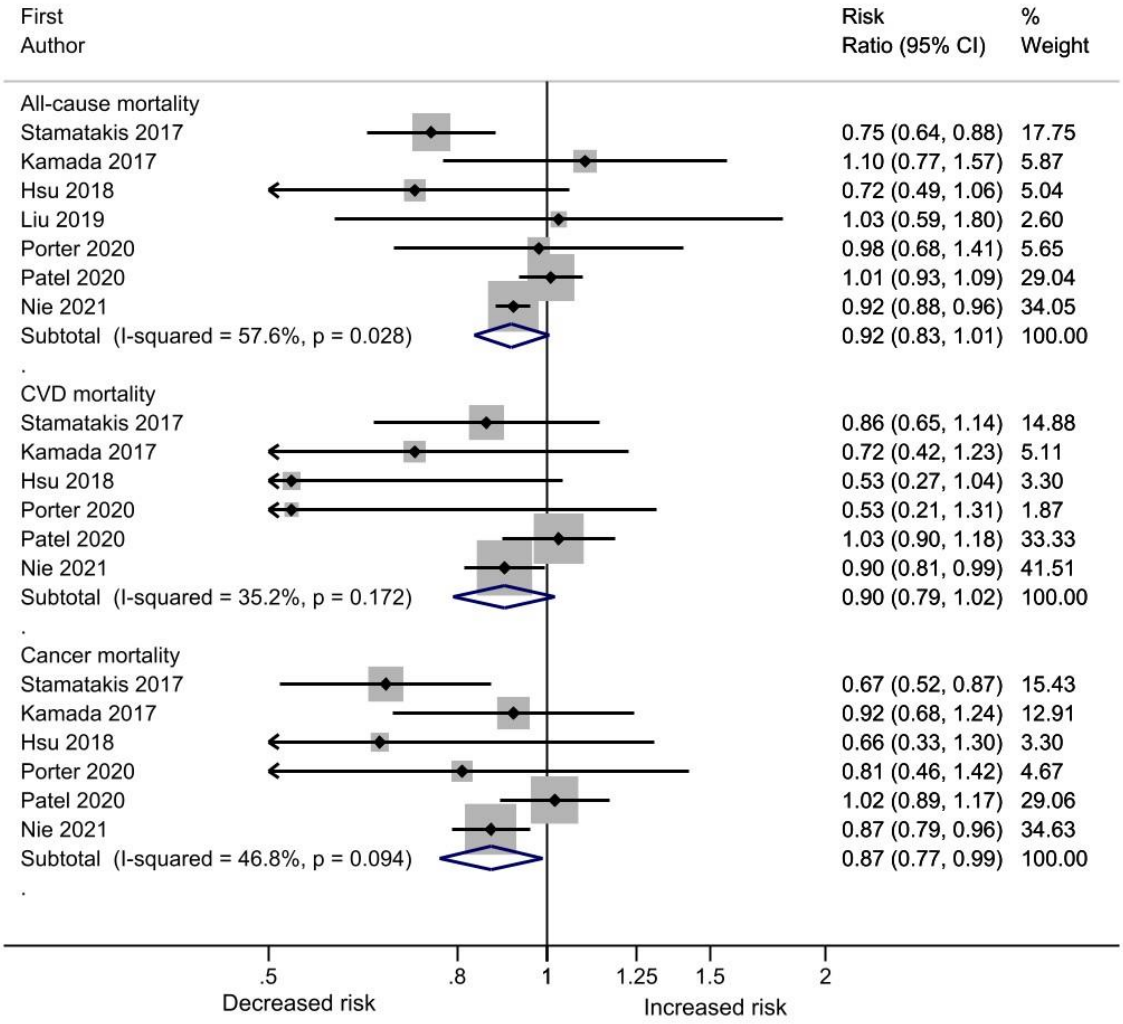
Supplementary table 2. Electronic search strategy for one of the databases (MEDLINE) was used:

MEDLINE search number	Search Query
1	mortality/
2	"cause of death"/
3	Mortality, Premature/
4	(death* or died or mortal* or fatalit*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
5	exp Neoplasms/
6	(Neoplas* or cancer* or malignan* or tumo?r* or carcino* or onco* or leuk?emia* or leucocyth?emi* or Leukos?s or lymphoma? or sarcoma? or germinoblastoma? or reticulolymphosarcoma? or Hodgkin* or astrocytoma? or Cholangiocarcinoma? or Craniopharyngioma? or DCIS or blastoma? or Esthesioneuroblastoma? or Retinoblastoma? or Histiocytoma? or Osteosarcoma? or Mesothelioma? or Myeloma?).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
7	1 or 2 or 3 or 4 or 5 or 6
8	resistance training/
9	Weight Lifting/
10	((strength* or resistance or weight?lifting or weight lifting or lift* weight* or muscle-strength*) adj3 (train* or program or exercis* or physical or activit*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
11	8 or 9 or 10
12	Risk factors/

13	risk/
14	prevalence/
15	incidence/
16	(risk* or likelihood or probability or incidence or prevalence or associat* or prevent*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
17	12 or 13 or 14 or 15 or 16
18	7 and 11 and 17
19	limit 18 to english language

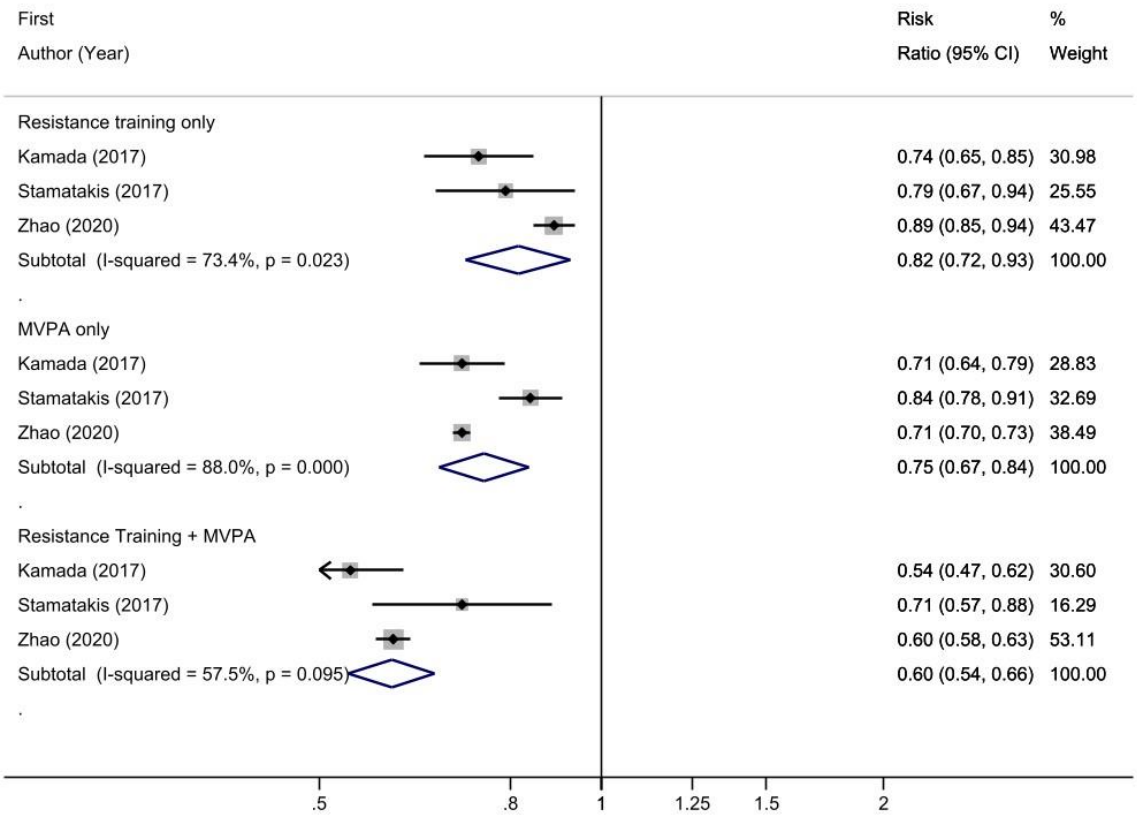
Appendix B

Chapter 2: Systematic review supplementary figures (high vest lowest forest plots etc.)

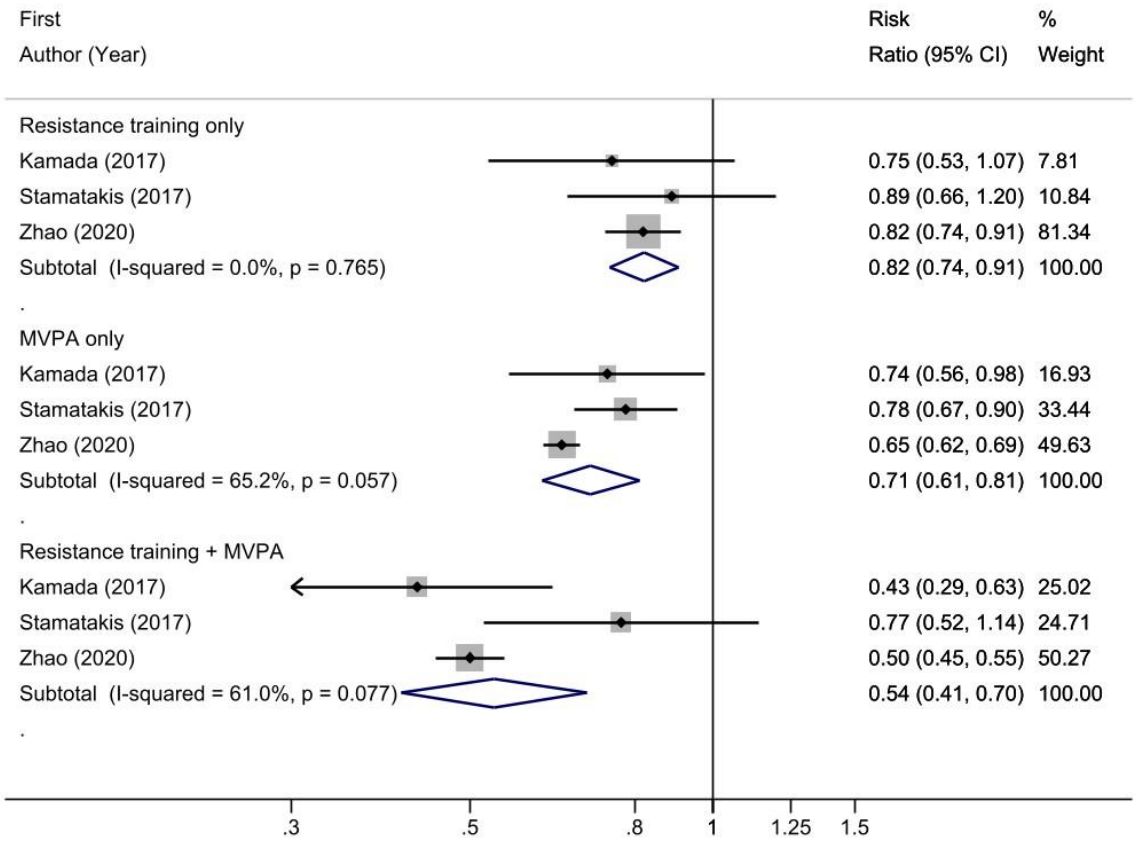


Supplementary Figure 1. Meta-analyses of the associations between highest and lowest levels of resistance training and the risk of all-cause, cancer and cardiovascular mortality

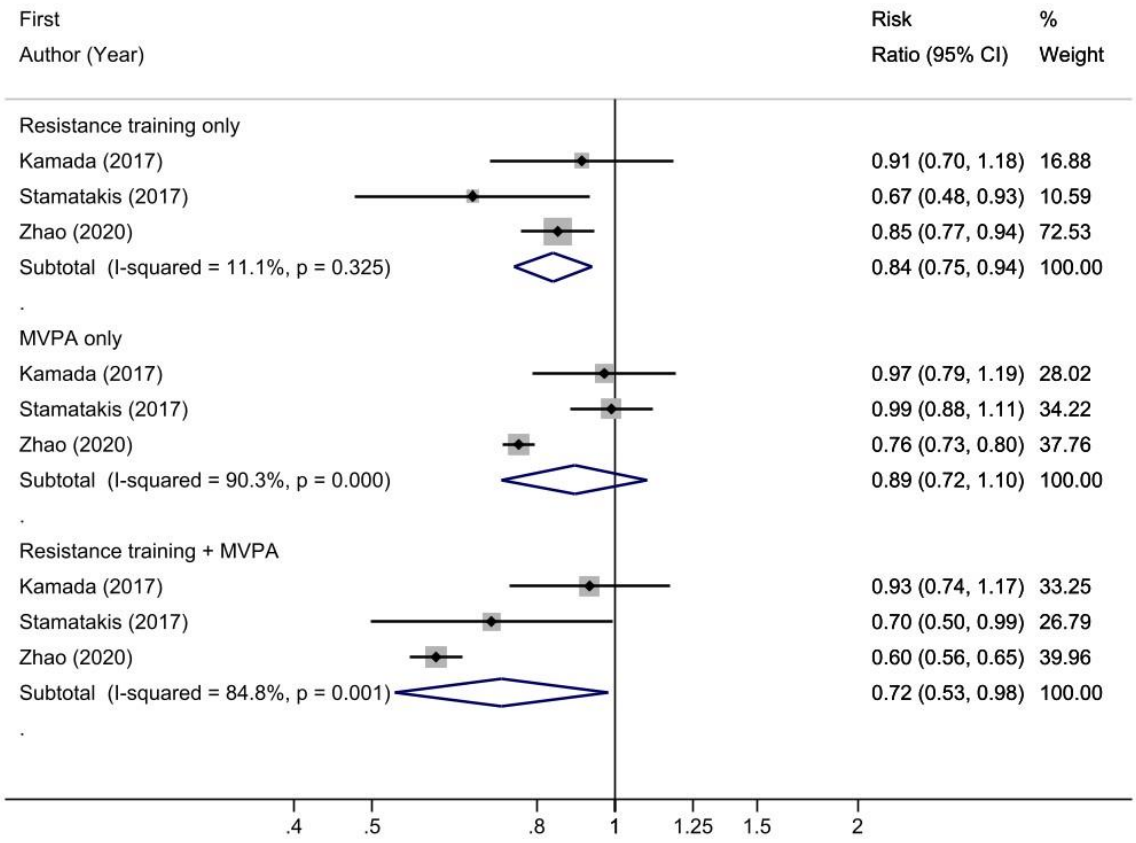
Abbreviations: CVD, Cardiovascular disease



Supplementary Figure 2. The joint association of resistance training and Moderate to Vigorous Physical Activity (MVPA) and all-cause mortality



Supplementary figure 3. The joint association of resistance training and Moderate to Vigorous Physical Activity (MVPA) and CVD mortality



Supplementary figure 4. The joint association of resistance training and Moderate to Vigorous Physical Activity (MVPA) and cancer mortality

Appendix C

Chapter 3: Cohort study (Supplementary tables)

Supplementary table 1. Sensitivity Analyses excluding participants who had died less than 730 days after the follow-up questionnaire data was entered and excluding participants who had been diagnosed with a CVD or Cancer event

	HR (95% CI)		
Weight training	**All-cause mortality**	**CVD**	**Cancer**
None vs Some			
No weight training	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Some weight training	0.913 (0.90; 0.93)	0.903 (0.881; 0.925)	0.914 (0.885; 0.943)
Some weight training[1]	0.912 (0.90; 0.94)	0.906 (0.883; 0.929)	0.930(0.900; 0.962)
Some weight training[2]	0.901 (0.873; 0.931)	0.876 (0.836; 0.917)	0.935 (0.883; 0.99)
Continuous (hrs/wk)			
0 hrs/wk of WT	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
+1 hr/wk of WT	0.99 (0.987; 1.00)	0.992 (0.982; 1.00)	0.989 (0.976; 1.00)
+1 hr/wk of WT[1]	0.99 (.0.99; 1.00)	0.990 (0.979; 1.00)	0.990 (0.978; 1.00)
+1 hr/wk of WT[2]	0.99 (0.978; 1.00)	0.989 (0.962; 0.999)	0.995 (0.974; 1.02)
Categorical (hrs/wk)			
None (0 hrs/wk)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Low (5 mins-1.5 hrs/wk)	0.91 (0.893; 0.929)	0.901 (0.877; 0.925)	0.909 (0.878; 0.941)
High (2 hrs - 10+ hrs/wk)	0.92 (0.889; 0.954)	0.909 (0.867; 0.954)	0.931 (0.876; 0.988)
Low (5 mins-1.5 hrs/wk)[1]	0.916 (0.897; 0.935)	0.905 (0.880; 0.930)	0.925 (0.892; 0.960)
High (2 hrs - 10+ hrs/wk)[1]	0.927 (0.894; 0.961)	0.911 (0.867; 0.956)	0.950 (0.892; 1.01)

Low (5 mins-1.5 hrs/wk)[2]	0.989 (0.867; 0.931)	0.871 (0.828; 0.915)	0.920 (0.864; 0.980)
High (2 hrs - 10+ hrs/wk)[2]	0.914 (0.860; 0.971)	0.894 (0.820; 0.974)	0.987 (0.8901; 1.09)

Note: Highlighted: Normal analysis (n= 218, 857)

1. Sensitivity analyses run after excluding participants who had died less than 730 days after the follow-up questionnaire data was entered (n= 212, 335).
2. Sensitivity analyses run after excluding participants who had been diagnosed with a CVD or Cancer event (n= 88,423).

Supplementary table 2. Sensitivity Analyses of the joint association excluding participants who had died less than 730 days after the follow-up questionnaire data was entered and excluding participants who had been diagnosed with a CVD or Cancer event

	HR (95% CI)		
Joint Association	All-cause	CVD	Cancer
No WT + No MVPA	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Yes WT + No MVPA	0.924 (0.886; 0.964)	0.896 (0.847; 0.949)	0.915 (0.847; 0.989)
No WT + Yes MVPA	0.831 (0.817; 0.847)	0.827 (0.807; 0.847)	0.884 (0.856; 0.913)
Yes WT + Yes MVPA	0.779 (0.760; 0.798)	0.769 (0.745; 0.794)	0.823 (0.789; 0.858)
No WT + No MVPA[1]	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Yes WT + No MVPA[1]	0.934 (0.893; 0.976)	0.908 (0.855; 0.962)	0.928 (0.854; 1.00)
No WT + Yes MVPA[1]	0.853 (0.837; 0.869)	0.848 (0.827; 0.869)	0.916 (0.885; 0.948)
Yes WT + Yes MVPA[1]	0.80 (0.780; 0.820)	0.787 (0.761; 0.813)	0.864 (0.827; 0.903)
No WT + No MVPA[2]	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Yes WT + No MVPA[2]	0.933 (0.865; 1.00)	0.849 (0.761; 0.947)	0.828 (0.806; 1.07)
No WT + Yes MVPA[2]	0.849 (0.822; 0.876)	0.847 (0.811; 0.884)	0.944 (0.891; 1.00)
Yes WT + Yes MVPA[2]	0.779 (0.747; 0.813)	0.765 (0.721; 0.812)	0.892 (0.827; 0.961)

Note: 1. Sensitivity analyses run after excluding participants who had died less than 730 days after the follow-up questionnaire data was entered (n= 212, 335).
2. Sensitivity analyses run after excluding participants who had been diagnosed with a CVD or Cancer event (n= 88,423).

Supplementary Table 3. Showing the results of the association between weight training and mortality **among males (NIH-AARP (n= 128,896))**

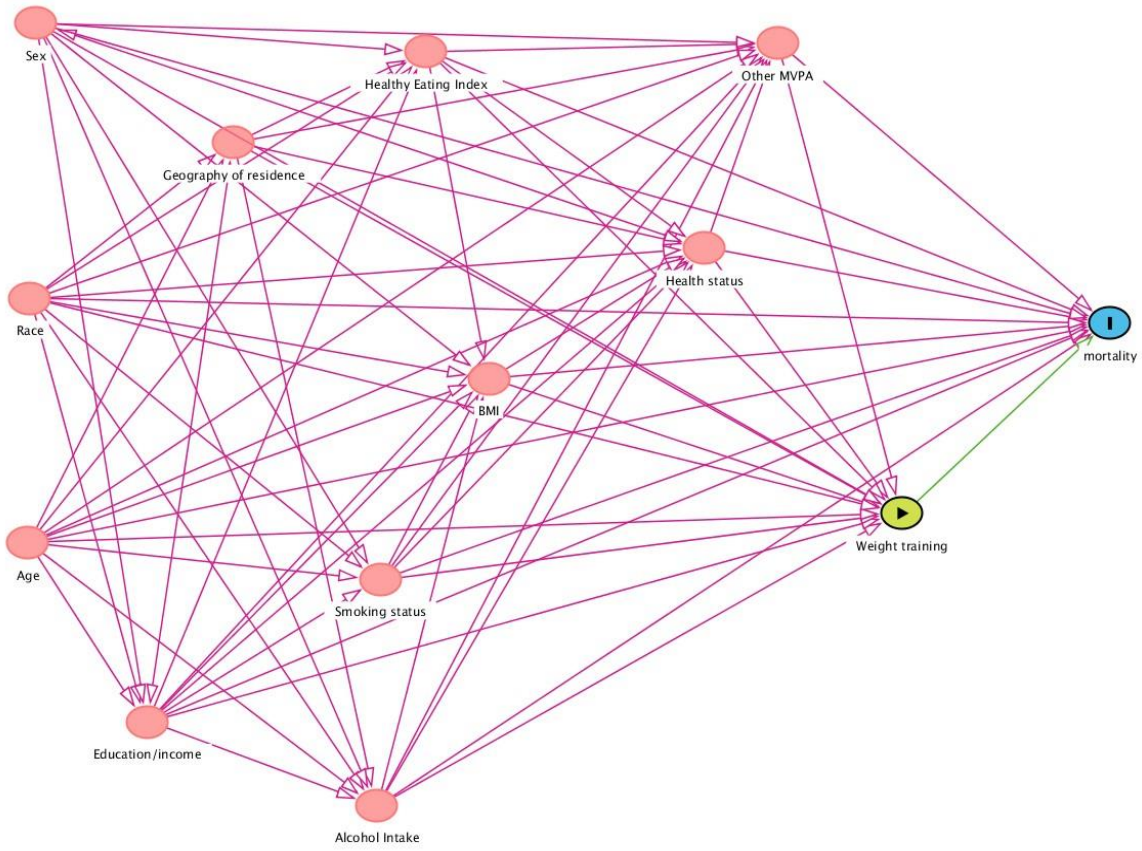
	HR (95% CI)		
Weight training	**All-cause mortality**	**CVD**	**Cancer**
None vs Some			
No weight training	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Some weight training	0.945 (0.93; 0.97)	0.936 (0.91; 0.96)	0.933 (0.90; 0.97)
Continuous (hrs/wk)			
0 hrs/wk of WT	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
+1 hr/wk of WT	0.998 (0.99 1.00)	0.999 (0.99; 1.01)	0.99 (0.97; 1.00)
Categorical (hrs/wk)			
None (0 hrs/wk)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Low (5 mins-1.5 hrs/wk)	0.944 (0.92; 0.97)	0.932 (0.90; 0.96)	0.933 (0.90; 0.97)
High (2 hrs - 10+ hrs/wk	0.95 (0.91; 0.99)	0.952 (0.90; 1.00)	0.932 (0.87; 1.00)

Supplementary Table 4. Showing the results of the association between weight training and mortality **among females (NIH-AARP (n= 92,958))**

	HR (95% CI)		
Weight training	**All-cause mortality**	**CVD**	**Cancer**
None vs Some			
No weight training	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Some weight training	0.84 (0.81; 0.87)	0.81 (0.78; 0.85)	0.87 (0.82; 0.92)
Continuous (hrs/wk)			
0 hrs/wk of WT	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
+1 hr/wk of WT	0.98 (0.97; 1.00)	0.96 (0.94; 0.98)	0.99 (0.96; 1.00)
Categorical (hrs/wk)			
None (0 hrs/wk)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Low (5 mins-1.5 hrs/wk)	0.84 (0.81; 0.87)	0.82 (0.78; 0.86)	0.85 (0.80; 0.91)
High (2 hrs - 10+ hrs/wk	0.85 (0.79; 0.91)	0.79 (0.71; 0.87)	0.93 (0.83; 1.04)

Appendix D

Chapter 3: Cohort study (Supplementary figure/s)



Supplementary Figure 1. Figure showing a directed acyclic graph to identify a minimal, sufficient set of confounders to include as covariates in statistical models, based on the possible determinants of weight- training and mortality risk factors

Appendix E

Statement of Authorship

Title of Paper	'Weight-ing to Live': Associations between resistance training and all-cause mortality, cardiovascular disease mortality and cancer mortality: a systematic review and meta-analysis
Publication Status	☐ Published ☐ Accepted for Publication ☒ Submitted for Publication ☐ Unpublished and Unsubmitted work written in manuscript style
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Contribution to the Paper Brief description of your work in this publication	**Involved in all aspects from conception to final writing**	
Overall Percentage (%)	70%	
Certification		
Signature	[redacted]	Date 12/12/2021

CO-AUTHOR CONTRIBUTIONS

By signing the Statement of Authorship, each author certifies that:

I. the candidate's stated contribution to the publication is accurate (as detailed above);

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