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Long-Term Leisure-Time Physical Activity Intensity and All-Cause and Cause-Specific Mortality: A Prospective Cohort of US Adults

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BACKGROUND: The 2018 physical activity guidelines for Americans recommend a minimum of 150 to 300 min/wk of moderate physical activity (MPA), 75 to 150 min/wk of vigorous physical activity (VPA), or an equivalent combination of both. However, it remains unclear whether higher levels of long-term VPA and MPA are, independently and jointly, associated with lower mortality.

METHODS: A total of 116221 adults from 2 large prospective US cohorts (Nurses' Health Study and Health Professionals Follow-up Study, 1988–2018) were analyzed. Detailed self-reported leisure-time physical activity was assessed with a validated questionnaire, repeated up to 15 times during the follow-up. Cox regression was used to estimate the hazard ratio and 95% CI of the association between long-term leisure-time physical activity intensity and all-cause and cause-specific mortality.

RESULTS: During 30 years of follow-up, we identified 47 596 deaths. In analyses mutually adjusted for MPA and VPA, hazard ratios comparing individuals meeting the long-term leisure-time VPA guideline (75–149 min/wk) versus no VPA were 0.81 (95% CI, 0.76–0.87) for all-cause mortality, 0.69 (95% CI, 0.60–0.78) for cardiovascular disease (CVD) mortality, and 0.85 (95% CI, 0.79–0.92) for non-CVD mortality. Meeting the long-term leisure-time MPA guideline (150–299 min/wk) was similarly associated with lower mortality: 19% to 25% lower risk of all-cause, CVD, and non-CVD mortality. Compared with those meeting the long-term leisure-time physical activity guidelines, participants who reported 2 to 4 times above the recommended minimum of long-term leisure-time VPA (150–299 min/wk) or MPA (300–599 min/wk) showed 2% to 4% and 3% to 13% lower mortality, respectively. Higher levels of either long-term leisure-time VPA (≥300 min/wk) or MPA (≥600 min/wk) did not clearly show further lower all-cause, CVD, and non-CVD mortality or harm. In joint analyses, for individuals who reported <300 min/wk of long-term leisure-time MPA, additional leisure-time VPA was associated with lower mortality; however, among those who reported ≥300 min/wk of long-term leisure-time MPA, additional leisure-time VPA did not appear to be associated with lower mortality beyond MPA.

CONCLUSIONS: The nearly maximum association with lower mortality was achieved by performing ≈150 to 300 min/wk of long-term leisure-time VPA, 300 to 600 min/wk of long-term leisure-time MPA, or an equivalent combination of both.

Key Words: cardiovascular diseases ■ exercise ■ guidelines as topic ■ mortality

Regular physical activity has consistently been associated with reduced risk of major noncommunicable diseases and premature death.[1] The 2018 physical activity guidelines recommend that adults engage in at least 150 to 300 min/wk of moderate physical activity (MPA), 75 to 150 min/wk of vigorous physical activity (VPA), or an equivalent combination of both intensities.[2] In the physically active population, a growing number of people are performing higher levels of leisure-time physical activity to maintain health and improve fitness.[3,4]

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Clinical Perspective

What Is New?

- A comprehensive analysis of the association between long-term physical activity intensity and mortality that uses repeated measures of physical activity is lacking.
- The nearly maximal benefit on mortality reduction was observed among individuals who reported ≈150 to 300 min/wk of long-term leisure-time vigorous physical activity, 300 to 600 min/wk of long-term leisure-time moderate physical activity, or an equivalent combination of both.
- No harmful association was shown among individuals who reported >4 times the recommended minimum levels of long-term leisure-time moderate and vigorous physical activity.

What Are the Clinical Implications?

- These findings support the current physical activity guidelines and further suggest higher levels of long-term leisure-time vigorous and moderate physical activity to achieve the maximum benefit of mortality reduction.

Nonstandard Abbreviations and Acronyms

BMI	body mass index
CVD	cardiovascular disease
HPFS	Health Professionals Follow-up Study
HR	hazard ratio
MET	metabolic equivalent task
MPA	moderate physical activity
NHS	Nurses' Health Study
VPA	vigorous physical activity

However, there are concerns about the potential harmful effects on cardiovascular health of accumulating an excessive amount of VPA such as exercise programs designed for individuals running a marathon.[5] It remains unclear whether engaging in a high level of prolonged MPA or VPA over the recommended levels provides additional benefit or harmful effects on health.

Several studies have examined graded associations between total physical activity and mortality, showing no additional benefits after reaching a certain threshold of total physical activity,[6,7] whereas some studies showed a clear U-shaped association between physical activity and mortality.[8] However, most studies had a single measure of self-reported or device-based physical activity at baseline with a short follow-up, which is prone to reverse causation bias and cannot identify long-term adherents to high levels of physical activity. Our previous methodological study showed that compared with a single measure of physical activity, repeated measures of physical activity reduce these common biases observed in previous studies of physical activity and mortality.[9] In addition, application of a 2-year lag period between physical activity assessment and mortality substantially reduces the influence of reverse causation, whereas longer lag periods (4–12 years) had minimal impact on the association beyond a 2-year lag. Despite the commonly recognized limitation of using single measures, previous studies generally did not incorporate the advanced methodological approach of using repeated measures of physical activity.

Furthermore, previous studies have not examined the long-term association of VPA and MPA, separately and jointly, with the explicit recognition that VPA and MPA may have different graded associations for different mortality outcomes. In addition to examining the independent association of physical activity intensity, it is critical to investigate the joint association of VPA and MPA. For instance, studies have not isolated the added benefit of VPA in individuals with low levels of MPA in contrast to those with high levels of MPA. A systematic review and meta-analysis of cohort studies suggested that for the same amount of total physical activity, a higher proportion of VPA to total physical activity was not associated with lower all-cause mortality.[10] However, in a large prospective study, for the same amount of total physical activity, a higher proportion of VPA was associated with a lower mortality risk.[11] In contrast, some studies performed in middle-aged recreational runners have suggested that a high amount of VPA has deleterious effects on cardiovascular disease (CVD) outcomes.[12–14] These findings suggest that the health benefits of physical activity may differ by dose (intensity and duration) and by the outcomes examined.

Therefore, the current study used 2 large prospective cohorts with up to 15 repeated measures of self-reported leisure-time physical activity over 30 years of follow-up to examine the graded association between long-term VPA and MPA and all-cause and cause-specific mortality. Moreover, the joint association of different physical activity intensities with mortality was further examined.

METHODS

Data Sharing

The data, analytical methods, and study materials will be available to other researchers from the corresponding author on reasonable request for the purposes of reproducing the results or replicating the procedure.

Study Population

The NHS (Nurses' Health Study) began in 1976 when 121 701 female nurses (age, 30–55 years) were enrolled. The HPFS (Health Professionals Follow-Up Study) began in 1986 when 51 529 male health professionals (age, 40–76 years) were enrolled. At enrollment and every 2 years, participants were

asked to complete questionnaires on demographic, lifestyle, and medical history information. The follow-up rate for both cohorts exceeded 90% for each questionnaire cycle. The present study included participants who had information on detailed leisure-time physical activity in 1986. To reduce the influence of reverse causation in the relationship between physical activity and mortality, the present study excluded participants diagnosed with CVD or cancer at baseline and applied a 2-year lag time between physical activity assessment and the time at risk of dying.[9] Thus, our baseline was defined as 1988 for both NHS and HPFS. The final analysis included a total of 116 221 participants. 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.

Physical Activity Assessment

Detailed information on leisure-time physical activity was first assessed by self-reported questionnaire in 1986 and updated every 2 years. Up to 15 repeated measures of physical activity (median, 11 [10th–90th percentile, 3–13]) were available, and the same questionnaires were used over the follow-up except that weight training information was added beginning in 1990 for HPFS and 2000 for NHS. The reproducibility and validity of physical activity questionnaire have previously been described.[15–18] From the biennial questionnaires, participants were asked to report average hours they spent during the past year on various activities, including walking, jogging, running, swimming, bicycling, performing calisthenics and other aerobic exercises, playing squash/racquetball or tennis, engaging in lower-intensity exercise, weightlifting, and working outdoors. To quantify the intensity of physical activity, we assigned a metabolic equivalent task (MET), which designates metabolic rates for a specific activity divided by metabolic rates at rest according to a compendium of physical activities.[19] Moderate activity was defined as activities <6 METs, including walking, performing lower-intensity exercise, weightlifting, and doing calisthenics. Vigorous activity was defined as activities ≥6 METs, including jogging, running, swimming, bicycling, engaging in other aerobic exercises, playing squash/racquetball or tennis, working outdoors, and climbing stairs. MPA and VPA were calculated by summing the corresponding physical activities in MET-hours per week.

Covariate Assessment

Information on age, race, height, weight, family history of disease, personal medical history, smoking, and sleep duration was assessed from the biennial questionnaires. Body mass index (BMI) was calculated by weight in kilograms divided by height in meters squared. Dietary information was assessed with validated semiquantitative food frequency questionnaires every 4 years.[20–22] The Alternate Healthy Eating Index was used to indicate overall diet quality (0–100).[23]

Outcomes Ascertainment

Deaths were identified from the National Death Index, next of kin, or postal system.[24,25] Through these methods, >98% of deaths were ascertained for both cohorts. Information on the cause of death was collected by physician review of medical records. When medical records were not available, death certificates were obtained. *International Classification of Diseases* (8th and 9th revisions) codes were used to classify deaths resulting from CVD (codes 390–459 and 795) and non–CVD-related causes. Moreover, CVD was defined as the composite of incident nonfatal myocardial infarction, fatal coronary heart disease, and fatal and nonfatal stroke. Nonfatal myocardial infarction and stroke were confirmed by physicians according to the World Health Organization criteria[26] and the National Survey of Stroke criteria,[27] respectively.

Statistical Analysis

Person-time was calculated from the baseline in 1988 until the time of death or the end of the follow-up period (January 2018 for HPFS and June 2018 for NHS), whichever occurred first. Cox proportional hazard regression model was used to estimate the hazard ratio (HR) and 95% CI of the association between long-term leisure-time physical activity intensity and deaths resulting from all causes, CVD deaths, and non–CVD-related deaths. Results from HPFS and NHS were pooled after testing for heterogeneity between cohorts (P>0.05). Cumulative average of repeated measures of physical activity was used to capture the long-term leisure-time physical activity intensity and to reduce within-person measurement error. With the use of the current physical activity guidelines, MPA and VPA were finely divided into 9 categories based on physical activity guidelines (0, 1–74, 75–149, 150–224, 225–299, 300–374, 375–449, 450–599, ≥600 min/wk).[2] Because a small number of participants consistently reported no MPA over the entire follow-up, the reference group for MPA was broadened to 0 to 19 min/wk (≈10% of the distribution). Multivariable-adjusted Cox regression model using age (month) as a timescale with stratification by calendar time (year) and cohort had additional adjustment for race (White or non-White), family history of CVD (yes or no), family history of cancer (yes or no), postmenopausal hormone use (women only; premenopausal, postmenopausal current user, or postmenopausal never/past user), alcohol intake (0, 0.1–4.9, 5–9.9, 10–14.9, or ≥15.0 g/d), total energy intake (quintiles), smoking status (never, past, or current: 1–14, 15–24, ≥25 cigarettes/d), sleep duration (≤6, 7–8, or >8 h/d), Alternate Healthy Eating Index score (quintiles), and BMI (<21, 21–22.9, 23–24.9, 25–26.9, 27–29.9, 30–34.9, 35–39.9, or ≥40 kg/m^2). To examine the independent association of long-term leisure-time physical activity intensity, VPA and MPA were mutually adjusted for in all models.

In addition, restricted cubic spline models were used with 3 knots to flexibly model the shape of the association of long-term leisure-time VPA and MPA with all-cause and cause-specific mortality.[28] Given that VPA and MPA are correlated (r=0.2), joint analyses of MPA and VPA were conducted to examine how the combination of VPA and MPA was associated with mortality. Moreover, stratified analyses by potential effect modifiers such as age, sex, BMI, smoking, and alcohol intake were performed. Several sensitivity analyses were done by not adjusting for BMI/calorie intake (potential mediator), further adjusting for physical limitation, or excluding those who did not engage in any physical activity (potential reverse causation). In addition, different approaches of characterizing physical activity were compared (ie, single measure at baseline, cumulative average of repeated measures for the first 10 years, 20 years,

and all follow-up years). As a secondary analysis, the long-term proportion of VPA to total physical activity instead of absolute level of MPA and VPA was used to examine the association between long-term leisure-time physical activity intensity and mortality. Last, the same analyses were repeated with incident CVD outcome, in addition to our primary mortality outcome, to examine the association between long-term leisure-time physical activity intensity and CVD risk.

All analyses were performed with SAS software version 9.4 (SAS Institute). Values of $P<0.05$ were considered statistically significant.

RESULTS

Participants' characteristics according to long-term leisure-time MPA and VPA are presented in Tables 1 and 2. The mean age and BMI of participants over the follow-up were 66 years and 26 kg/m^2. The majority of participants were White, and the percentage of women was 63%. Participants were also free of major chronic diseases (ie, CVD and cancer) at baseline. Among participants with any physical activity, participants with higher long-term leisure-time VPA were younger, whereas participants with higher long-term leisure-time MPA were older. Moreover, participants with higher long-term leisure-time VPA or MPA were leaner and had higher alcohol intake and diet quality score and lower prevalence of current smoking.

During 2984545 person-years of follow-up (median, 26 years), we documented 47 596 deaths. Compared with those with no long-term leisure-time VPA, participants who met the long-term leisure-time physical activity guidelines (75-149 min/wk of VPA) had 19% lower all-cause mortality (HR, 0.81 [95% CI, 0.76–0.87]), 31% lower CVD mortality (HR, 0.69 [95% CI, 0.60–0.78]), and 15% lower non-CVD mortality (HR, 0.85 [95% CI, 0.79–0.92]; Table 3). Participants who reported 2 to 4 times the recommended minimum of long-term leisure-time VPA (150–299 min/wk) had further lower mortality (ie, ≈21%–23% lower all-cause mortality, 27%–33% lower CVD mortality, and 19% lower non-CVD mortality). Higher levels of long-term leisure-time VPA (≥300 min/wk) did not have further lower mortality. In the restricted cubic spline models, long-term leisure-time VPA was associated with substantially lower risk of all-cause, CVD, and non-CVD mortality, and the inverse association for long-term leisure-time VPA tended to level off in the higher range (Figure 1).

In terms of long-term leisure-time MPA, compared with those with almost no long-term leisure-time MPA, participants who met the long-term leisure-time physical activity guidelines (150–224 and 225–299 min/wk of MPA) had 20% to 21% lower all-cause mortality (HR, 0.80 [95% CI, 0.77–0.83]; HR, 0.79 [95% CI, 0.76–0.82]), 22% to 25% lower CVD mortality (HR, 0.78 [95% CI, 0.72–0.84]; HR, 0.75 [95% CI, 0.68–0.82]), and 19% to 20% lower non-CVD mortality (HR, 0.81 [95% CI, 0.78–0.85]; HR, 0.80 [95% CI, 0.77–0.84]; Table 4). Participants who reported 2 to 4 times the recommend minimum of long-term leisure-time MPA (300–599 min/wk) gradually had 3% to 13% further lower mortality (ie, ≈26%–31% lower all-cause mortality, 28%–38% lower CVD mortality, and 25%–27% lower non-CVD). A higher level of long-term leisure-time MPA (≥600 min/wk) showed associations with mortality similar to 300 to 599 min/wk of MPA. In the restricted cubic spline models, long-term leisure-time MPA was associated with substantially lower risk of all-cause, CVD, and non-CVD mortality, and the inverse association for long-term leisure-time MPA continued to strengthen over the entire range of activity assessed in the cohort (Figure 1).

In the joint analyses of long-term leisure-time VPA and MPA, a strong inverse association between VPA and all-cause and cause-specific mortality was found among those who had insufficient long-term leisure-time MPA (<150 min/wk), whereas a weaker inverse association was shown among those who met the long-term leisure-time MPA guideline (Figure 2). There was no clear inverse association of long-term leisure-time VPA among those who met ≥2 times the long-term leisure-time MPA guidelines. In the stratified analyses, an inverse association of long-term leisure-time MPA and VPA with all-cause mortality was consistently found regardless of age, sex, BMI, smoking, and alcohol intake (Table S1). However, the inverse association tended to be stronger among individuals with lower BMI.

In sensitivity analyses, the association between long-term leisure-time VPA and MPA and mortality was consistent without adjustment for BMI/calorie intake or with additional adjustment for physical limitations. When we excluded participants with no physical activity, long-term leisure-time MPA showed similar associations with mortality, but long-term leisure-time VPA tended to show more clearly that high levels of VPA do not provide additional benefit (Table S2). Compared with the cumulative average of repeated physical activity measures, use of a single measure at baseline showed weaker inverse associations with mortality and tended to show a U-shaped association (Table S3). However, the use of a cumulative average of first 10 and 20 years of physical activity measures showed consistently inverse associations with mortality with no clear indication of higher mortality in the higher range of physical activity. In secondary analyses using proportion of VPA to total physical activity, compared with those with no long-term leisure-time VPA, participants with any long-term leisure-time VPA had lower all-cause and cause-specific mortality (Table S4). However, participants reporting >25% of long-term leisure-time VPA did not show further lower mortality. The joint analyses of long-term leisure-time proportion of VPA and total physical activity showed that a higher proportion of long-term leisure-time VPA was inversely associated with mortality among those who had insufficient physical activity (1–149 min/wk) or met the physical activity guidelines

Table 1. Age and Sex Standardized Characteristics of Person-Years According to Vigorous Physical Activity (N=116221)*

PA guideline	VPA, min/wk								
	0 (Inactive)	1–74 (Insufficient)	75–149 (Sufficient)	150–224 (×2)	225–299 (×3)	300–374 (×4)	375–449 (×5)	450–599 (×6)	≥600 (×8 or more)
Person-years	91 573	1 776 378	539 846	269 767	122 439	79 642	39 875	38 387	26 638
Age, y	61.5 (9.4)	66.0 (10.6)	66.7 (10.4)	65.4 (10.7)	66.0 (10.4)	64.3 (10.9)	65.3 (10.5)	64.5 (10.8)	63.1 (10.8)
Male, %	3.1	33.7	36.2	43.6	48.8	55.1	55.9	59.5	59.8
BMI, kg/m^2	26.7 (5.6)	26.3 (4.5)	25.6 (4)	25.1 (3.7)	24.9 (3.5)	24.7 (3.4)	24.5 (3.4)	24.4 (3.4)	24.2 (3.6)
White, %	96.2	96.7	96.9	96.7	96.2	96.1	95.7	95.6	94.6
Calories, kcal/d	1680 (455)	1815 (503)	1845 (493)	1869 (506)	1904 (519)	1910 (531)	1922 (536)	1958 (550)	2012 (590)
Alcohol, g/d	6.0 (11.1)	7.4 (11.4)	7.8 (10.7)	8.3 (10.7)	8.8 (11)	9.5 (11.7)	9.3 (11.2)	9.6 (11.3)	9.4 (11.9)
AHEI score	49.8 (9.6)	51.1 (9.6)	54.3 (9.5)	55.9 (9.8)	57.0 (9.9)	57.6 (10)	58.3 (10)	58.6 (10)	59.0 (10.3)
Sleep (7–8 h/d), %	54.7	49.0	52.0	49.3	48.1	45.4	45.9	43.5	38.1
Family history of MI, %	38.5	35.3	35.4	35.6	34.9	34.3	34.1	35.2	34.8
Family history of cancer, %	39.5	31.2	31.2	29.9	28.8	27.2	27.5	26.0	24.2
Smoking, %									
Never	44.4	45.3	46.6	46.7	47.0	47.3	47.8	47.5	50.7
Past	38.8	43.3	45.1	45.1	45.2	44.5	43.9	43.6	40.7
Current	13.5	8.4	5.9	5.2	4.4	4.2	4.3	4.1	3.6
Total PA, h/wk	1.9 (2.5)	2.8 (2.7)	4.8 (2.7)	6.4 (2.9)	8.1 (3.0)	9.2 (3.2)	11.0 (3.3)	12.7 (3.5)	18.9 (7.3)
MPA, h/wk	1.9 (2.5)	2.4 (2.6)	3.0 (2.6)	3.4 (2.8)	3.8 (2.9)	3.7 (3.2)	4.2 (3.3)	4.2 (3.4)	5.2 (4.2)
VPA, h/wk	0	0.4 (0.4)	1.8 (0.4)	3.0 (0.4)	4.3 (0.4)	5.5 (0.4)	6.8 (0.4)	8.5 (0.7)	13.7 (5.4)

AHEI indicates Alternate Healthy Eating Index; BMI, body mass index; MI, myocardial infarction; MPA, moderate physical activity; PA, physical activity; and VPA, vigorous physical activity.

*Data were updated over the follow-up.

(150–299 min/wk; Figure S1). Higher long-term leisure-time proportion of VPA was not associated with further lower mortality among active participants with ≥2 times the physical activity guidelines.

In additional analyses using incident CVD outcome, an inverse association of long-term leisure-time VPA and MPA with CVD risk was consistently observed (Table S5). Compared with those with no long-term leisure-time VPA, participants who met the long-term leisure-time VPA guideline (75–149 min/wk of VPA) had 22% lower CVD (HR, 0.78 [95% CI, 0.70–0.87]), 25% lower coronary heart disease (HR, 0.75 [95% CI, 0.64–0.87]), and 14% lower stroke (HR, 0.86 [95% CI, 0.73–1.01]). Meeting the long-term leisure-time MPA guideline (150–299 min/wk) showed weaker associations: 5% to 11% lower risk of CVD, coronary heart disease, and stroke. Participants who reported 2 to ≥4 times the recommended minimum of long-term leisure-time VPA or MPA had small but additionally lower CVD and coronary heart disease risk (Figure S2). In the joint analyses of long-term leisure-time VPA and MPA, an inverse association between long-term leisure-time VPA and CVD risk was observed among those who had long-term leisure-time MPA <300 min/wk (Figure S3). Sensitivity analyses showed patterns similar to those of the mortality outcomes (Tables S2–S4).

DISCUSSION

In 2 large prospective cohort studies with up to 15 repeated measures of self-reported leisure-time physical activity, the nearly lowest mortality was observed among individuals who reported ≈150 to 300 min/wk of long-term leisure-time VPA or 300 to 600 min/wk of long-term leisure-time MPA. Higher levels of either VPA or MPA did not clearly show further lower all-cause, CVD, and non-CVD mortality or harm. Moreover, for individuals who reported <300 min/wk of long-term leisure-time MPA, additional leisure-time VPA was associated with lower mortality; however, among those who reported ≥300 min/wk of long-term leisure-time MPA, additional leisure-time VPA did not appear to be associated with lower mortality beyond MPA.

Comparison With Other Studies

A pooled analysis of 6 cohort studies (all self-reported) showed that meeting the recommended physical activity guidelines for either leisure-time MPA or VPA was associated with substantially lower risk of mortality, with the maximal benefits observed at ≈3 to 5 times the recommended physical activity guideline (22.5–40 MET-h/wk).[7] A meta-analysis of 48 studies (5 device based and all others

Table 2. Age and Sex Standardized Characteristics of Person Years According to Moderate Physical Activity (N=116221)*

	MPA, min/wk								
PA guideline	0–19 (Inactive)	20–74 (Insufficient)	75–149 (Insufficient)	150–224 (Sufficient)	225–299 (×1.5)	300–374 (×2)	375–449 (×2.5)	450–599 (×3)	≥600 (×4 or more)
Person-years	318 798	736 140	686 117	480 277	260 727	198 179	101 430	118 494	84 382
Age, y	60.9 (10.6)	64.2 (10.5)	66.9 (10.2)	66.9 (10.3)	68.7 (9.8)	67.0 (10.5)	68.7 (10.1)	68.1 (10.6)	67.9 (10.8)
Male, %	34.2	27.0	30.9	35.7	39.8	46.8	52.3	62.1	76.9
BMI, kg/m^2	26.8 (5.2)	26.5 (4.8)	25.9 (4.2)	25.6 (4.0)	25.4 (3.8)	25.3 (3.7)	25.4 (3.8)	25.3 (3.6)	25.4 (3.7)
White, %	95.0	96.7	97.1	97.0	97.1	96.6	96.6	95.8	95.6
Calories, kcal/d	1735 (501)	1772 (482)	1814 (484)	1842 (496)	1886 (507)	1902 (524)	1941 (534)	1990 (558)	2086 (599)
Alcohol, g/d	6.9 (11.9)	6.6 (10.7)	7.1 (10.5)	7.8 (11)	8.2 (11.1)	9.0 (12)	9.4 (12)	10.2 (12.9)	11.4 (13.8)
AHEI score	49.5 (9.9)	51.0 (9.4)	52.9 (9.5)	54.0 (9.7)	54.6 (9.8)	54.9 (10.1)	54.7 (10.2)	54.7 (10.4)	54.1 (10.7)
Sleep (7–8 h/d), %	39.6	49.1	52.0	51.6	52.7	49.0	51.2	46.8	38.2
Family history of MI, %	36.1	36.0	35.5	35.6	34.8	34.5	34.1	33.5	31.7
Family history of cancer, %	30.6	33.5	32.1	31.2	30.5	28.2	27.9	25.4	21.3
Smoking, %									
Never	42.9	45.8	46.8	46.3	46.8	45.5	45.2	45.5	44.8
Past	41.5	43.0	44.3	44.6	44.7	44.8	44.7	43.3	42.4
Current	11.0	8.5	6.6	6.3	6.0	6.1	7.3	6.9	7.6
Total PA, h/wk	1.0 (1.8)	1.8 (1.7)	3.2 (1.9)	4.7 (2.2)	6.2 (2.3)	7.4 (2.7)	9.0 (2.8)	10.7 (3.3)	14.9 (5.1)
MPA, h/wk	0.1 (0.1)	0.8 (0.3)	1.8 (0.4)	3.0 (0.4)	4.3 (0.4)	5.4 (0.4)	6.8 (0.3)	8.5 (0.6)	12.8 (2.4)
VPA, h/wk	0.8 (1.8)	1.0 (1.6)	1.4 (1.8)	1.7 (2.1)	1.9 (2.2)	2.0 (2.4)	2.2 (2.7)	2.3 (3.1)	2.5 (4.3)

AHEI indicates Alternate Healthy Eating Index; BMI, body mass index; MI, myocardial infarction; MPA, moderate physical activity; PA, physical activity; and VPA, vigorous physical activity.

*Data were updated over the follow-up.

self-reported) reported consistent results that a high amount of total physical activity, at ≈5 to 7 times the physical activity guidelines, was associated with reduced risk of mortality.[6] However, these studies relied on physical activity measured at a single time, and the detailed association of physical activity intensity and dose with cause-specific mortality was not examined. Moreover, no studies examined the joint association of long-term VPA and MPA with mortality. Relatively little is known about the association between long-term physical activity intensity and mortality.[10] A review of 5 prospective cohorts showed that for the same amount of physical activity, VPA and MPA provide similar benefits on mortality reduction.[10] A large study of US adults from the National Health Interview Survey also showed comparable associations between the recommendations of MPA (150–299 min/wk versus 0 min/wk) and VPA (75–149 min/wk versus 0 min/wk).[11] However, among participants with any physical activity, a higher proportion of VPA to total physical activity (50%–75%) was associated with a 17% lower risk of all-cause mortality (after adjustment for total physical activity), although no consistent inverse association was observed for CVD and cancer mortality.

Our findings are in line with previous studies supporting the current recommended physical activity level (either MPA or VPA) for health benefits, but our study adds new evidence that may inform the current physical activity guidelines for optimal health outcomes for the general public. First, our study leveraged repeated measures of self-reported leisure-time physical activity over decades; thus, our findings better reflected participants' long-term average physical activity intensity during middle and late adulthood. In contrast, most previous studies assessed physical activity intensity at 1 time point. A previous study evaluated the influence of biases in the physical activity–mortality analysis and found evidence that compared with the use of repeated measures, the use of a single physical activity measure was more susceptible to measurement error and reverse causation and consequently affected the shape of the graded association, particularly in the higher level of physical activity.[9] This bias in the dose response presumably results because inconsistent or sporadic high physical activity may not represent consistently high physical activity (life-course approach). In the past several years, accelerometry-measured studies have drawn great attention because of their strength to reduce measurement error compared with studies with self-reported questionnaires.[29] However, an important caveat is that almost all accelerometry studies had a single measure of physical activity at baseline and relatively

Table 3. Associations Between Long-Term Leisure-Time VPA and All-Cause and Cause-Specific Mortality (Pooled Results of HPFS and NHS, 1988–2018)

Outcome	Deaths	Person-years	Age-adjusted HR (95% CI)	Multivariable-adjusted HR (95% CI)*
All-cause mortality				
VPA, min/wk				
0	1194	91 573	1 (Reference)	1 (Reference)
1–74	31 297	1 776 378	0.63 (0.59–0.67)	0.87 (0.82–0.93)
75–149	7907	539 846	0.50 (0.47–0.53)	0.81 (0.76–0.87)
150–224	3494	269 767	0.48 (0.45–0.52)	0.79 (0.74–0.85)
225–299	1595	122 439	0.46 (0.43–0.50)	0.77 (0.72–0.84)
300–374	937	79 642	0.47 (0.43–0.51)	0.78 (0.72–0.85)
375–449	459	39 875	0.43 (0.38–0.48)	0.73 (0.65–0.81)
450–599	444	38 387	0.45 (0.40–0.50)	0.76 (0.68–0.85)
≥600	269	26 638	0.45 (0.39–0.51)	0.74 (0.65–0.85)
CVD mortality				
VPA, min/wk				
0	285	92 503	1 (Reference)	1 (Reference)
1–74	6896	1 805 615	0.56 (0.50–0.64)	0.76 (0.67–0.86)
75–149	1625	547 572	0.44 (0.39–0.50)	0.69 (0.60–0.78)
150–224	788	273 018	0.45 (0.40–0.52)	0.73 (0.64–0.85)
225–299	341	123 927	0.40 (0.34–0.47)	0.67 (0.57–0.79)
300–374	203	80 485	0.39 (0.33–0.47)	0.68 (0.56–0.82)
375–449	105	40 288	0.38 (0.31–0.48)	0.65 (0.52–0.82)
450–599	99	38 787	0.37 (0.29–0.47)	0.67 (0.53–0.84)
≥600	68	26 886	0.41 (0.31–0.54)	0.71 (0.54–0.93)
Non-CVD mortality				
VPA, min/wk				
0	909	91 874	1 (Reference)	1 (Reference)
1–74	24 401	1 784 220	0.65 (0.61–0.70)	0.91 (0.85–0.97)
75–149	6282	541 810	0.53 (0.49–0.57)	0.85 (0.79–0.92)
150–224	2706	270 676	0.50 (0.46–0.54)	0.81 (0.75–0.88)
225–299	1254	122 803	0.50 (0.45–0.54)	0.81 (0.74–0.89)
300–374	734	79 866	0.51 (0.46–0.56)	0.82(0.74–0.91)
375–449	354	39 988	0.45 (0.40–0.51)	0.76 (0.67–0.86)
450–599	345	38 507	0.49 (0.43–0.55)	0.80 (0.70–0.90)
≥600	201	26 704	0.47 (0.40–0.55)	0.76 (0.65–0.89)

CVD indicates cardiovascular disease; HPFS, Health Professionals Follow-up Study; HR, hazard ratio; MPA, moderate physical activity; NHS, Nurses' Health Study; and VPA, vigorous physical activity.

We applied 2-year lag time between physical activity assessment and the time at risk of death.

Multivariable-adjusted model used Cox regression model with age (month) as the timescale with stratification by calendar time (year) and cohort, and we additionally adjusted for race (White or non-White), family history of CVD (yes or no), family history of cancer (yes or no), postmenopausal hormone use (women only; premenopausal, postmenopausal current user, or postmenopausal never/past user), alcohol intake (0, 0.1–4.9, 5–9.9, 10–14.9, or ≥15.0 g/d), total energy intake (quintiles), smoking status (never, past, or current: 1–14, 15–24, ≥25 cigarettes/d), sleep duration (≤6, 7–8, or >8 h/d), Alternate Healthy Eating Index score (quintiles), and body mass index (<21, 21–22.9, 23–24.9, 25–26.9, 27–29.9, 30–34.9, 35–39.9, or ≥40 kg/m^2).

*VPA and MPA were mutually adjusted.

short follow-up times (≈5 years).[30] Thus, these studies currently cannot solve the issue of inconsistent/sporadic versus consistent/high physical activity and are at risk of reverse causation, as well as measurement error to some extent.

Second, our study quantified the graded association of long-term leisure-time MPA and VPA levels >4 to 8 times the recommended physical activity guidelines. An intriguing finding is that different shapes of the dose–response relationship for long-term leisure-time MPA

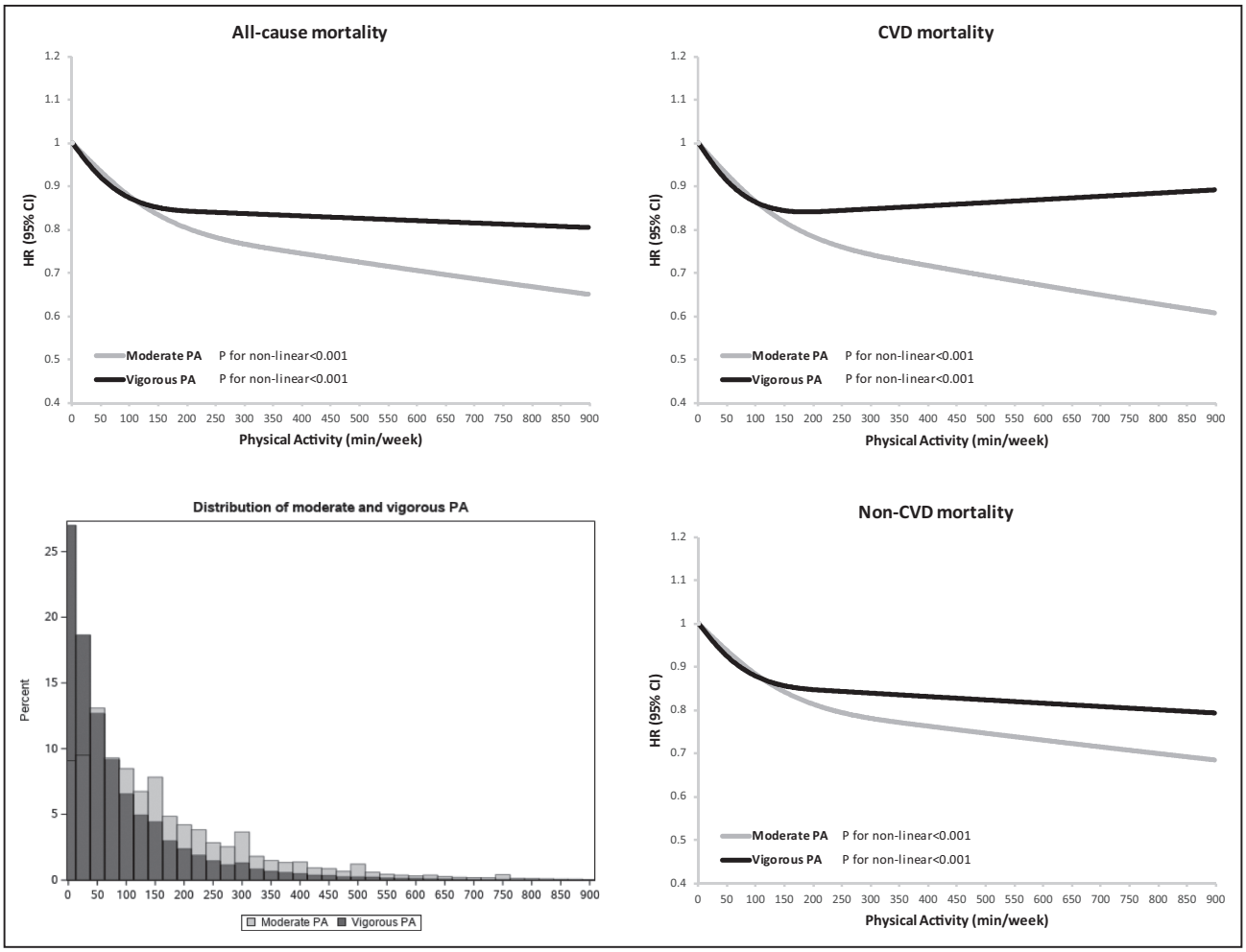

Figure 1. Dose–response relationship of long-term leisure-time MPA and VPA with all-cause mortality (pooled results of HPFS and NHS, 1988–2018).

Restricted cubic spline model with 3 knots specified at 10th, 50th, and 90th percentiles was performed with age (month) as the timescale with stratification by calendar time (year) and cohort and additional adjustment for race (White or non-White), family history of cardiovascular disease (CVD; yes or no), family history of cancer (yes or no), postmenopausal hormone use (premenopausal, postmenopausal current user, or postmenopausal never/past user), alcohol intake (0, 0.1–4.9, 5–9.9, 10–14.9, or ≥15.0 g/d), total energy intake (quintiles), smoking status (never, past, or current: 1–14, 15–24, ≥25 cigarettes/d), sleep duration (≤6, 7–8, or ≥8 h/d), Alternate Healthy Eating Index score (quintiles), and body mass index (<21, 21–22.9, 23–24.9, 25–26.9, 27–29.9, 30–34.9, 35–39.9, or ≥40 kg/m^2). Vigorous physical activity (VPA) and moderate physical activity (MPA) were mutually adjusted. HPFS indicates Health Professionals Follow-Up Study; HR, hazard ratio; NHS, Nurses' Health Study; and PA, physical activity.

and VPA were found, depending on cause of death. Previous studies focused mainly on quantifying the upper threshold of benefits for total physical activity,[6,7] but it is also critical to tease out the effects of MPA and VPA to provide more refined physical activity guidelines in terms of dose and intensity. Our study supports the current physical activity guidelines and further suggests that performing a high level of long-term leisure-time MPA beyond 4 times the minimum recommended physical activity guideline (≈600 min/wk of MPA) was consistently inversely associated with all-cause, CVD, and non-CVD mortality. However, there was no monotonic linear inverse association across all ranges of long-term leisure-time VPA. The nearly maximal benefit on mortality reduction of VPA was observed at ≈150 to 300 min/wk, twice the currently recommended VPA range of 75 to 150 min/wk. There was no greater risk of mortality even at very high levels of VPA, although no additionally lower mortality was observed beyond 300 min/wk of VPA.

Third, our joint analyses of long-term leisure-time MPA and VPA offer practical evidence for the optimal level of combined MPA and VPA. As expected, a substantially lower risk of mortality was observed among individuals who had adequate levels of both long-term leisure-time MPA and VPA. More specifically, higher levels of long-term leisure-time VPA were associated with lower mortality among those with long-term leisure-time MPA levels <300 min/wk but not among those who already had high levels of long-term leisure-time MPA ≥300 min/wk. Similarly, higher levels of long-term leisure-time MPA were associated with lower mortality among those with long-term leisure-time VPA levels <150 min/

Table 4. Associations Between Long-Term Leisure-Time MPA and All-Cause and Cause-Specific Mortality (Pooled Results of HPFS and NHS, 1988–2018)

Outcome	Deaths	Person-years	Age-adjusted HR (95% CI)	Multivariable-adjusted HR (95% CI)*
All-cause mortality				
MPA, min/wk				
0–19	4606	318 798	1 (Reference)	1 (Reference)
20–74	11 143	736 140	0.75 (0.72–0.78)	0.91 (0.88–0.94)
75–149	11 158	686 117	0.62 (0.60–0.64)	0.84 (0.81–0.88)
150–224	7451	480 277	0.57 (0.55–0.60)	0.80 (0.77–0.83)
225–299	4586	260 727	0.55 (0.53–0.57)	0.79 (0.76–0.82)
300–374	3111	198 179	0.54 (0.51–0.56)	0.74 (0.70–0.77)
375–449	1843	101 430	0.53 (0.50–0.56)	0.74 (0.70–0.78)
450–599	2135	118 494	0.51 (0.48–0.54)	0.69 (0.65–0.73)
≥600	1563	84 382	0.51 (0.49–0.55)	0.68 (0.64–0.73)
CVD mortality				
MPA, min/wk				
0–19	1050	322 738	1 (Reference)	1 (Reference)
20–74	2344	746 570	0.73 (0.67–0.78)	0.87 (0.81–0.94)
75–149	2295	697 063	0.58 (0.54–0.62)	0.79 (0.73–0.85)
150–224	1632	487 337	0.55 (0.51–0.60)	0.78 (0.72–0.84)
225–299	1016	265 158	0.52 (0.47–0.57)	0.75(0.68–0.82)
300–374	738	201 109	0.51 (0.46–0.56)	0.72 (0.65–0.79)
375–449	441	103 025	0.49 (0.44–0.55)	0.71 (0.63–0.79)
450–599	499	120 364	0.44 (0.40–0.49)	0.62 (0.55–0.69)
≥600	395	85 717	0.46 (0.41–0.52)	0.63 (0.56–0.71)
Non-CVD mortality				
MPA, min/wk				
0–19	3556	319 904	1 (reference)	1 (reference)
20–74	8799	738 754	0.76 (0.73–0.79)	0.92 (0.88–0.96)
75–149	8863	688 821	0.64 (0.61–0.66)	0.86 (0.83–0.90)
150–224	5819	482 197	0.59 (0.56–0.61)	0.81 (0.78–0.85)
225–299	3570	261 938	0.57(0.54–0.59)	0.80 (0.77–0.84)
300–374	2373	198 983	0.55 (0.52–0.58)	0.75 (0.71–0.79)
375–449	1402	101 948	0.55 (0.51–0.58)	0.75 (0.71–0.80)
450–599	1636	119 083	0.54 (0.51–0.58)	0.73 (0.68–0.77)
≥600	1168	84 819	0.54 (0.51–0.58)	0.71 (0.67–0.76)

CVD indicates cardiovascular disease; HPFS, Health Professionals Follow-up Study; HR, hazard ratio; MPA, moderate physical activity; NHS, Nurses' Health Study; and VPA, vigorous physical activity.

We applied 2-year lag time between physical activity assessment and the time at risk of death.

Multivariable-adjusted model used Cox regression model with age (month) as the timescale with stratification by calendar time (year) and cohort, and we additionally adjusted for race (White or non-White), family history of CVD (yes or no), family history of cancer (yes or no), postmenopausal hormone use (women only; premenopausal, postmenopausal current user, or postmenopausal never/past user), alcohol intake (0, 0.1–4.9, 5–9.9, 10–14.9, or ≥15.0 g/d), total energy intake (quintiles), smoking status (never, past, or current: 1–14, 15–24, ≥25 cigarettes/d), sleep duration (≤6, 7–8, or >8 h/d), Alternate Healthy Eating Index score (quintiles), and body mass index (<21, 21–22.9, 23–24.9, 25–26.9, 27–29.9, 30–34.9, 35–39.9, or ≥40 kg/m^2).

*VPA and MPA were mutually adjusted.

wk but not among those who already had high levels of long-term leisure-time VPA ≥150 min/wk. Our findings suggest that any combinations of medium to high levels of VPA (75–300 min/wk) and MPA (150–600 min/wk) can provide nearly the maximum mortality reduction (≈35%–42%). More important, insufficiently active people (<75 min/wk of VPA or <150 min/wk of MPA) could get greater benefits on mortality reduction (≈22%–31%) by adding modest levels of either VPA (75–150 min/wk) or MPA (150–300 min/wk). Our study provides evidence

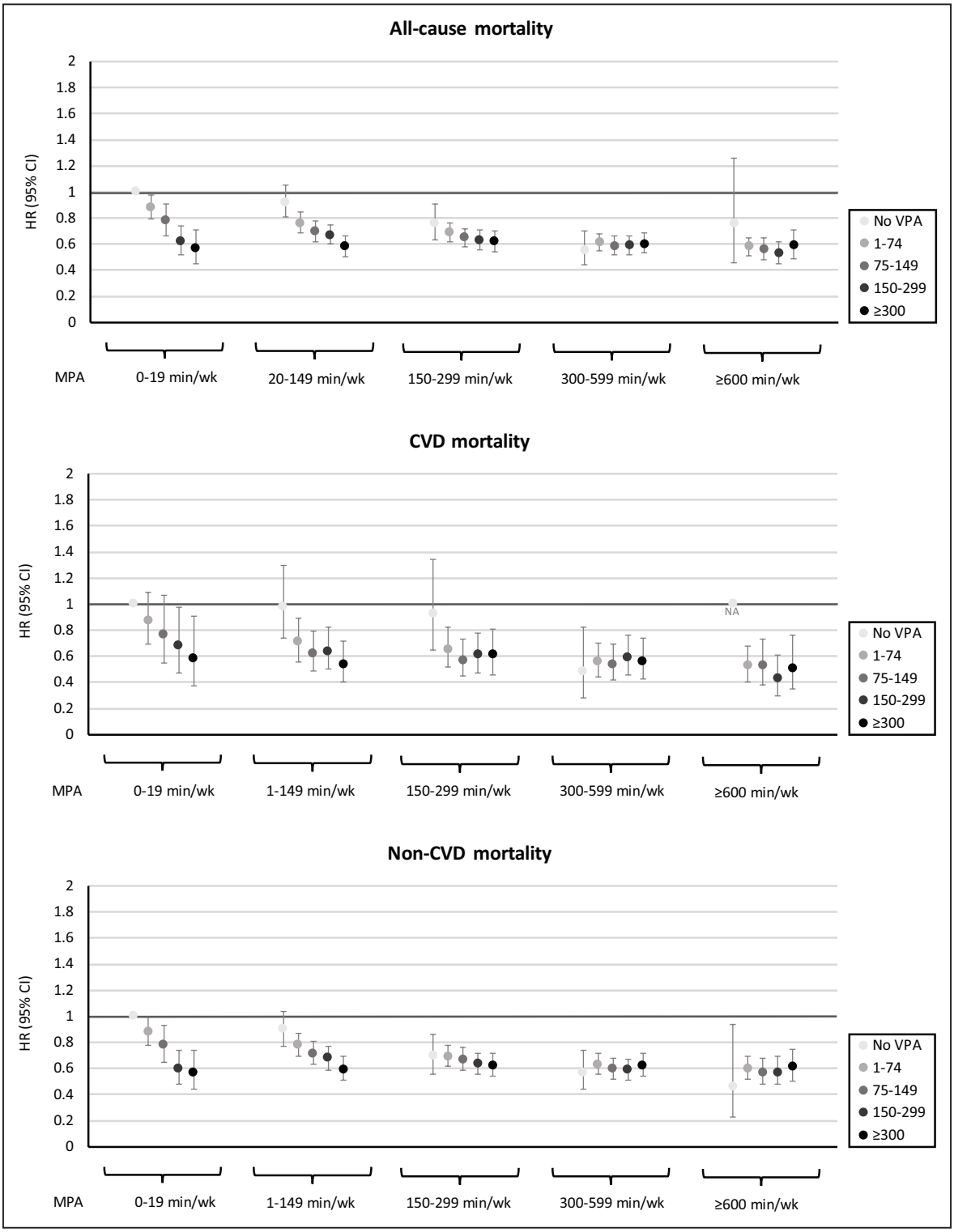

Figure 2. Joint association of long-term leisure-time VPA and MPA with all-cause and cause-specific mortality (pooled results of HPFS and NHS, 1988–2018).

Multivariable-adjusted model used Cox regression model with age (month) as timescale with stratification by calendar time (year) and cohort and additional adjustment for race (White or non-White), family history of cardiovascular disease (CVD; yes or no), family history of cancer (yes or no), postmenopausal hormone use (women only; premenopausal, postmenopausal current user, or postmenopausal never/past user), alcohol intake (0, 0.1–4.9, 5–9.9, 10–14.9, or ≥15.0 g/d), total energy intake (quintiles), smoking status (never, past, or current: 1–14, 15–24, ≥25 cigarettes/d), sleep duration (≤6, 7–8, or >8 h/d), Alternate Healthy Eating Index score (quintiles), and body mass index (<21, 21–22.9, 23–24.9, 25–26.9, 27–29.9, 30–34.9, 35–39.9, or ≥40 kg/m^2). HPFS indicates Health Professionals Follow-Up Study; HR, hazard ratio; MPA, moderate physical activity; NA, not available because of insufficient power (<10 deaths); NHS, Nurses' Health Study; and VPA, vigorous physical activity.

to guide generally healthy individuals to choose the right amount and intensity of physical activity over their lifetime to maintain their overall health.

Our stratified analyses consistently found an inverse association between long-term leisure-time VPA and MPA and mortality regardless of age. There is a natural propensity toward more VPA in younger individuals and more MPA in older individuals. The similar pattern was observed in our cohorts, but there was no evidence that either long-term leisure-time VPA or MPA is particularly more strongly associated with mortality in older individuals compared with younger individuals. Our study suggests that in addition to long-term leisure-time MPA, long-term leisure-time VPA in generally healthy older adults can be an effective means of improving health.

In regard to cause-specific mortality, similar shapes of the association between long-term leisure-time VPA and MPA and different causes of mortality (eg, CVD versus non-CVD) were observed. It is well documented that light to moderate regular physical activity prevents CVD, but previous studies also showed evidence that long-term high-intensity endurance exercise (eg, marathons, triathlons, long-distance bicycle races) may cause adverse events such as myocardial fibrosis, coronary artery calcification, and atrial fibrillation, as well as sudden cardiac death.[12–14] Our findings on the graded association suggest that there is no harmful effect of high long-term leisure-time VPA on cardiovascular health. However, more studies, ideally with repeated objective physical activity measures and long follow-up, are needed to investigate the effect of high amounts of VPA on CVD outcomes and to identify the optimal dose and intensity of long-term physical activity for health benefits.

Strengths and Limitations

Our study has several strengths, including a large study population, long follow-up time, and detailed information on covariates. Moreover, up to 15 repeated measures of detailed leisure-time physical activity over 30 years can minimize reverse causation and within-person measurement error and allow examination of the long-term associations of VPA and MPA, both separately and jointly, with mortality. There are several limitations as well. First, although our study used validated physical activity questionnaires, there is inevitable measurement error. Moreover, non–leisure-time physical activity such as occupational and transport-related physical activity, which may have differential associations with health outcomes,[31] was not reported. However, our study included health professionals, and thus, occupational physical activity is likely low with limited variability. Although it is the beyond the scope of our study, the cumulative average of repeated measures may not account for potential large variations of physical activity across the life span. In our cohorts, ≈33% to 44% (MPA) and 46% to 62% (VPA) of participants had relatively stable physical activity over time; the other participants either decreased or increased their physical activity over time (Table S6). This further supports the importance of using repeated measures of physical activity to better understand physical activity over the life span. Our study focused on the long-term aspects of physical activity intensity, but more studies with repeated measures are needed to explore the trajectory of physical activity intensity in relation to health outcomes. Second, given the nature of observational studies, residual confounding may exist. Third, our cohorts included primarily White health professionals, which may limit the generalizability of our findings; however, this may enhance internal validity by increased adherence, more accurate reporting, and possibly lower potential for residual confounding. In addition, there is no convincing evidence that the biological relationships between physical activity and health outcomes are qualitatively different across racial and ethnic groups.

Conclusions

Our study supports the current physical activity guidelines and further suggests that the nearly maximum association with lower mortality can be achieved by performing ≈150 to 300 min/wk of long-term leisure-time VPA, 300 to 600 min/wk of long-term leisure-time MPA, or an equivalent combination of both. There was no clear additional association beyond these levels, although higher levels of long-term leisure-time VPA and MPA were consistently inversely associated with mortality. Moreover, the addition of long-term leisure-time VPA was associated with substantially lower mortality for individuals who reported <300 min/wk of long-term leisure-time MPA, but no additional association of long-term leisure-time VPA was observed for those who already reported ≥300 min/wk of long-term leisure-time MPA.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Figures S1–S3

Tables S1–S6

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