Long-term resistance training with all-cause and cause-specific mortality: assessing dose-response and joint associations with aerobic physical activity

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ABSTRACT

Objective To examine whether resistance training is associated with lower all-cause and cause-specific mortality, the dose-response relationship, and joint effects with aerobic activity.

Methods We included participants from three large prospective cohorts (Health Professionals Follow-up Study, 1992–2022; Nurses' Health Study, 2002–2021; Nurses' Health Study II, 2003–2021). Weekly resistance training duration and aerobic exercise duration were assessed using validated questionnaires at baseline and biennially thereafter. Cox proportional hazard models were used to estimate hazard ratios (HR) and 95% confidence intervals (95% CI).

Results Among 147 374 participants (31 540 men and 115 834 women) followed for up to 30 years, we documented 35 798 deaths. Compared with no resistance training, 90–119 min/week of resistance training was associated with a 13% lower risk of all-cause mortality (HR 0.87, 95% CI 0.81 to 0.95), 19% lower risk of cardiovascular mortality (HR 0.81, 95% CI 0.67 to 0.97) and 27% lower risk of neurological disease mortality (HR 0.73, 95% CI 0.58 to 0.92), adjusting for aerobic activity. No additional benefit was observed above 120 min/week. Reduced cancer mortality risk was seen only at lower levels of resistance training: HR 0.91 (95% CI 0.86 to 0.97) for 1–29 min/week and HR 0.88 (95% CI 0.81 to 0.97) for 30–59 min/week. In joint analyses, compared with those with inadequate aerobic activity (<7.5 metabolic equivalent of task (MET)-hours/week) and no resistance training, mortality risk was lowest among participants with both high aerobic and resistance training (eg, HR 0.55 (95% CI 0.50 to 0.60) for 30 to <45 MET-hours/week of aerobic and 60–119 min/week of resistance training), as well as among those attaining ≥45 MET-hours/week of aerobic activity regardless of resistance training level (HRs from 0.53 to 0.58).

Conclusion Using repeated measures of resistance training over up to 30 years of follow-up, moderate long-term resistance training was associated with lower all-cause mortality, with lowest risks plateauing at around ≥120 min/week of resistance training. Resistance training was associated with further reduced mortality risk at all levels of aerobic activity up to around ≥45 MET-hours/week of aerobic activity.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The mortality benefits of aerobic physical activity are well established; however, the role of resistance training in reducing all-cause and cause-specific mortality, its dose-response relationship and its joint effects with aerobic activity remain less clear.

WHAT THIS STUDY ADDS

⇒ Using repeated measures of resistance training over up to 30 years of follow-up, we found that performing 90–119 min/week of long-term resistance training was associated with 13% lower all-cause, 19% lower cardiovascular and 27% lower neurological disease mortality, after multivariable adjustment including aerobic activity. Levels higher than 120 min/week did not lower these risks further.

⇒ For cancer mortality, a reduced risk was observed only at lower levels of resistance training (1–59 min/week).

⇒ Engaging in either adequate aerobic activity or resistance training alone was associated with lower mortality, with the risk reduction more pronounced with aerobic activity.

⇒ The lowest mortality risk was observed when both activities were performed at high levels or when aerobic activity level was very high (≥45 metabolic equivalent of task (MET)-hours/week).

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our findings on different dose-response relationships between long-term resistance training with all-cause and cause-specific mortality suggest that different amounts of resistance training may be needed to optimise benefits across outcomes.

⇒ The observed pattern that adding resistance training further reduced mortality risk across all levels of aerobic activity up to ≥45 MET-hours/week supports current recommendations encouraging both types of activity to maximise mortality benefits.

INTRODUCTION

While the beneficial effect of aerobic activity on mortality risk reduction is well documented,[1] it is less clear whether resistance training offers similar benefits. The 2018 Physical Activity Guidelines recommend 150–300 min/week of moderate or 75–150 min/week of vigorous aerobic activity (7.5–15 metabolic equivalent task (MET) hours/week), or an equivalent combination.[2] Importantly,

the guidelines also advise muscle-strengthening activities at least 2 days per week, reflecting the available evidence at the time of guideline development.[2] Several studies suggest resistance training ≥2 versus <2 times/week is associated with a lower mortality risk.[3–6] However, this dichotomised comparison reflects the predominant data available was on resistance training frequency and may not fully capture the underlying dose-response relationship with respect to resistance training volume. A 2022 meta-analysis of six cohort studies suggested a J-shaped association, with the lowest risk observed at around 40 min/week of resistance training and diminishing effect at higher levels (≥150 min/week).[7] Furthermore, most existing studies assessed resistance training exposure only once at baseline,[8] which may introduce measurement error and limit their ability to evaluate the dose-response of long-term resistance training on mortality.

Fewer studies have examined the joint association of aerobic activity and resistance training with mortality, and it remains unclear whether resistance training alone can provide mortality benefits when aerobic activity is limited. While most studies suggest the maximum mortality benefit comes from performing both,[5 6 9–12] some reported no benefit from resistance training alone in the absence of aerobic activity.[6 11 12] Clarifying this relationship is of significant public health importance, as it would offer clearer guidance on how to best incorporate these two forms of physical activity to maximise mortality risk reduction. Furthermore, while many studies have examined resistance training in relation to cardiovascular disease (CVD) mortality and cancer mortality,[6 10 11 13 14] its impact on neurological disease mortality is less clear. As the global population ages, neurological disease mortality rates have increased in both sexes and across most developed countries, with the USA experiencing the most substantial rise.[15 16] Both epidemiological and animal studies support a protective effect of physical exercise against neurodegenerative diseases.[17 18] However, the specific effects of resistance training on neurological disease mortality are less well understood.

In this study, we used data from three large US prospective cohort studies with repeated measures of weekly resistance training duration and up to 30 years of follow-up to examine the association of long-term resistance training duration and all-cause and cause-specific mortality. We specifically focused on dose-response patterns by duration and conducted detailed analyses of the joint associations with aerobic activity.

METHODS

Study population

The Health Professionals Follow-up Study (HPFS) was initiated in 1986 with 51 529 male health professionals, aged 40–75 years at enrolment. The Nurses' Health Study (NHS) was initiated in 1976 with 121 700 female registered nurses, aged 30–55 years at enrolment. The NHSII was initiated in 1989 with 116 429 female nurses, aged 25–42 years at enrolment. Participants in each cohort were biennially followed with self-administered questionnaires collecting medical, lifestyle and health information, with follow-up rates of over 90% at each cycle. Diet assessment, based on food frequency questionnaires (FFQs) every 4 years, demonstrated good reproducibility and validity.[19–21] Participants were not intimately involved in the design or implementation of the studies or of these results.

Assessment of physical activity

Resistance training was assessed with questionnaires in 1990 for HPFS, 2000 for NHS and 2001 for NHSII and updated throughout follow-up (every 2 years for HPFS; every 2–4 years for NHS and NHSII; online supplemental eMethods). In each cycle, participants were asked to report average weekly time spent in resistance training (weight machine/resistance training). There were 10 response categories ranging from none to >11 hours/week. Participants also reported average time spent performing aerobic leisure-time physical activities (walking, jogging, running, bicycling, lap swimming, tennis or squash, other aerobics, heavy outdoor work and climbing stairs) in the same questionnaires. We assigned a MET score for each aerobic activity and calculated a weekly MET-hour score summing across each of them. To capture the long-term physical activity pattern and to reduce within-person measurement error, we calculated the cumulative average of repeated measures of resistance training or aerobic activities from baseline to time at risk. The validity and reproducibility of the physical activity questionnaires in both men and women have been previously described.[22–25] For resistance training specifically, the correlation was high (r=0.79) between the questionnaire and 1 week activity diary in HPFS.[23] We did not have a parallel validation study of resistance training in NHS I/II. However, because the resistance training question and its administration were highly similar across cohorts and the key population characteristics (eg, race/ethnicity, occupation and education level) were broadly comparable, we anticipate comparable validity.

Outcome ascertainment

Deaths were ascertained through reports by family members, autopsy reports, and linkage with the National Death Index. Underlying causes of death were determined by study physicians based on all available data from medical records and death certificates and were blinded to any exposure information. International Classification of Diseases, 9th revision (ICD-9) codes were used to classify deaths resulting from CVD (codes 390–459 and 795), cancer (codes 140–209), respiratory disease (codes 460–519), and neurological disease (codes 290, 340, 342 and 348). We also defined physical activity-related cancer deaths which included death from bladder, breast, colon, endometrial, oesophageal, gastric, and renal cancers.[26] Mortality ascertainment in the cohort was over 98%.[27] Death outcomes were ascertained from baseline (1992 for HPFS, 2002 for NHS, 2003 for NHSII) through the end of follow-up (December 2022 for HPFS, and June 2021 for NHS and NHSII).

Covariate assessment

Race was self-reported at baseline. Information on age, weight, and for women, menopausal status and postmenopausal hormone use, was collected at baseline and biennially thereafter. Smoking status (current, past, never) and quantity (number of cigarettes per day if currently smoking) were reported on biennial questionnaires. Family history of cancer and myocardial infarction was self-reported at baseline and subsequently on selected questionnaires. Body mass index (BMI) was calculated using self-reported height and weight. Using the FFQ data, we calculated total energy, alcohol intake, and the Alternate Healthy Eating Index (AHEI 2010) to assess overall diet quality.[28] A higher AHEI score indicates a healthier dietary pattern. Cigarettes smoking status, smoking pack-years, and postmenopausal hormone use were updated at each cycle using the most recent information.[29] For BMI and dietary variables such as alcohol intake, total calories and AHEI scores, we calculated cumulative averages up to each questionnaire cycle and modelled them as time-varying covariates.[30–32]

Population for analysis

We included participants who reported resistance training in 1990 for HPFS, 2000 for NHS and 2001 for NHSII. To reduce the influence of reverse causation in the relationship between physical activity and mortality, we excluded participants diagnosed with cancer (except non-melanoma skin cancer), heart disease or stroke before the start of follow-up and applied a 2-year lag time between resistance training assessment and the time at risk of outcome. Thus, our analytic baseline was defined as 1992 for HPFS, 2002 for NHS and 2003 for NHSII. Of participants originally enrolled in HPFS (n=51 529), NHS (n=121 700), and NHSII (n=116 429), we additionally excluded those with missing age or withdrawal of consent and death before the analytic baseline, leaving 147 374 participants in the final analytic sample, including 31 540 men and 115 834 women (HPFS, n=31 540; NHS, n=45 034; NHSII, n=70 800). A flowchart detailing cohort-specific exclusions is presented in online supplemental figure 1. The study protocol was approved by the institutional review boards of the Brigham and Women's Hospital, Harvard T.H. Chan School of Public Health, and the participating registries as required.

Statistical analysis

Person-time was accumulated from baseline until death or end of follow-up (December 2022 for HPFS, June 2021 for NHS and NHSII), whichever came first. Cox proportional hazards models were applied to estimate the hazard ratio (HR) and 95% confidence interval (95% CI) of the association of resistance training with all-cause and cause-specific mortality risk. For analyses of cause-specific mortality (eg, CVD death), participants who died from other causes were censored at the time of death and no longer contributed person-time to the analysis.

To characterise long-term (habitual) resistance training behaviour, we used the repeated, biennially updated questionnaire reports rather than a single baseline measure.[32–34] Specifically, resistance training (hours/week) was modelled as a time-varying cumulative average (cumulative mean) to represent better usual resistance training behaviour over time and reduce measurement error.[35] We also applied a 2-year lag between resistance training assessment and time at risk of death to reduce reverse causation.[35] At each questionnaire cycle, we calculated the mean of all available resistance training reports from baseline up to that cycle and assigned this value to the subsequent risk interval. For example, the mean of the 1990 and 1992 reports was used for follow-up from 1994 to 1996; the mean of the 1990, 1992 and 1994 reports was used for follow-up from 1996 to 1998, and so on. We created six groups for categorical analysis of resistance training: 0, 1 to <30, 30 to <60, 60 to <90, 90 to <120, and ≥120 min/week. We selected the following covariates based on knowledge of the literature[10 35] and use of directed acyclic graphs to select potential confounders. Multivariable-adjusted model with age (month) as timescale and stratification by calendar time (year) and cohort had additional adjustment for race (white/non-white), family history of cancer (yes/no), family history of CVD (yes/no), cigarette smoking status (never, former quitting ≥10 years, former quitting <10 years, current), cigarette smoking pack-years (0, 1–4, 5–14, 15–24, ≥25 pack-years), alcohol intake (<5.0, 5.0–14.9, ≥15.0 g/day), total calories (quintiles), AHEI score (quintiles), and for women, postmenopausal hormone use (premenopausal, never user, former user, current user). We further adjusted for aerobic activity (quartiles) to examine the independent effect. As adiposity is a potential mediator between physical activity and mortality, we additionally adjusted for BMI (<24.0, 24.0–25.9, 26.0–27.4, 27.5–29.9, or ≥30 kg/m^2) in a separate model. If covariates data for a given cycle were missing, values from the previous cycle were carried forward. Linear trend was examined by treating the resistance training time as a continuous variable with winsorisation at 99th percentile (5 hours/week). Analyses were performed in each cohort as well as the pooled data of all three cohorts after no heterogeneity was found between cohorts. We used restricted cubic spline models with three knots at the 75th, 90th and 95th percentiles (corresponding to resistance training time of 30, 90 and 150 min/week) to model flexibly the shape of the association between resistance training and all-cause and cause-specific mortality. To test for a potential non-linear association, a likelihood ratio test was used to compare the model with only the linear term of total leisure-time physical activity with the model with both the linear and the cubic spline terms, with $p<0.05$ denoting significant non-linearity. The proportional hazards assumption was evaluated by adding interaction terms between age (timescale) and the exposures and found to be satisfied. The association between resistance training and aerobic activity was assessed using the Pearson correlation coefficient.

We next examined the joint association between resistance training and aerobic physical activity. We categorised aerobic physical activity into five groups: <7.5, 7.5 to <15, 15 to <30, 30 to <45, and ≥45 MET-hours/week. The cutoffs were chosen in multiples of 7.5 MET-hours/week to align with the guideline recommended level and facilitate interpretation. Resistance training time was categorised into four levels: 0, 1 to <60, 60 to <120, and ≥120 min/week. The categorisation was chosen to ensure a sufficient number of cases in each joint level. Thus, the joint exposure group had 20 levels in total, and we considered participants with inadequate aerobic activity (<7.5 MET-hours/week) and no resistance training (0 min/week) as the reference group. To examine the additive effects between aerobic activity and resistance training, we calculated Relative Excess Risk due to Interaction (RERI) (online supplemental eMethods).[36–38] In sensitivity analyses, we applied longer lag-time (4-, 8- and 12-year) between resistance training and all-cause and cause-specific mortality and evaluated the association separately by sex. As we previously reported, resistance training was associated with lower risk of bladder and kidney cancers in HPFS[34]; here we also examined mortality for each specific cancer type. We also conducted stratified analyses by potential effect modifiers such as age, BMI, smoking and diet and evaluated potential interactions (online supplemental eMethods). As few studies have specifically examined the association between resistance training and mortality in younger populations, we conducted an analysis focusing on participants under age 55. All analyses were performed using SAS software, version 9.4 (SAS Institute, NC, USA), at a two-tailed p value of 0.05.

Equity, diversity and inclusion statement

Although our study cohorts include both men and women, they were established in an era when diversity was not the primary consideration in study design or recruitment. We acknowledge this in the limitation discussion. Our research team is diverse, with balanced representation in gender, background, academic rank and geographic region.

RESULTS

The median age of participants at baseline was 54 years. Participants with higher long-term resistance training time were younger, with lower BMI, less likely to be smoking, have a

Table 1 Age-standardized participant's characteristics by resistance training time throughout follow-up in three cohorts pooled

	Resistance training time, min/week					
	0	1 to <30	30 to <60	60 to <90	90 to <120	≥120
Person-years	751 289	290 733	130 578	95 073	42 583	98 511
Resistance training time, min/week	0 (0)	12 (6)	42 (6)	72 (6)	102 (6)	204 (126)
Percentage of follow-up time reaching resistance training target*	0% (0%)	6% (11%)	35% (18%)	67% (25%)	75% (24%)	86% (21%)
Aerobic physical activity, MET-hours/week	17.5 (19.6)	22.1 (19.4)	28.2 (21.4)	31.1 (22.9)	35.8 (24.0)	44.1 (34.1)
Age in years	64.7 (11.9)	66.5 (11.6)	65.5 (10.8)	62.8 (11.2)	64.3 (10.4)	61.1 (10.8)
White, %	96	96	97	97	97	97
Female, %	72	69	74	78	75	82
Family history of CVD, %	43	42	43	43	43	44
Family history of cancer, %	51	56	59	58	59	58
BMI, kg/m^2	26.5 (5.1)	25.7 (4.5)	25.3 (4.3)	25.0 (4.1)	24.7 (4.0)	24.4 (3.9)
Current smoker, %	7	4	3	3	3	4
Pack-year of smoking	9.7 (16.9)	6.9 (13.2)	6.8 (12.6)	6.9 (12.5)	6.7 (12.5)	7.2 (12.8)
AHEI score	51.8 (9.5)	55.6 (9.5)	57.4 (9.6)	58.2 (9.7)	59.5 (9.8)	59.8 (10.0)
Alcohol intake, g/day	6.2 (9.9)	6.9 (9.5)	7.2 (9.3)	7.2 (9.0)	7.6 (9.2)	7.2 (9.0)

Values were age-standardised except age itself and were presented as mean (SD) or percentages.
*Resistance training target: defined as ≥60 min/week of resistance training.
AHEI, Alternative Healthy Eating Index; BMI, body mass index; CVD, cardiovascular disease; MET, metabolic equivalent of task.

healthier diet, and conduct higher aerobic activity compared with those with no resistance training (table 1). The distribution of aerobic activity time by resistance training level is shown in figure 1. Throughout follow-up, 74% of participants performed >7.5 MET-hours/week of aerobic activity and 46% engaged in non-zero amount of resistance training. Non-participation in resistance training was highest among those with <7.5 MET-hours/week of aerobic activity (78%), decreasing to 38% and 35% among those with 30 to <45 and ≥45 MET-hours/week, respectively. The overall correlation between resistance and aerobic activity was 0.36 across cohorts.

During up to 30 years of follow-up, we documented 35 798 deaths. Higher long-term resistance training was associated with lower risk of all-cause mortality (table 2). In the multivariable-adjusted models, participants with 90–119 min/week of resistance training had a 13% lower risk of all-cause mortality (HR 0.87, 95% CI 0.81 to 0.95). No additional benefit was observed at ≥120 min/week (HR 0.92, 95% CI 0.86 to 0.98). A significant quadratic association was observed for all-cause mortality (p-quadratic <0.001, figure 2). Further adjustment of BMI did not substantially change the observed association. For cause-specific mortality (table 2), participants with 90–119 min/

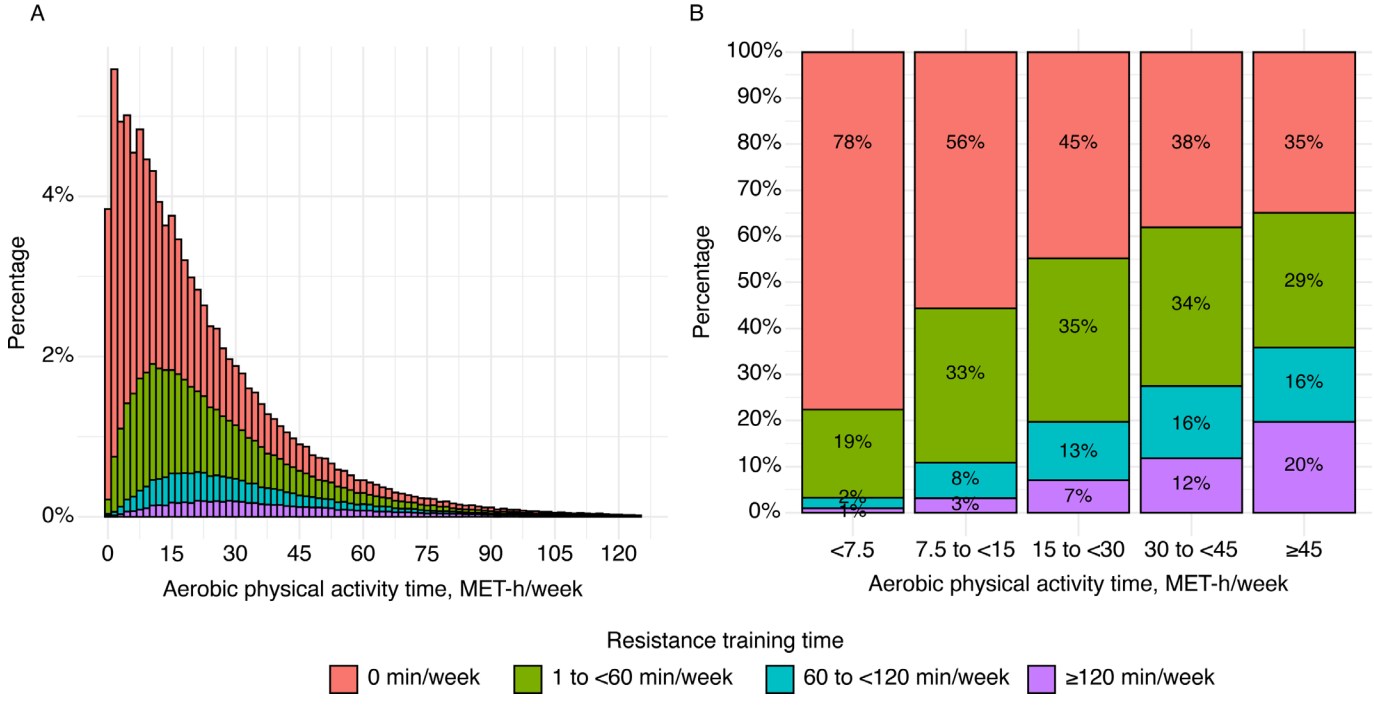

Figure 1 Distribution of aerobic physical activity time by resistance training time level throughout follow-up in three cohorts pooled. (A) The distribution resistance training time groups across all aerobic physical activity time level. (B) The percentage of resistance training time groups in each aerobic physical activity time groups. MET, metabolic equivalent of the task.

Table 2 Association between resistance training time and all-cause and cause-specific mortality in three cohorts pooled

	Resistance training time, min/week						
	0	1 to <30	30 to <60	60 to <90	90 to <120	≥120	P-linear trend*
All-cause mortality (n=35 798)							
Cases	21 307	8570	2693	1463	672	1093	
Age model†	Ref	0.83 (0.81 to 0.85)	0.73 (0.70 to 0.76)	0.70 (0.67 to 0.74)	0.66 (0.61 to 0.72)	0.68 (0.64 to 0.72)	<0.001
MV model‡	Ref	0.90 (0.88 to 0.93)	0.82 (0.78 to 0.85)	0.81 (0.76 to 0.85)	0.76 (0.70 to 0.82)	0.79 (0.74 to 0.84)	<0.001
MV+aerobic PA model§	Ref	0.95 (0.92 to 0.97)	0.91 (0.87 to 0.95)	0.91 (0.86 to 0.96)	0.87 (0.81 to 0.95)	0.92 (0.86 to 0.98)	<0.001
MV+aerobic PA + BMI model¶	Ref	0.95 (0.92 to 0.98)	0.91 (0.87 to 0.95)	0.92 (0.87 to 0.97)	0.88 (0.81 to 0.95)	0.93 (0.87 to 0.99)	0.001
CVD mortality (n=8404)							
Cases	4997	2150	610	322	130	195	
Age model†	Ref	0.88 (0.84 to 0.93)	0.76 (0.70 to 0.83)	0.73 (0.65 to 0.82)	0.62 (0.52 to 0.74)	0.64 (0.55 to 0.74)	<0.001
MV model‡	Ref	0.95 (0.90 to 1.00)	0.85 (0.77 to 0.92)	0.82 (0.73 to 0.93)	0.70 (0.58 to 0.83)	0.73 (0.63 to 0.85)	<0.001
MV+aerobic PA model§	Ref	0.99 (0.94 to 1.05)	0.95 (0.87 to 1.04)	0.94 (0.84 to 1.06)	0.81 (0.67 to 0.97)	0.86 (0.75 to 1.00)	0.002
MV+aerobic PA + BMI model¶	Ref	1.01 (0.95 to 1.06)	0.97 (0.88 to 1.06)	0.96 (0.86 to 1.09)	0.83 (0.69 to 0.99)	0.90 (0.78 to 1.05)	0.02
Cancer mortality (n=7597)							
Cases	4561	1648	576	361	171	280	
Age model†	Ref	0.83 (0.79 to 0.88)	0.77 (0.70 to 0.84)	0.84 (0.75 to 0.94)	0.82 (0.71 to 0.96)	0.80 (0.71 to 0.90)	<0.001
MV model‡	Ref	0.89 (0.84 to 0.95)	0.84 (0.77 to 0.92)	0.94 (0.84 to 1.05)	0.92 (0.78 to 1.07)	0.90 (0.79 to 1.02)	0.09
MV+aerobic PA model§	Ref	0.91 (0.86 to 0.97)	0.88 (0.81 to 0.97)	1.00 (0.89 to 1.11)	0.98 (0.83 to 1.14)	0.96 (0.85 to 1.09)	0.92
MV+aerobic PA + BMI model¶	Ref	0.92 (0.86 to 0.97)	0.89 (0.81 to 0.97)	1.00 (0.90 to 1.12)	0.98 (0.84 to 1.15)	0.97 (0.85 to 1.10)	0.99
Physical activity-related cancer mortality (n=1715)							
Cases	1094	331	128	72	30	60	
Age model†	Ref	0.72 (0.64 to 0.82)	0.72 (0.60 to 0.87)	0.70 (0.55 to 0.89)	0.59 (0.41 to 0.85)	0.69 (0.53 to 0.89)	<0.001
MV model‡	Ref	0.77 (0.67 to 0.88)	0.78 (0.65 to 0.95)	0.77 (0.61 to 0.99)	0.65 (0.45 to 0.94)	0.77 (0.59 to 1.01)	0.02
MV+aerobic PA model§	Ref	0.79 (0.69 to 0.90)	0.82 (0.68 to 0.99)	0.81 (0.64 to 1.04)	0.69 (0.48 to 1.00)	0.82 (0.62 to 1.07)	0.12
MV+aerobic PA + BMI model¶	Ref	0.79 (0.70 to 0.90)	0.83 (0.68 to 1.00)	0.83 (0.65 to 1.06)	0.70 (0.48 to 1.01)	0.83 (0.63 to 1.09)	0.17
Respiratory disease mortality (n=2949)							
Cases	1806	730	190	115	49	59	
Age model†	Ref	0.87 (0.80 to 0.96)	0.65 (0.55 to 0.75)	0.69 (0.57 to 0.84)	0.64 (0.48 to 0.86)	0.49 (0.38 to 0.64)	<0.001
MV model‡	Ref	1.03 (0.94 to 1.13)	0.82 (0.70 to 0.96)	0.90 (0.74 to 1.10)	0.83 (0.62 to 1.10)	0.66 (0.50 to 0.86)	<0.001
MV+aerobic PA model§	Ref	1.10 (1.00 to 1.21)	0.97 (0.83 to 1.13)	1.10 (0.90 to 1.34)	1.05 (0.78 to 1.41)	0.86 (0.66 to 1.13)	0.62
MV+aerobic PA + BMI model¶	Ref	1.09 (0.99 to 1.20)	0.96 (0.82 to 1.12)	1.08 (0.88 to 1.32)	1.04 (0.77 to 1.39)	0.85 (0.65 to 1.11)	0.47
Neurological disease mortality (n=4635)							
Cases	2789	1121	346	172	79	128	
Age model†	Ref	0.80 (0.74 to 0.86)	0.72 (0.64 to 0.81)	0.65 (0.56 to 0.76)	0.61 (0.49 to 0.77)	0.65 (0.55 to 0.78)	<0.001
MV model‡	Ref	0.82 (0.77 to 0.89)	0.76 (0.67 to 0.85)	0.70 (0.59 to 0.82)	0.65 (0.52 to 0.82)	0.70 (0.58 to 0.83)	<0.001
MV+aerobic PA model§	Ref	0.86 (0.80 to 0.93)	0.83 (0.73 to 0.93)	0.77 (0.65 to 0.90)	0.73 (0.58 to 0.92)	0.78 (0.65 to 0.94)	<0.001
MV+aerobic PA + BMI model¶	Ref	0.85 (0.79 to 0.92)	0.82 (0.73 to 0.92)	0.75 (0.64 to 0.88)	0.72 (0.57 to 0.90)	0.76 (0.63 to 0.92)	<0.001
Other death mortality (n=12 213)**							
Cases	7154	2921	971	493	243	431	
Age model†	Ref	0.81 (0.78 to 0.85)	0.72 (0.67 to 0.77)	0.65 (0.59 to 0.72)	0.64 (0.56 to 0.73)	0.69 (0.62 to 0.76)	<0.001
MV model‡	Ref	0.89 (0.85 to 0.93)	0.83 (0.77 to 0.88)	0.76 (0.69 to 0.83)	0.76 (0.67 to 0.86)	0.82 (0.74 to 0.91)	<0.001
MV+aerobic PA model§	Ref	0.94 (0.90 to 0.98)	0.93 (0.86 to 0.99)	0.87 (0.79 to 0.95)	0.88 (0.77 to 1.00)	0.97 (0.87 to 1.07)	0.25
MV+aerobic PA + BMI model¶	Ref	0.95 (0.90 to 0.99)	0.93 (0.87 to 1.00)	0.88 (0.80 to 0.96)	0.89 (0.78 to 1.02)	0.99 (0.89 to 1.09)	0.42

Resistance training exposures were 2-year lagged relative to the outcomes.
*P for linear trend was calculated by treating the resistance training time as a continuous variable (winsorised at 99%).
†Age model: adjusted for age (month), calendar time (year), and cohort (HPFS/NHS/NHSII).
‡MV model: additionally adjusted for race (white/non-white), family history of CVD (yes/no), family history of cancer (yes/no), cigarette smoking status (never, former quitting ≥10 years, former quitting <10 years, current), cigarette smoking pack-years (0, 1–4, 5–14, 15–24, ≥25 pack-years), alcohol intake (<5.0, 5.0–14.9, ≥15.0 g/day), total calories (quartiles), AHEI score (quartiles), aerobic physical activity (quartiles), and for women, postmenopausal hormone use (premenopausal, never user, former user, current user).
§MV+aerobic PA model: additionally adjusted for aerobic physical activity (quartiles).
¶MV+aerobic PA + BMI model: additionally adjusted for BMI (<24.0, 24.0–25.9, 26.0–27.4, 27.5–29.9 or ≥30 kg/m^2).
**Other death was defined as death from disease other than CVD, cancer, respiratory disease, and neurological disease.
AHEI, Alternative Healthy Eating Index; BMI, body mass index; CVD, cardiovascular disease; HPFS, Health Professionals Follow-up Study; MV, multivariable; NHS, Nurses' Health Study; PA, physical activity; Ref, reference.

week of long-term resistance training had a 19% lower risk of CVD mortality (HR 0.81, 95% CI 0.67 to 0.97). An inverse linear trend was observed (p-for-trend=0.002) which attenuated after adjusting for BMI (p-for-trend=0.02). For cancer mortality, reduced risk was seen only at lower levels of resistance training: 1–29 min/week (HR 0.91, 95% CI 0.86 to 0.97) and 30–59 min/week (HR 0.88, 95% CI 0.81 to 0.97). A stronger inverse association was observed for resistance training

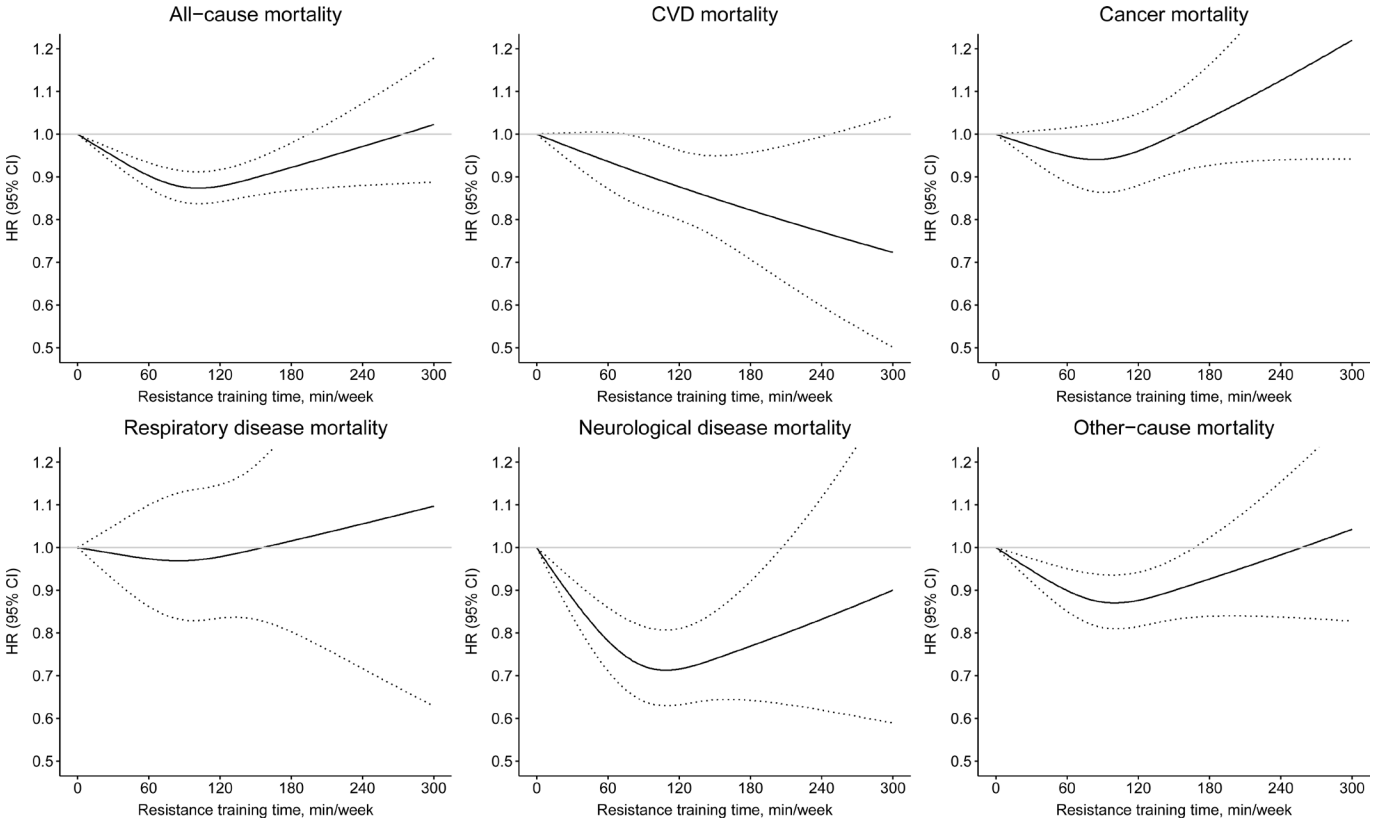

Figure 2 Dose-response relationship between resistance training time and all-cause and cause specific mortality in three cohorts pooled. Model was adjusted for age (month), calendar time (year), cohort (HPFS/NHS/NHSII), race (white/non-white), family history of CVD (yes/no), family history of cancer (yes/no), cigarette smoking status (never, former quitting ≥10 years, former quitting <10 years, current), cigarette smoking pack-years (0, 1–4, 5–14, 15–24, ≥25 pack-years), alcohol intake (<5.0, 5.0–14.9, ≥15.0 g/day), total calories (quartiles), AHEI score (quartiles), aerobic physical activity (quartiles), and for women, postmenopausal hormone use (premenopausal, never user, former user, current user). Resistance training exposures were 2-year lagged relative to the outcomes. P for non-linearity: <0.001 for all-cause mortality; 0.98 for CVD mortality; 0.05 for cancer mortality; 0.63 for respiratory disease mortality; 0.002 for neurological disease mortality, and 0.005 for other-cause mortality. AHEI, Alternative Healthy Eating Index; BMI, body mass index; CVD, cardiovascular disease; HPFS, Health Professionals Follow-up Study; MV, multivariable; NHS, Nurses' Health Study.

and physical activity-related cancer mortality, and similarly mainly at lower levels: 1–29 min/week (HR 0.79, 95% CI 0.69 to 0.90) and 30–59 min/week (HR 0.82, 95% CI 0.68 to 0.99). Further analysis by cancer type suggested that associations were primarily driven by lower mortality from colorectal (HR 0.77, 95% CI 0.62 to 0.96), bladder (HR 0.66, 95% CI 0.48 to 0.91) and breast cancer (HR 0.67, 95% CI 0.48 to 0.93), though case numbers were small (online supplemental table 1). A 27% significantly lower risk of neurological disease mortality was observed for 90–119 min/week of resistance training (HR 0.73, 95% CI 0.58 to 0.92), with a non-linear dose-response (p-quadratic=0.002; figure 2). These patterns were consistent by sexes (online supplemental table 2) and remained similar after applying an 8-year lag (online supplemental table 3). In stratified analysis, overall, the association between resistance training and all-cause mortality was similar across subgroups by BMI (<25 vs ≥25 kg/m^2; p for interaction=0.85), age (<65 vs ≥65 years; p for interaction=0.08) and diet quality (low vs high; p for interaction=0.22; online supplemental figure 2). The inverse association with mortality was consistent among never or past smokers ≥10 years, but not among current or past smokers <10 years, likely due to the smaller number of participants and limited statistical power in this subgroup. When restricted to age <55, compared with those with no resistance training, the HRs for 1–29 and ≥30 min/week were 0.73 (95% CI 0.56 to 0.94) and 0.85 (95% CI 0.68 to 1.05), respectively, with limited number of cases (n=624; data not shown).

In the joint analysis of aerobic activity and resistance training (table 3, figure 3), compared with those participants with inadequate aerobic activity (<7.5 MET-hours/week) and no resistance training, those engaging in 1–59 and 60–119 min/week of resistance training alone had 7–11% lower mortality risk (HR 0.93, 95% CI 0.88 to 0.97 and HR 0.89, 95% CI 0.76 to 1.05, respectively). In contrast, aerobic activity alone at any level above 7.5 MET-hours/week was associated with 26–43% lower mortality risk (HRs ranging from 0.74 to 0.57 across increasing aerobic activity levels). The lowest mortality risk was observed among participants with both high aerobic and resistance training (eg, HR was 0.55, 95% CI 0.50 to 0.60, for 30 to <45 MET-hours/week of aerobic and 60–119 min/week of resistance training), or among those with very high aerobic activity (≥45 MET-hours/week) regardless of their resistance training level (HRs ranging from 0.53 to 0.58 across resistance training categories). The linear trend for higher resistance training and lower all-cause mortality was significant for aerobic activity strata of <7.5 (p=0.01), 7.5 to <15 (p=0.06), 15 to <30 (p<0.001), and 30 to <45 MET-hours/week (p<0.001), but not among those with ≥45 MET-hours/week (p=0.55). These joint patterns were consistent for CVD, cancer and neurological disease mortality (online supplemental table 4, online supplemental figure 3). The

Table 3 Joint association between aerobic physical activity volume and resistance training time in relation to all-cause mortality in three cohorts pooled

Aerobic physical activity time, MET-hours/week		Resistance training time, min/week			
		0	1 to <60	60 to <120	≥120
<7.5	Case/person-years	8667/7993400	1946/3751695	152/275033	58/88698
	MV model	Ref	0.93 (0.88 to 0.97)	0.89 (0.76 to 1.05)	0.97 (0.75 to 1.26)
7.5 to <15	Case/person-years	4317/4763780	2381/5844887	313/1040307	107/319975
	MV model	0.74 (0.72 to 0.77)	0.73 (0.70 to 0.76)	0.70 (0.63 to 0.79)	0.69 (0.57 to 0.84)
15 to <30	Case/person-years	4625/4033754	3434/7254683	640/2618340	304/1233542
	MV model	0.68 (0.65 to 0.70)	0.62 (0.59 to 0.65)	0.56 (0.52 to 0.61)	0.61 (0.55 to 0.69)
30 to <45	Case/person-years	2034/1216999	1929/2656568	478/1614731	225/1200998
	MV model	0.63 (0.60 to 0.66)	0.59 (0.56 to 0.62)	0.55 (0.50 to 0.60)	0.53 (0.46 to 0.61)
≥45	Case/person-years	1664/747578	1573/1538274	552/1252844	399/1986311
	MV model	0.57 (0.54 to 0.60)	0.53 (0.50 to 0.56)	0.57 (0.52 to 0.63)	0.58 (0.52 to 0.64)

Model was adjusted for age (month), calendar time (year), cohort (HPFS/NHS/NHSII), race (white/non-white), family history of CVD (yes/no), family history of cancer (yes/no), cigarette smoking status (never, former quitting ≥10 years, former quitting <10 years, current), cigarette smoking pack-years (0, 1–4, 5–14, 15–24,≥25 pack-years), alcohol intake (<5.0, 5.0–14.9, ≥15.0 g/day), total calories (quartiles), AHEI score (quartiles), and for women, postmenopausal hormone use (premenopausal, never user, former user, current user). Resistance training exposures were 2-year lagged relative to the outcomes.
AHEI, Alternative Healthy Eating Index; BMI, body mass index; CVD, cardiovascular disease; HPFS, Health Professionals Follow-up Study; MET, metabolic equivalent of task; MV, multivariable; NHS, Nurses' Health Study; Ref, reference.

RERI for all-cause mortality comparing participants with both low resistance training (0 min/week) and low aerobic activity (<7.5 MET-hours/week) to those with only one low or neither low was 0.07 (95% CI −0.37 to 0.52), suggesting that the excess risk associated with being low in both resistance training and aerobic activity was not statistically significantly greater than the sum of the risks associated with each exposure alone.

DISCUSSION

In this study of three large prospective cohorts, moderate resistance training (60–119 min/week) was associated with lower all-cause, CVD and neurological disease mortality, with no added benefit at ≥120 min/week. Cancer mortality was lower at moderate levels (1–59 min/week). Joint analysis showed that resistance training further reduced mortality risk at all levels of aerobic activity up to around ≥45 MET-hours/week of aerobic activity.

Our findings align with two prior meta-analyses showing that any resistance training, compared with none, was associated with a 15% lower all-cause mortality.[7 8] Both reported a J-shaped association, with the greatest benefit at 40–60 min/week and a diminished effect at higher levels.[7 8] Evidence for cancer mortality is less consistent,[3 6 11 39] with some reporting reduced risk while others reported null association.[4 10 13] In our study, only low levels of resistance training (1–59 min/week) were associated with lower cancer mortality, whereas higher

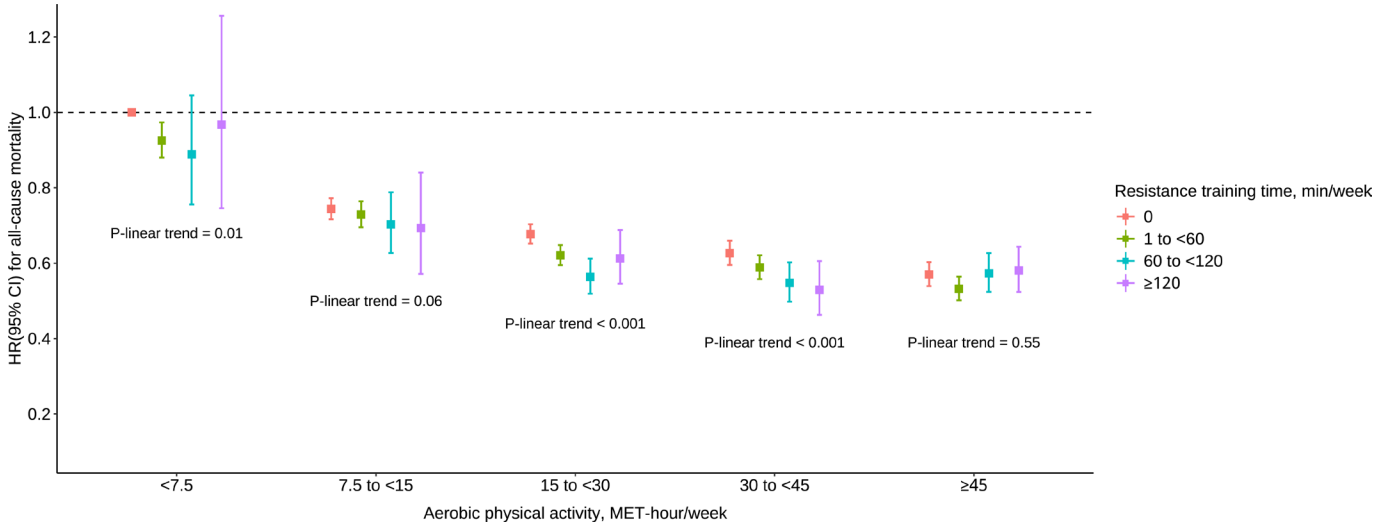

Figure 3 Joint association between aerobic physical activity volume and resistance training time in relation to all-cause mortality in three cohorts pooled. Model was adjusted for age (month), calendar time (year), cohort (HPFS/NHS/NHSII), race (white/non-white), family history of CVD (yes/no), family history of cancer (yes/no), cigarette smoking status (never, former quitting ≥10 years, former quitting <10 years, current), cigarette smoking pack-years (0, 1–4, 5–14, 15–24, ≥25 pack-years), alcohol intake (<5.0, 5.0–14.9, ≥15.0 g/day), total calories (quartiles), AHEI score (quartiles), and for women, postmenopausal hormone use (premenopausal, never user, former user, current user). The p-linear trend was calculated by assigning ordinal values to resistance training time categories and modelling it as a continuous variable. Resistance training exposures were 2-year lagged relative to the outcomes. AHEI, Alternative Healthy Eating Index; CVD, cardiovascular disease; HPFS, Health Professionals Follow-up Study; MET, metabolic equivalent of task; MV, multivariable; NHS, Nurses' Health Study.

levels (≥60 min/week) were not. This aligns with a 2021 meta-analysis that reported an HR of 0.91 (95% CI 0.82 to 1.01) for 1–59 min/week of muscle-strengthening activity and 0.98 (95% CI 0.89 to 1.07) for ≥60 min/week, compared with none, though based on only two studies.[40] The potential mechanism for increased cancer mortality at higher levels of resistance training is unclear but may involve elevated insulin-like growth factor 1 (IGF-1), particularly in older adults, as higher IGF-1 levels are linked to increased risks of colorectal, prostate and breast cancers.[41 42]

Our finding that resistance training is associated with lower CVD mortality aligns with most prior studies.[6 10 11 13] Although some have reported a U-shaped relationship,[14] we observed a linear trend. Differences in participant age, resistance training duration (acute vs long-term) and concurrent aerobic activity may explain these discrepancies. Resistance training may influence arterial stiffness, a strong predictor of CVD events.[43] Meta-analyses have shown that resistance training increases arterial stiffness in younger but not middle-aged adults,[44] and our study population consists primarily of middle-aged to older adults. Moreover, acute resistance training may increase arterial stiffness, whereas long-term regular training may reduce it.[45 46] Our use of cumulative averages likely better reflects long-term resistance training patterns. Finally, aerobic activity is known to reduce arterial stiffness, and performing it after high-intensity resistance training may help mitigate stiffness.[47] In our population, individuals with high resistance training often also engaged in high aerobic activity, thereby potentially reducing arterial stiffness. Indeed, our joint analyses showed that resistance training combined with >7.5 MET-hours/week of aerobic activity was consistently associated with lower CVD mortality.

We observed a significant inverse association between resistance training and neurological disease mortality. Limited population-based studies have examined this, with one reporting combined aerobic and resistance training associated with lower Alzheimer's disease mortality, but not resistance training alone, although they had much fewer Alzheimer's disease death (n=1091) compared with our neurologic disease death (n=4635).[5] Randomised controlled trials (RCTs) using structural neuroimaging suggest that resistance training can induce brain changes in older adults that could reduce risk or progression of Alzheimer's disease, with effects appearing to follow a dose-response pattern.[48] However, our findings should be interpreted with caution. Reverse causation remains possible, given the decades long prodromal stage of neurodegenerative diseases like Alzheimer's, and there is a progressive reduction in physical activities long before dementia is diagnosed,[49] although we still observed inverse associations even after applying 8- or 12-year time lags. Furthermore, most neurological disease deaths in our cohorts were attributed to dementia, a cause of death known to be subject to considerable misclassification, especially under-detection.[50] Further research is needed to clarify the effect of resistance training on neurological disease risk.

Our joint analysis of resistance and aerobic activity showed the lowest mortality risk among participants who engaged in both, consistent with previous studies.[5–7 9–11] Importantly, we observed that while either sufficient aerobic or resistance training alone reduced mortality risk, aerobic activity conferred greater benefit. Furthermore, we found that resistance training further reduced mortality risk at all levels of aerobic activity up to around ≥45 MET-hours/week of aerobic activity. Aerobic exercise is generally linked to improved hemodynamics, lipid profiles and cardiorespiratory fitness, whereas resistance training may improve glucose metabolism, body composition and muscular strength.[2] Meta-analyses of RCTs in coronary artery disease patients showed that, compared with aerobic activity alone, combining aerobic and resistance training yields greater improvements in cardiorespiratory fitness and body composition.[51] Of note, our study did not specifically assess the effect of resistance training on mortality risk in individuals who were physically restricted to perform aerobic activity, nor did it evaluate its impact on quality of life. Prior research suggests resistance training can improve physical function, mental health and social well-being in older adults.[52] Future studies are warranted to assess these specific aspects.

Limitations

Our study has several limitations. First, measurement error was inevitable as resistance training was self-reported. However, the use of validated questionnaires[22–25] and cumulative averages from repeated assessments likely reduced this error compared with studies relying on a single baseline measurement. Furthermore, given the prospective study design, any mismeasurement in the exposure would likely be non-differential regarding the outcome, generally attenuating the associations. Second, while current guidelines recommend muscle strengthening in days/week, our questionnaire assessed hours/week and did not capture other forms of strength training like callisthenics and Pilates. Furthermore, we did not collect specific details such as the duration of active exercise or the time between sets. Currently, the literature on resistance training includes a variety of frequency, intensity and duration, and the type of resistance training programmes also varied across studies.[53] It is possible that the health effect of resistance training may differ by intensity, and we could not assess this dimension as intensity data were not collected. Future studies with more uniform definition of resistance training with precise assessment of duration and structure are warranted. Third, the validity of resistance training in NHS I/II was not directly evaluated. However, because the questionnaires and key population characteristics (eg, race/ethnicity, occupation and education level) were similar across HPFS and NHS I/II, we expect comparable validity. Fourth, resistance training was assessed via pre-existing (historically collected) cohort questionnaires reporting average weekly duration of resistance training. Therefore, they could not be redesigned or subjected to a new cross-cohort harmonisation study for the purpose of the current analysis. We harmonised the exposure across cohorts using a common hour/week scale, but we could not perform additional cross-cohort harmonisation analyses to evaluate comparability of specific resistance training characteristics (eg, intensity, load, sets/repetitions). Lastly, generalizability may be limited as participants were mostly white middle-age to elderly health professionals, though previous studies suggest that the mortality benefits of meeting activity guidelines are consistent across racial and ethnic groups.[54] Although women accounted for 78% of the study population, the number of men was still substantial (n=31 540 men), and our sex-stratified analyses showed consistent inverse associations between resistance training and both all-cause and CVD mortality in men and women (online supplemental table 2). Currently, most studies examining resistance training and mortality have focused on older populations,[6 10 11 13] since mortality is naturally more common in older populations. In our limited sample of participants under 55 years old, engaging in 1–29 min/week of resistance training was associated with lower all-cause mortality, though the number of events was limited. Future research is needed to evaluate the effects of resistance training on other health aspects and in younger populations.

Study strengths include the large sample size comprising both men and women, repeated resistance training assessments, long follow-up duration and detailed evaluation of dose-response and joint associations with aerobic activity.

CONCLUSION

In summary, we found that moderate long-term resistance training was associated with lower all-cause mortality in both men and women, with lower risk levelling at around ≥120 min/week. Engaging in sufficient aerobic or resistance training alone is linked to lower mortality, with a stronger effect from aerobic activity. The lowest risk occurs with high levels of both, though resistance training offers no added benefit beyond ≥45 MET-hours/week of aerobic activity.

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Contributors YZ had full access to all the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. Study conception, design, acquisition of data and statistical analysis: YZ and EG. Interpretation of data: all authors. Drafting of the paper: YZ. Critical revision of the paper for important intellectual content: all authors. Supervision: EG. YZ is the guarantor.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and the protocol was approved by the institutional review boards of the Brigham and Women's Hospital and Harvard T.H. Chan School of Public Health, and those of participating registries as required. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data may be obtained from a third party and are not publicly available. Data sharing: Because of participant confidentiality and privacy concerns, data cannot be shared publicly and requests to access NHS/NHSII/HPFS data must be submitted in writing. Information including the procedures to obtain and access data from the Nurses' Health Studies and Health Professionals Follow-up Study is described at https://www.nurseshealthstudy.org/researchers (contact email: nhsaccess@channing.harvard.edu) and https://sites.sph.harvard.edu/hpfs/for-collaborators/.

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