Original Investigation

Leisure Time Physical Activity and Mortality
A Detailed Pooled Analysis of the Dose-Response Relationship

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IMPORTANCE The 2008 Physical Activity Guidelines for Americans recommended a minimum of 75 vigorous-intensity or 150 moderate-intensity minutes per week (7.5 metabolic-equivalent hours per week) of aerobic activity for substantial health benefit and suggested additional benefits by doing more than double this amount. However, the upper limit of longevity benefit or possible harm with more physical activity is unclear.

OBJECTIVE To quantify the dose-response association between leisure time physical activity and mortality and define the upper limit of benefit or harm associated with increased levels of physical activity.

DESIGN, SETTING, AND PARTICIPANTS We pooled data from 6 studies in the National Cancer Institute Cohort Consortium (baseline 1992-2003). Population-based prospective cohorts in the United States and Europe with self-reported physical activity were analyzed in 2014. A total of 661 137 men and women (median age, 62 years; range, 21-98 years) and 116 686 deaths were included. We used Cox proportional hazards regression with cohort stratification to generate multivariable-adjusted hazard ratios (HRs) and 95% CIs. Median follow-up time was 14.2 years.

EXPOSURES Leisure time moderate- to vigorous-intensity physical activity.

MAIN OUTCOMES AND MEASURES The upper limit of mortality benefit from high levels of leisure time physical activity.

RESULTS Compared with individuals reporting no leisure time physical activity, we observed a 20% lower mortality risk among those performing less than the recommended minimum of 7.5 metabolic-equivalent hours per week (HR, 0.80 [95% CI, 0.78-0.82]), a 31% lower risk at 1 to 2 times the recommended minimum (HR, 0.69 [95% CI, 0.67-0.70]), and a 37% lower risk at 2 to 3 times the minimum (HR, 0.63 [95% CI, 0.62-0.65]). An upper threshold for mortality benefit occurred at 3 to 5 times the physical activity recommendation (HR, 0.61 [95% CI, 0.59-0.62]); however, compared with the recommended minimum, the additional benefit was modest (31% vs 39%). There was no evidence of harm at 10 or more times the recommended minimum (HR, 0.69 [95% CI, 0.59-0.78]). A similar dose-response relationship was observed for mortality due to cardiovascular disease and to cancer.

CONCLUSIONS AND RELEVANCE Meeting the 2008 Physical Activity Guidelines for Americans minimum by either moderate- or vigorous-intensity activities was associated with nearly the maximum longevity benefit. We observed a benefit threshold at approximately 3 to 5 times the recommended leisure time physical activity minimum and no excess risk at 10 or more times the minimum. In regard to mortality, health care professionals should encourage inactive adults to perform leisure time physical activity and do not need to discourage adults who already participate in high-activity levels.

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Regular physical activity has consistently been associated with a reduced risk of mortality.[1-3] However, the 2008 Physical Activity Guidelines for Americans[4] were the first recommendations published by the federal government to describe types and amounts of physical activity that offer health benefits. The 2008 guidelines recommended 150 to 300 minutes of moderate-intensity or 75 to 150 minutes of vigorous-intensity aerobic activity weekly for substantial health benefits. However, the guidelines noted that the upper threshold of benefit for aerobic activity and potential harms associated with very high levels of activity were undefined.

Few prospective cohorts have been able to examine the association between activity levels above these recommendations and mortality owing to few deaths among participants reporting higher activity levels. However, in recent years, endurance training has increased as indicated by a record 541 000 individuals in the United States completing a marathon in 2013[5] and 510 859 USA Triathlon members in 2012.[6] Previous studies have suggested a higher risk of arrhythmias with prolonged endurance training[7] or sudden death due to electrical and myocardial remodeling,[8] raising concerns among individuals performing such activities and making health effects of very high levels of exercise a potential clinical concern. The 2008 guidelines[9] reviewed this evidence and concluded that, although cardiac risk increases when an individual becomes more active than usual (eg, someone inactive undertakes vigorous activities), these cardiac events are rare, and individuals who are regularly physically active have the lowest risk of cardiac events even while active.

A previous publication[10] using these 6 pooled cohort studies showed lower mortality among persons performing 3 times the minimum recommended leisure time physical activity (LTPA) level. In the present study with additional follow-up, we evaluated the previously unaddressed question of an upper limit of benefit from physical activity. In this pooled analysis, we had a sufficient number of deaths to examine the shape of the mortality dose-response curve for adults performing more than the recommended physical activity minimum (ie, 150 min/wk of moderate- or 75 min/wk of vigorous-intensity activity or some combination expending equivalent energy) and 10 or more times the recommended minimum.

To fill the gap in scientific knowledge of the dose-response relationship between LTPA and mortality, we aimed to quantify (1) the upper threshold for longevity benefit from LTPA and (2) mortality risks associated with very high levels of exercise. In secondary analyses, we evaluated the mortality dose-response for moderate- and vigorous-intensity LTPA separately.

Methods

Study Population

The 6 cohorts in our pooled analysis previously participated in the National Cancer Institute Cohort Consortium analyses of body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared) or physical activity and mortality.[10,11] We used the same inclusion criteria as those previous studies: a prospective design, at least 5 years of follow-up, at least 1000 deaths among non-Hispanic white participants, baseline data collected in 1970 or later, and assessment of height, weight, and smoking status as well as LTPA. Of the 19 studies in the BMI and mortality analysis, 8 had information on time spent in moderate- or vigorous-intensity LTPA and 5 agreed to participate. The Cancer Prevention Study II later joined the consortium, met the criteria, and agreed to participate. We excluded individuals with missing BMI data or reporting a BMI of less than 15 or more than 60. Each participating study was approved by the institutional review board of the host institute.

The included cohorts have been previously described. In short, the National Institutes of Health (NIH)-AARP [formerly the American Association of Retired Persons] Diet and Health Study collected information on diet and health risk factors among members of the AARP.[12] The Cancer Prevention Study II assessed environmental and lifestyle cancer risk factors among US and Puerto Rican individuals.[13] The Campaign Against Cancer and Stroke II investigated cardiovascular and cancer risk factors among Washington County, Maryland, residents.[14] In the US Radiologic Technologists study,[15] radiologic technologists residing in the United States and certified by the American Registry of Radiologic Technologists were recruited for the study of cancer risk factors. The Women's Health Study[16-18] was a randomized clinical trial testing the use of low-dose aspirin and vitamin E for preventing cardiovascular disease and cancer in female health professionals from 1992 to 2004, after which participants were followed observationally. The Women's Lifestyle and Health Study is a population-based cohort study on disease risk among Swedish women sampled from the Uppsala Health Care Region.[19] Informed consent was obtained in written form by respective cohorts.

Exposure Assessment

Physical activity construct validity and intensity levels are presented in eTable 1 in the Supplement. In short, the Cancer Prevention Study II, Campaign Against Cancer and Heart Disease, and Women's Health Study had 7 to 8 line items querying the average weekly time spent performing the following activities over the prior year: walking, jogging/running, swimming, tennis/racquetball, bicycling, aerobics, and dance. The physical activity questionnaires were adapted from the Nurses' Health Study questionnaire, which has shown[20] correlation coefficients ranging from 0.79 to 0.83 compared with recalls and from 0.59 to 0.62 compared with diaries.

The NIH-AARP[12] and Women's Lifestyle and Health Study[21] used physical activity questionnaires that have not formally been validated but have shown expected associations between physical activity and mortality in previous studies, and the US Radiologic Technologists study has shown expected inverse associations with breast cancer.[15] The NIH-AARP[12] study included a single line item for all moderate- or vigorous-intensity LTPAs with categorical responses measured in hours per week. The Women's Lifestyle and Health Study[21] questionnaire included separate line items about hours per day in LTPA, such as walking, horseback riding, or strenuous activities, and the US Radiologic Technologists study[15] had separate line items for hours per week spent walking for exercise and exercising strenuously. For all 6 studies, we calculated energy expended per activity by multiplying the estimated metabolic equivalent (MET) (a multiple of the resting metabolic rate) value[22] by the number of hours per week and summed across activities to estimate overall LTPA energy expenditure in MET hours per week.

We used standardized categories to harmonize data between cohorts as follows: race/ethnicity (black, white, and other), educational level (did not finish high school, finished high school, post–high school training, some college, finished college, and missing), smoking status (never, former, current, and missing), history of cancer (yes, no/missing), history of heart disease (yes, no/missing), alcohol consumption (0, >0 to <15, 15 to <30, and ≥30 g/d), marital status (married, divorced, widowed, unmarried, and missing), and BMI (<18.5, 18.5 to <25.0, 25.0 to <30.0, 30.0 to <35.0, and ≥35.0). We imputed the value for alcohol using the median value because nondrinkers and true missing values were grouped differently between studies. In subsequent analysis, we tested associations using a missing category for alcohol instead of the imputed value and found no change in our physical activity results (all hazard ratios [HRs] were within 0.02 of previous estimates). Questionnaires did not distinguish between *missing* and *no* for history of heart disease and cancer history; thus, individuals were dichotomized into groups of *yes* or *no/missing*. Missing data were less than 5% for all covariates. We performed analyses calculating follow-up time in 2 ways: first, using age at study entry to age at death or end of follow-up and second, calculating time from the baseline questionnaire to the date of death or end of follow-up. Because results did not differ from analyses using age as the time metric or using follow-up time and adjusting for age, in further analyses we used the latter method and adjusted for continuous age. The National Death Index, death certificates, or medical records were used to ascertain the date of death (eTable 1 in the Supplement).

Statistical Analysis

We performed Cox proportional hazards regression stratified by cohort to generate HRs and 95% CIs for LTPA and mortality. Final models were adjusted for age, sex, educational level, smoking status, cancer history, heart disease, alcohol consumption, marital status, and BMI. We created 7 categories for MET hours per week (0, 0.1 to <7.5, 7.5 to <15.0, 15.0 to <22.5, 22.5 to <40.0, 40.0 to <75.0, and ≥75.0). These categories were established to reflect multiples of the federal physical activity recommendations and ranged from 1 to 2 times the recommended minimum (7.5 to <15.0 MET h/wk) to up to 10 or more times the recommended levels (≥75.0 MET h/wk). We further examined intensity in the 5 cohorts with line items for individual activities (Campaign Against Cancer and Heart Disease, Cancer Prevention Study II, US Radiologic Technologists study, Women's Health Study, and Women's Lifestyle and Health Study) by separating moderate-intensity (3.0 to <6.0 METs) and vigorous-intensity (≥6.0 METs) activities and creating mutually adjusted models. In intensity analyses, categories of MET hours per week were adjusted (0, 0.1 to <7.5, 7.5 to <15.0, 15.0 to <30.0, and ≥30.0) owing to a lower range of MET hours per week for each intensity and fewer deaths in the highest categories. We also examined heart disease and cancer-specific mortality. The proportional hazards assumption was tested by creating an interaction term between continuous LTPA and follow-up time and using the Wald test for significance of the interaction term.

To test for statistical significance of interactions, we created interaction terms between continuous LTPA and the exposures of interest and used the Wald test for dichotomous variables and the likelihood ratio test for multilevel variables. We also created separate models by cohort and used random-effects meta-analyses to generate summary risk estimates and the I^2 statistic for heterogeneity. To explore individual random effects, we created Cox proportional hazards regression frailty models. To further test influence by specific cohorts, we performed analyses excluding 1 cohort at a time. We used a restricted cubic spline to explore whether mortality risk increased at the highest LTPA levels.[23] We excluded individuals reporting more than 100.0 MET h/wk to test the influence of outliers and also restricted the data set to those performing more than 15.0 MET h/wk to test the *P* trend for LTPA and mortality at levels only among individuals reporting more than double the recommended minimum. We also stratified by potential effect modifiers of age, sex, educational level, race, BMI, smoking status, heart disease, and previous cancer.

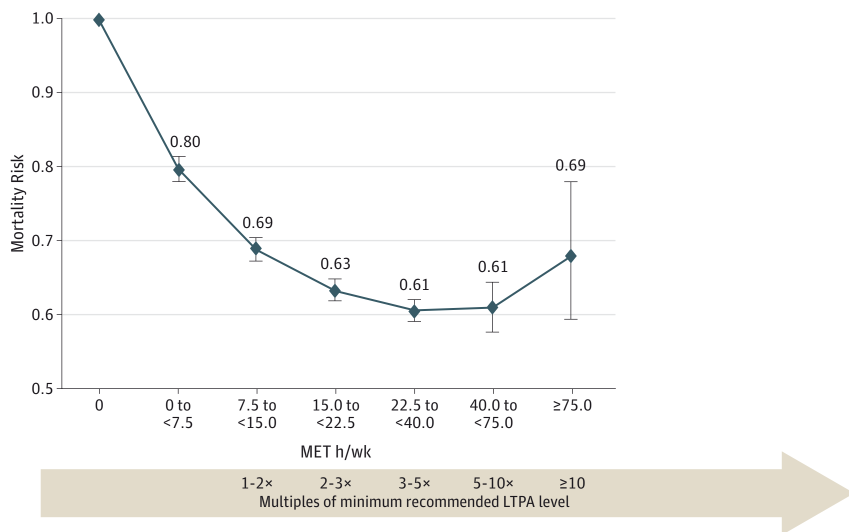
All analyses were performed in SAS, version 9.3 (SAS Institute Inc) other than the random-effects meta-analysis (Stata, version 11; StataCorp). The **Figure** was generated using GraphPad Prism 6 (GraphPad Software, Inc).

Results

Our pooled data set included 661 137 participants (291 485 men and 369 652 women). With a median 14.2 follow-up years (range, 0-15.2 years), we observed 116 686 deaths. Descriptive characteristics of the 6 cohorts are included in eTable 2 in the Supplement. Median age at study entry was 62 years (range, 21-98 years), and the median LTPA was 8.0 MET h/wk (interquartile range, 4-22). Individuals performing the most LTPA tended to be younger, to be never smokers, to have a lower BMI, to be married, and to have fewer comorbidities (**Table 1**).

Compared with no baseline LTPA, any level of activity was associated with a significantly lower risk of mortality (Figure and eTable 3 in the Supplement). Specifically, among individuals performing less than the recommended LTPA minimum (0.1 to <7.5 MET h/wk), we observed a 20% lower risk of mortality (HR, 0.80 [95% CI, 0.78-0.82]). This inverse association grew stronger among those performing 1 to 2 times the recommended minimum (7.5 to <15.0 MET h/wk: HR, 0.69 [95% CI, 0.67-0.70]) or 2 to 3 times the minimum (15.0 to <22.5 MET h/wk: HR, 0.63 [95% CI, 0.62-0.65]) but appeared to reach a threshold of a 39% lower mortality risk among persons performing 3 to 10 times the recommended minimum (22.5 to <40.0 MET h/wk: HR. 0.61 [95% CI, 0.59-0.62]; 40.0 to <75.0 MET h/wk: HR. 0.61 [95% CI, 0.58-0.64]). We observed a still reduced, but not as strong, 31% lower mortality risk for those performing 10 or more times the recommended minimum LTPA

Figure. Hazard Ratios (HRs) and 95% CIs for Leisure Time Moderate- to Vigorous-Intensity Physical Activity and Mortality



The dose-response curve and category-specific HR estimates of exercise levels compared with the federally recommended minimum of 7.5 metabolic equivalent (MET) hours per week. Models were stratified by cohort and use age as the underlying time scale. The model was adjusted for sex, smoking (never, former, current, or missing), alcohol (none, <15 g/day, 15 to <30 g/day, or ≥30 g/day), educational level (dropout, high school, post–high school training, some college, college graduate, postcollege, or missing), marital status (married, divorced, widowed, single, or missing), history of cancer, history of heart disease, and body mass index (calculated as weight in kilograms divided by height in meters squared) (<18.5, 18.5 to <25.0, 25.0 to <30.0, 30.0 to <35.0, or ≥35.0).The dotted line between categories illustrates an assumed dose-response curve rather than individual data points. Crude and adjusted risk estimates are presented in eTable 3 in the Supplement.

levels (≥75.0 MET h/wk: HR, 0.69 [95% CI, 0.59-0.78]) after adjustment for other known mortality risk factors (comparing 40.0 to <75.0 vs ≥75.0 MET h/wk; *P* = .13).

To test for heterogeneity, we modeled the association between LTPA and mortality by random-effects meta-analysis. We found similar patterns of association, suggesting a relative threshold for benefit among those meeting or exceeding the LTPA recommended minimum (eTable 4 in the Supplement). Heterogeneity between cohorts was statistically significant for all LTPA categories (*P* < .05). We also created separate models for each cohort to examine cohort-specific risk estimates. The direction of association was inverse for all cohorts and did not show evidence of additional mortality benefit at the highest LTPA levels (eTable 4 in the Supplement). Excluding cohorts from analysis one at a time to further test for influence showed results consistent with the main findings (eTable 5 in the Supplement).

We also created separate moderate- vs vigorous-intensity categories ranging from 0 to more than 30.0 MET h/wk and ran models mutually adjusted for both LTPA intensities. In this subset analysis of 348 725 individuals, although we observed some mortality benefit with low levels of moderate-intensity activity (0.1 to <7.5 MET h/wk: HR, 0.80 [95% CI, 0.78-0.83]), the maximum observed mortality benefit accrued with meeting the recommended minimum of 7.5 MET h/wk (7.5 to <15.0 MET h/wk: HR, 0.73 [95% CI, 0.71-0.75]); higher moderate-intensity activity levels did not yield additional benefit (≥30.0 MET h/wk: HR, 0.72 [95% CI, 0.68-0.76]) (**Table 2**). For vigorous-intensity LTPA, any level of activity, even below the recommended minimum, was associated with an approximate 20% lower mortality risk. Associations were similar between men and women.

In analyses of LTPA and cause-specific mortality, we found a monotonic inverse trend for cancer deaths, with a 31% lower cancer mortality risk (HR, 0.69 [95% CI, 0.55-0.87]) among individuals performing 10 or more times the recommended minimum (≥75.0 MET h/wk) compared with those reporting no activity (**Table 3**). For CVD deaths, however, the upper threshold was observed among those reporting 3 to 5 times the recommended minimum (22.5 to <40.0 MET h/wk: HR, 0.58 [95% CI, 0.56-0.61]). There was no additional benefit for those reporting 5 to less than 10 or 10 or more times the recommended minimum (HR, 0.61 [95% CI, 0.55-0.67] and HR, 0.71 [95% CI, 0.56-0.91], respectively). There was no statistically significant difference between these 2 highest physical activity categories (*P* = .23).

In stratified analyses, we found that the upper limit of mortality benefit appeared to be consistent across covariate strata, although we observed some variation in point estimates where number of deaths was low (**Table 4**). Although we found statistically significant differences by age, sex, educational level, BMI, smoking status, and heart disease possibly attributable to the large sample sizes (*P* < .001), examination of point estimates did not show results contradictory to our main findings. When we tested differences between the 2 highest physical activity categories that appeared to diverge (eg, men reporting 40.0 to <75.0 vs ≥75.0 MET h/wk), the 2 categories were not significantly different (*P* = .07).

Table 1. Descriptive Characteristics of 661 137 Study Participants

Characteristic	No. of Participants	LTPA Level, MET h/wk, No. (%)[a]						
		0	0.1 to <7.5	7.5 to <15.0	15.0 to <22.5	22.5 to <40.0	40.0 to <75.0	≥75.0
Participants	661 137	52 848 (8.0)	172 203 (26.1)	170 563 (25.8)	118 169 (17.9)	124 446 (18.8)	18 831 (2.9)	4077 (0.6)
Deaths	116 686	11 523 (9.9)	33 511 (28.7)	28 957 (24.8)	19 979 (17.1)	21 114 (18.1)	1390 (1.2)	212 (0.2)
Age, y								
<60	276 418	25 554 (50)	75 671 (45)	71 031 (43)	45 451 (39)	44 721 (36)	11 261 (65)	2729 (76)
60 to <70	307 556	19 694 (39)	75 954 (45)	79 553 (48)	60 978 (53)	66 113 (54)	4631 (27)	633 (18)
≥70	61 356	5924 (12)	16 838 (10)	16 022 (10)	9190 (8)	11 838 (10)	1332 (8)	212 (6)
Sex								
Men	291 485	19 867 (38)	71 564 (42)	74 298 (44)	61 553 (49)	5685 (49)	5685 (30)	1123 (28)
Women	369 652	32 981 (62)	100 639 (58)	96 265 (56)	60 774 (51)	62 893 (51)	13 146 (70)	2954 (72)
Smoking status								
Never	275 388	21 168 (41)	73 112 (43)	72 824 (43)	47 519 (41)	49 729 (41)	8984 (48)	2052 (51)
Former	298 256	21 239 (41)	74 182 (44)	76 979 (46)	56 663 (49)	59 759 (49)	7900 (42)	1534 (38)
Current	74 977	9730 (19)	21 866 (13)	17 721 (11)	11 272 (10)	12 101 (10)	1826 (10)	461 (11)
Alcohol intake								
None	179 676	19 935 (38)	52 463 (30)	44 710 (26)	26 271 (22)	30 912 (25)	4415 (23)	970 (24)
1 Drink/d	376 861	26 750 (51)	95 829 (56)	99 981 (59)	69 817 (59)	69 498 (56)	12 298 (65)	2688 (66)
2 Drinks/d	54 063	2542 (5)	11 550 (7)	13 745 (8)	12 114 (10)	12 609 (10)	1273 (7)	230 (6)
Educational level								
College graduate	250 564	14 324 (29)	61 415 (37)	67 527 (41)	50 433 (44)	48 175 (40)	7257 (44)	1433 (43)
Marital status								
Married	474 338	38 407 (77)	123 151 (77)	123 954 (77)	83 143 (74)	89 568 (76)	13 176 (81)	2939 (76)
BMI								
<25.0	277 193	18 841 (36)	63 975 (38)	70 716 (42)	51 582 (44)	58 629 (48)	11 043 (60)	2407 (60)
25.0 to <30.0	256 713	19 133 (37)	66 709 (39)	67 480 (40)	47 325 (40)	49 015 (40)	5867 (32)	1184 (30)
≥30.0	119 988	14 046 (27)	39 736 (23)	30 758 (18)	18 057 (15)	15 367 (12)	1632 (9)	392 (10)
Race								
White	627 393	49 915 (96)	162 946 (96)	162 468 (97)	111 831 (96)	118 415 (97)	18 042 (96)	3776 (93)
Comorbidities								
Heart disease	61 158	4380 (8)	15 450 (9)	15 462 (9)	12 512 (11)	12 445 (10)	777 (4)	132 (3)
Cancer	46 358	4381 (8)	13 140 (8)	12 214 (7)	7099 (6)	8109 (7)	1198 (6)	217 (5)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); LTPA, leisure time physical activity; MET, metabolic equivalent.

[a] Frequencies are column percentage.

Excluding individuals reporting more than 100.0 MET h/wk from analyses to assess the influence of outliers did not change our conclusions. We also performed an analysis limited to those reporting 15.0 or more MET h/wk and used a continuous term to see whether the risk trend existed beyond the 15.0 MET h/wk threshold. In that analysis, we found that the *P* value trend for continuous physical activity was highly significant ($P < .001$). A cubic spline showed that the association between physical activity and mortality was not linear, but the patterns of risk observed in the splines paralleled risk estimates in the categorical analyses (eFigure in the Supplement).

Discussion

Our findings on the shape of the physical activity–mortality dose-response curve offer 3 unique and important contributions to inform health care professionals and future guidelines: (1) the currently recommended amounts of LTPA provide most of the longevity benefits, (2) the longevity benefit threshold appears to be approximately 3 to 5 times the recommended physical activity minimum, and (3) there does not appear to be an elevated mortality risk with LTPA levels as high as 10 or more times the recommended minimum. Examples of activities to achieve these categories are specified in eTable 6 in the Supplement. In our study population, both moderate- and vigorous-intensity activities were associated with longevity benefit.

Two recent studies[10,24] quantified the minimal amounts of LTPA for longevity benefit but did not estimate mortality risk beyond approximately 3 times the recommended minimum and therefore were unable to quantify the upper threshold of benefit. A Taiwanese study[24] found that, compared with individuals who were inactive, those who were meeting US federal physical activity recommendations had a 26% lower mortality risk (HR, 0.74 [95% CI, 0.70-0.77]). The previous publication[10] on these pooled cohorts with a shorter fol-

Table 2. LTPA and Mortality by Activity Intensity in 108 902 Men and 239 823 Women[a]

Intensity of Activity	LTPA Level, MET h/wk: 0	0.1 to <7.5	7.5 to <15.0	15.0 to <30.0	≥30.0
Moderate					
Participants, No. (%)	53 376 (15.3)	122 522 (35.1)	100 687 (28.9)	59 304 (17.0)	12 836 (3.7)
Deaths, No. (%)	8359 (18.2)	16 203 (35.2)	11 667 (25.4)	8054 (17.5)	1696 (3.7)
Age-adjusted HR (95% CI)[b]	1.00	0.70 (0.68-0.72)	0.62 (0.60-0.64)	0.63 (0.61-0.65)	0.63 (0.60-0.67)
Fully adjusted HR (95% CI)[c]	1.00	0.80 (0.78-0.83)	0.73 (0.71-0.75)	0.71 (0.68-0.73)	0.72 (0.68-0.76)
Men	1.00	0.84 (0.81-0.87)	0.77 (0.74-0.80)	0.73 (0.71-0.76)	0.74 (0.69-0.79)
Women	1.00	0.76 (0.73-0.80)	0.68 (0.65-0.71)	0.67 (0.63-0.70)	0.69 (0.64-0.75)
Vigorous					
Participants, No. (%)	243 598 (69.9)	55 160 (15.8)	23 792 (6.8)	10 816 (3.1)	15 359 (4.4)
Deaths, No. (%)	40 229 (87.5)	3525 (7.7)	638 (1.4)	892 (1.9)	695 (1.5)
Age-adjusted HR (95% CI)[b]	1.00	0.75 (0.73-0.78)	0.72 (0.67-0.78)	0.71 (0.67-0.76)	0.72 (0.67-0.78)
Fully adjusted HR (95% CI)[c]	1.00	0.80 (0.78-0.83)	0.77 (0.71-0.84)	0.78 (0.73-0.83)	0.79 (0.73-0.85)
Men	1.00	0.78 (0.75-0.82)	0.69 (0.61-0.78)	0.72 (0.66-0.79)	0.77 (0.70-0.85)
Women	1.00	0.83 (0.79-0.88)	0.85 (0.77-0.94)	0.86 (0.78-0.94)	0.81 (0.72-0.91)

Abbreviations: HR, hazard ratio; LTPA, leisure time physical activity; MET, metabolic equivalent.

[a] The AARP (formerly the American Association of Retired Persons) was not included in this analysis because the questionnaire did not distinguish between moderate- and vigorous-intensity activities.

[b] Models were stratified by cohort, adjusted for age, and mutually adjusted for both moderate- and vigorous-intensity activities.

[c] Models were additionally adjusted for sex (in nonstratified models), smoking (never, former, current, or missing), alcohol use (none, <15 g/d, 15 to <30 g/d, or ≥30 g/d), educational level (less than high school, high school graduate, post–high school training, some college, college graduate, postcollege, or missing), marital status (married, divorced, widowed, single, or missing), history of cancer, history of heart disease, and body mass index (calculated as weight in kilograms divided by height in meters squared) (<18.5, 18.5 to <25.0, 25.0 to <30.0, 30.0 to <35.0, or ≥35.0).

Table 3. LTPA and Cause-Specific Mortality in 661 137 Participants

Characteristic	LTPA Level, MET h/wk: 0	0.1 to <7.5	7.5 to <15.0	15.0 to <22.5	22.5 to <40.0	40.0 to <75.0	≥75.0
Participants, No. (%)	52 848 (8.0)	172 203 (26.1)	170 563 (25.8)	118 169 (17.9)	124 446 (18.8)	18 831 (2.9)	4077 (0.6)
Cancer deaths, No. (%)	3143 (10.7)	8584 (29.3)	7375 (25.2)	4373 (14.9)	5187 (17.7)	557 (1.9)	75 (0.3)
HR (95% CI)[a]	1.00	0.87 (0.83-0.90)	0.79 (0.75-0.82)	0.75 (0.72-0.79)	0.74 (0.71-0.77)	0.72 (0.66-0.79)	0.69 (0.55-0.87)
CVD deaths, No. (%)	3238 (12.8)	7952 (31.4)	6316 (24.9)	3293 (13.0)	4044 (15.9)	457 (1.8)	69 (0.3)
HR (95% CI)[a]	1.00	0.80 (0.77-0.84)	0.67 (0.65-0.70)	0.59 (0.57-0.63)	0.58 (0.56-0.61)	0.61 (0.55-0.67)	0.71 (0.56-0.91)

Abbreviations: HR, hazard ratio; LTPA, leisure time physical activity; MET, metabolic equivalent.

[a] Multivariable-adjusted models with stratification by cohort were adjusted for age, sex, smoking (never, former, current, or missing), alcohol use (none, <15 g/d, 15 to <30 g/d, or ≥30 g/d), educational level (less than high school, high school graduate, post–high school training, some college, college graduate, postcollege, or missing), marital status (married, divorced, widowed, single, or missing), history of cancer, history of heart disease, and body mass index (calculated as weight in kilograms divided by height in meters squared) (<18.5, 18.5 to <25.0, 25.0 to <30.0, 30.0 to <35.0, or ≥35).

low-up showed major longevity benefits with LTPA of 3 or more times the recommended minimum compared with no physical activity (HR, 0.59 [95% CI, 0.57-0.61]) but did not detail mortality benefits for physical activity of 22.5 or more MET h/wk or estimate separate risk estimates by activity intensity. The present study confirms and extends previous research by quantifying the upper threshold of benefit, which in turn demonstrates that adults who perform LTPA at recommended levels achieve most of the mortality benefits.

Previous studies on associations between intensity-specific LTPA (ie, moderate vs vigorous) and mortality have shown equivocal results. A study of LTPA and mortality in middle-aged British men supported an association between vigorous-intensity but not moderate-intensity physical activity and all-cause and CVD mortality.[25] Other studies have shown reductions in the mortality rate from moderate activities but greater reductions associated with vigorous-intensity activities.[26] Few studies examining MET expenditures and types of high-intensity activities have been reported among older adults; given the low prevalence of older individuals performing very high levels of activity or high intensity on a population level, previous epidemiologic studies are not available for comparison. However, comprehensive reviews[27,28] of the literature on physical activity and mortality report that overall volume of physical activity is associated with lower mortality risk but report mixed findings on the relative contributions of moderate- vs vigorous-intensity activities. Other studies also support associations between moderate-

Table 4. LTPA and Mortality

Characteristic	HR (95% CI)[a] LTPA, MET h/wk: 0	0.1 to <7.5	7.5 to <15.0	15.0 to <22.5	22.5 to <40.0	40.0 to <75.0	≥75.0	P Value for Interaction[b]
Age, y								
<50	1.00	0.73 (0.61-0.87)	0.75 (0.62-0.90)	0.81 (0.65-1.01)	0.70 (0.56-0.89)	0.80 (0.61-1.03)	0.72 (0.47-1.11)	<.001
50 to <60	1.00	0.78 (0.74-0.83)	0.67 (0.64-0.71)	0.66 (0.62-0.70)	0.65 (0.61-0.69)	0.63 (0.54-0.72)	0.60 (0.43-0.84)	
60 to <70	1.00	0.81 (0.78-0.83)	0.70 (0.68-0.72)	0.63 (0.61-0.65)	0.59 (0.57-0.61)	0.61 (0.56-0.66)	0.70 (0.57-0.86)	
≥70	1.00	0.77 (0.74-0.81)	0.65 (0.62-0.68)	0.62 (0.59-0.65)	0.60 (0.57-0.62)	0.54 (0.49-0.60)	0.67 (0.52-0.85)	
Sex								
Male	1.00	0.82 (0.80-0.85)	0.71 (0.69-0.73)	0.63 (0.61-0.65)	0.61 (0.59-0.63)	0.62 (0.58-0.67)	0.74 (0.62-0.89)	.002
Female	1.00	0.77 (0.74-0.79)	0.67 (0.64-0.69)	0.64 (0.61-0.66)	0.60 (0.57-0.62)	0.59 (0.54-0.65)	0.61 (0.49-0.75)	
Educational level								
≤High school	1.00	0.78 (0.76-0.81)	0.65 (0.63-0.68)	0.61 (0.59-0.64)	0.58 (0.56-0.61)	0.58 (0.52-0.66)	0.58 (0.40-0.85)	.09
Some college or post-high school training	1.00	0.74 (0.71-0.77)	0.63 (0.61-0.65)	0.56 (0.54-0.59)	0.53 (0.51-0.55)	0.53 (0.48-0.59)	0.56 (0.43-0.71)	
College graduate	1.00	0.75 (0.72-0.79)	0.63 (0.61-0.66)	0.57 (0.54-0.59)	0.56 (0.53-0.58)	0.55 (0.50-0.60)	0.68 (0.55-0.83)	
Race								
Non-Hispanic white	1.00	0.79 (0.78-0.81)	0.68 (0.67-0.70)	0.62 (0.61-0.64)	0.60 (0.59-0.61)	0.61 (0.57-0.64)	0.68 (0.59-0.78)	.24
African American	1.00	0.80 (0.71-0.91)	0.66 (0.58-0.76)	0.70 (0.61-0.81)	0.60 (0.51-0.69)	0.57 (0.38-0.85)	0.80 (0.42-1.52)	
BMI								
18.5 to <25.0	1.00	0.78 (0.75-0.81)	0.66 (0.63-0.68)	0.59 (0.57-0.62)	0.56 (0.54-0.58)	0.54 (0.50-0.59)	0.63 (0.52-0.76)	<.001
25.0 to <30.0	1.00	0.79 (0.76-0.82)	0.70 (0.67-0.72)	0.64 (0.61-0.66)	0.62 (0.59-0.64)	0.67 (0.62-0.74)	0.76 (0.60-0.95)	
≥30.0	1.00	0.83 (0.79-0.86)	0.72 (0.68-0.75)	0.67 (0.64-0.71)	0.66 (0.63-0.69)	0.72 (0.61-0.85)	0.62 (0.39-1.01)	
Smoking status								
Never	1.00	0.80 (0.76-0.83)	0.69 (0.66-0.72)	0.66 (0.63-0.69)	0.64 (0.61-0.67)	0.67 (0.61-0.74)	0.67 (0.53-0.86)	<.001
Former	1.00	0.77 (0.75-0.79)	0.65 (0.63-0.67)	0.59 (0.57-0.61)	0.56 (0.54-0.58)	0.55 (0.51-0.59)	0.61 (0.51-0.74)	
Current	1.00	0.85 (0.81-0.89)	0.77 (0.73-0.81)	0.72 (0.68-0.76)	0.69 (0.65-0.72)	0.72 (0.61-0.84)	0.83 (0.59-1.18)	
Heart disease								
No	1.00	0.80 (0.78-0.82)	0.70 (0.68-0.72)	0.65 (0.63-0.66)	0.62 (0.60-0.64)	0.62 (0.58-0.66)	0.69 (0.60-0.80)	<.001
Yes	1.00	0.79 (0.75-0.83)	0.65 (0.62-0.68)	0.58 (0.55-0.61)	0.55 (0.52-0.58)	0.56 (0.48-0.65)	0.66 (0.45-0.98)	
Previous cancer								
No	1.00	0.80 (0.78-0.82)	0.69 (0.68-0.71)	0.64 (0.62-0.65)	0.61 (0.59-0.63)	0.63 (0.59-0.67)	0.70 (0.61-0.82)	.22
Yes	1.00	0.79 (0.75-0.83)	0.66 (0.63-0.70)	0.61 (0.57-0.65)	0.58 (0.54-0.61)	0.54 (0.47-0.62)	0.59 (0.41-0.84)	

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); HR, hazard ratio; LTPA, leisure time physical activity; MET, metabolic equivalent.

[a] Multivariable models with stratification by cohort were adjusted for age, sex, smoking (never, former, current, or missing), alcohol use (none, <15 g/d, 15 to <30 g/d, or ≥30 g/d), educational level (less than high school, high school graduate, post–high school training, some college, college graduate, postcollege, or missing), marital status (married, divorced, widowed, single, or missing), history of cancer, history of heart disease, and body mass index (calculated as weight in kilograms divided by height in meters squared) (<18.5, 18.5 to <25.0, 25.0 to <30.0, 30.0 to <35.0, or ≥35.0). The variable used for stratification was not included in the given model.

[b] Interaction was tested using a continuous LTPA term and the exposure of interest, using a Wald test for dichotomous variables and a likelihood ratio test for multilevel variables.

intensity activities, including walking, and lower risk of coronary heart disease[29-31] or mortality.[24,26] Although more research is needed on physical activity intensity vs dose, our finding that moderate-intensity activities were associated with mortality benefit is consistent with the 2008 Physical Activity Guidelines for Americans.

An analysis in the 2011 Behavioral Risk Factor Surveillance System[32] reported that walking contributed 47.4% of overall aerobic exercise, running/jogging accounted for 13.4%, and conditioning exercises (including stationary biking, stair climbing/stair machine, and active gaming) accounted for 8.5%; sports as a group accounted for 9.2% of activity. Walking for exercise was also the largest contributor to overall MET hours per week in our analysis, which is consistent with the Behavioral Risk Factor Surveillance System findings. Thus, the major activities listed on these questionnaires were prevalent both at the time of data collection and at the time of the 2011 survey.

Possible harms previously associated with high levels of LTPA may be explained by cause of death. The 2008 guideline's evaluation of harms stated that risk of cardiac events was transiently increased during vigorous-intensity physical activity, particularly among inactive individuals, but that, on average, physically active individuals have a lower risk of adverse cardiac events.[4] Prior studies[7,33-38] have suggested cardiac remodeling and higher CVD and mortality risk with extremely high physical activity levels, but these studies were largely performed in athletic populations with a younger median age. Our cohort was older, as the mean age even for those younger than 60 years was 52 years. Although our study is not poised to examine the risk during or immediately after exercise or comorbid cardiac conditions, such as atrial fibrillation, our findings do not support the hypothesis for increased mortality risk at LTPA levels of 10 or more times the federal guidelines. The present findings align with other studies that have shown lower risks of mortality among long-term long-distance runners[39] as well as Tour de France cyclists.[40] Thus, current trends in increasing marathon or triathlon participation should not cause alarm, at least with regard to mortality.

Strengths of our study include the prospective nature of the cohorts, extended follow-up time, and detailed covariate information. We were uniquely positioned to estimate the threshold for longevity benefit from high LTPA levels and potential harms with respect to mortality because, by pooling, we had enough individuals reporting this high level of exercise. Our stratified results further strengthen our finding, indicating that the upper threshold of benefit was consistent in men and women, different age groups, various lifestyle factors, and individuals with and without CVD and cancer. However, the smaller sample size in our highest physical activity category led to wider 95% CIs in this category.

Limitations of our study include the reliance on self-reported physical activity, which was reported at a single time point. We also did not examine non-leisure time activities[41,42] or sedentary time,[43] both of which have shown associations with mortality. In addition, although we attempted to adjust for confounding by history of disease or other known mortality risk factors, unaccounted risk factors may have influenced our observed results. Validation studies were not specifically designed for older adults performing very high levels of physical activity. Still, self-reported activity has indicated construct validity in our cohorts by showing expected associations with mortality and disease-specific outcomes (eTable 1 in the Supplement). The prospective design minimizes recall bias, but measurement error in self-reported LTPA is likely to result in attenuation of the associations observed. Differences in the questionnaires between cohorts, variation in baseline age, relative physical fitness, and length of follow-up may explain some of the heterogeneity we observed between individual study results. However, additional analyses excluding each cohort showed that estimates were not unduly influenced by a single cohort. Our median reported LTPA levels were above mean US values, which may be the result of the higher educational level of our study participants. In addition, MET-hour-per-week intensities were assigned using absolute, compendium-derived values that may not account for interindividual variation. Finally, we cannot exclude the possibility of inflation in upper physical activity categories.

Conclusions

Meeting the recommended guidelines by either moderate- or vigorous-intensity activities was associated with nearly the maximum longevity benefit. We observed this benefit threshold at approximately 3 to 5 times the recommended LTPA minimum and no excess risk at 10 or more times the recommended minimum. These findings are informative for individuals at both ends of the physical activity spectrum: they provide important evidence to inactive individuals by showing that modest amounts of activity provide substantial benefit for postponing mortality while reassuring very active individuals of no exercise-associated increase in mortality risk. These data will be useful to inform future updates on physical activity guidelines regarding an appropriate amount of physical activity to recommend for longevity.

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