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Prevention of heart failure in older adults may require higher levels of physical activity than needed for other cardiovascular events

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Abstract

Background—Little is known if the levels of physical activity required for the prevention of incident heart failure (HF) and other cardiovascular events vary in community-dwelling older adults.

Methods—We studied 5503 Cardiovascular Health Study (CHS) participants, age ≥65 years, free of baseline HF. Weekly metabolic equivalent task-minutes (MET-minutes), estimated using baseline total leisure-time energy expenditure, were used to categorize participants into four physical activity groups: inactive (0 MET-minutes; n=489; reference), low (1–499; n=1458), medium (500–999; n=1086) and high (≥1000; n=2470).

Results—Participants had a mean (±SD) age of 73 (±6) years, 58% were women, and 15% African American. During 13 years of follow-up, centrally-adjudicated incident HF occurred in 26%, 23%, 20%, and 19% of participants with no, low, medium and high physical activity, respectively (trend p <0.001). Compared with inactive older adults, age-sex-race-adjusted hazard ratios (95% confidence intervals) for incident HF associated with low, medium and high physical activity were 0.87 (0.71–1.06; p=0.170), 0.68 (0.54–0.85; p=0.001) and 0.60 (0.49–0.74; p<0.001), respectively (trend p <0.001). Only high physical activity had significant independent association with lower risk of incident HF (HR, 0.79; 95% CI, 0.64–0.97; p=0.026). All levels of

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physical activity had significant independent association with lower risk of incident acute myocardial infarction (AMI), stroke and cardiovascular mortality.

Conclusion—In community-dwelling older adults, high level of physical activity was associated with lower risk of incident HF, but all levels of physical activity were associated with lower risk of incident AMI, stroke, and cardiovascular mortality.

Keywords

Physical activity; MET-minutes; Incident heart failure; Older adults

1. Introduction

Physical activity has been shown to reduce the risk of incident cardiovascular events including incident heart failure (HF) [1–4]. However, the association of physical activity expressed as metabolic equivalent task-minutes (MET-minutes) with incident HF and other cardiovascular events in community-dwelling older adults has not been previously studied. The United States Department of Health and Human Services' 2008 Physical Activity Guidelines for Americans categorized physical activity into three categories based on weekly MET-minutes: 1–499, 500–999, and 1000 and recommended that physical activity at 1–499 MET-minutes per week would provide some health benefits, physical activity at 500–999 MET-minutes per week would provide substantial health benefits, and physical activity at 1000 MET-minutes per week would provide additional health benefits [5]. Therefore, the purpose of the current study is to determine the association of physical activity by weekly MET-minutes categories with incident HF and other cardiovascular events in community-dwelling older adults and to examine if these associations varied by levels of physical activity.

2. Methods

2.1. Data source and study participants

Sponsored by the National Heart, Lung and Blood Institute (NHLBI), the Cardiovascular Health Study (CHS) is an ongoing, prospective, community-based epidemiologic study of cardiovascular disease risk factors in older adults. CHS participants included 5888 community-dwelling older adults, aged 65 years and older, and were recruited from Forsyth County, North Carolina, Sacramento County, California, Washington County, Maryland, and Pittsburgh County, Pennsylvania. The rationale and design of the CHS have been previously reported [6]. Participants were recruited from a random sample of Medicare-eligible older adults in two phases. An initial cohort of 5201 participants was recruited between 1989 and 1990, and a second cohort of 687 African American participants were recruited between 1992 and 1993 [6]. The current analysis is based on a public-use copy of the CHS data. Of the 5888 CHS participants, 93 did not consent to be included in the de-identified public-use data. Of the remaining 5795 participants, 20 without data on baseline physical activity (kilocalories of energy expended per week in leisure-time) and 272 with baseline prevalent HF were excluded and the final cohort was comprised of 5503 CHS participants.

2.2. Physical activity and other baseline characteristics

Baseline leisure-time physical activity was assessed using a modified Minnesota Leisure-Time Activities questionnaire, which evaluated frequency and duration of 15 different activities during a 2 week period and was used to estimate kilocalories of energy expended per week [7]. MET-minutes were calculated by following formula, total kilocalories per week = total MET-minutes per week \times 0.0175 \times body weight in kilogram. Based on the MET-minutes cutoffs used in the 2008 Physical Activity Guidelines for Americans, we categorized participants into four physical activity groups: inactive (0; n=489), low (1–499; n=1458), medium (500–999; n=1086), and high (\geq 1000; n=2470) [5]. Data on other characteristics (Table 1) were collected at baseline. Missing values for covariates were imputed based on values predicted by age, sex and race.

2.3. Incident heart failure and other cardiovascular events

The primary outcome for this study was incident HF during 13 years of follow-up. Incident HF was centrally-adjudicated by the CHS Events Committee [8–15]. The process began with self-reports of physician-diagnosed HF, which was then confirmed by review of medical records for symptoms, signs, medications, and other evidence of HF. The CHS criteria for HF diagnosis have been shown to be more stringent than those used in the Framingham Heart Study [16]. Secondary outcomes included incident acute myocardial infarction (AMI), angina pectoris, stroke, all-cause mortality and cause-specific mortality.

2.4. Statistical analysis

For descriptive analyses, we used Pearson's Chi-square test for categorical variables and ANOVA analysis for continuous variables. Kaplan Meier survival analysis was used to determine the association of physical activity with incident HF during 13 years of follow-up. Hazard ratios (HR) and 95% confidence intervals (CI) for centrally-adjudicated incident HF and other secondary outcomes were estimated using Cox proportional hazard models adjusting for all variables in Table 1. Trend tests were conducted using median values for the four MET-minutes categories. In addition, we also separately examined the effect of physical activity using kilocalories of energy expended per week in leisure-time [17]. All statistical tests were two-sided, and tests with p-value $<$ 0.05 were considered significant. SPSS for Windows (Version 20) was used for data analysis.

3. Results

3.1. Baseline characteristics

Participants (n=5503) had a mean (\pm SD) age of 73 (\pm 6) years, 58% were women, and 15% were African American. Participants with higher levels of prevalent physical activity were more likely to be younger, male, Caucasians, and have higher levels of education and income (Table 1). They were also more likely to have lower prevalence of cardiovascular risk factors such as hypertension, diabetes, coronary artery disease, AMI, stroke, left ventricular hypertrophy, and have lower mean blood pressure, serum cholesterol, serum creatinine and serum C-reactive protein (Table 1).

3.2. Association of baseline physical activity with incident heart failure

During 13 years of follow-up, centrally-adjudicated incident HF occurred in 26%, 23%, 20%, and 19% of participants with no, low, medium and high physical activity, respectively, with corresponding HRs of 1.00 (reference), 0.79 (95% CI, 0.64–0.97; $p=0.022$), 0.61 (95% CI, 0.49–0.75; $p<0.001$) and 0.53 (95% CI, 0.44–0.65; $p<0.001$; Table 2 and Figure 1). When adjusted for age, sex, and race, only medium (HR, 0.68; 95% CI, 0.54–0.85; $p=0.001$) and high (HR, 0.60; 95% CI, 0.49–0.74; $p<0.001$) levels of physical activity were associated with reduced risk of incident HF (Table 2). After additional adjustment for other risk factors, only high level physical activity was associated with a significant independent reduction in the risk of incident HF (HR, 0.79; 95% CI, 0.64–0.97; $p=0.026$; Table 2). In all models, there were significant dose-response relationships between levels of physical activity and risk of incident HF (Table 2).

3.3. Association of baseline physical activity with other incident cardiovascular events

Compared with no physical activity, all levels of prevalent physical activity were associated with unadjusted and age-sex-race-adjusted reduced risk of incident angina pectoris, AMI and stroke (Table 3). In addition, all levels of physical activity had significant multivariable-adjusted independent associations with reduced risk of AMI and stroke (Table 3).

3.4. Association of baseline physical activity with mortality

Compared with no physical activity, all levels of physical activity were associated with unadjusted and age-sex-race-adjusted lower risk all-cause and cardiovascular mortality (Table 4). All levels of physical activity also had significant multivariable-adjusted associations with lower risk of cardiovascular mortality (Table 4). In all models, there were significant dose-response relationship between levels of physical activity and risk of total and cardiovascular mortality (Table 4).

3.5. Association of baseline physical activity (Kcal/week) with outcomes

When we categorized participants into four physical activity groups using Kcal/week cutoffs: inactive (0; $n=489$), low (1–499; $n=1165$), medium (500–999; $n=981$), and high (> 1000; $n=2868$), similar associations with outcomes were observed.

4. Discussion

Findings from the current study demonstrate that among community-dwelling older adults, all levels of physical activity had significant independent associations with lower risk of incident AMI, stroke, and cardiovascular mortality. However, only high level of physical activity was associated with significant independent lower risk of incident HF and non-cardiovascular mortality. These findings suggest that although low physical activity may reduce the risk of AMI, a major HF risk factor, to reduce the risk of HF, high level of physical activity may be required.

The modest attenuation of the unadjusted associations of physical activity with incident HF and other outcomes after adjustment for age, sex and race is likely due to younger age of those with higher physical activity. Further attenuation of these associations after

multivariable adjustment suggests confounding by other baseline characteristics. Although some of the baseline characteristics such as arthritis, chronic obstructive pulmonary disease and stroke may have affected baseline physical activity, HF risk factors such as hypertension, coronary artery disease, and diabetes may have a bi-directional association with physical activity. Baseline physical activity in CHS was ascertained by that performed during two weeks prior to study baseline. However, if the onset of physical activity was long before baseline, then it may have affected some baseline HF risk factors (mediators), and in that case, an adjustment of these potential mediators may result in underestimation of true associations [18, 19]. Therefore, the age-sex-race-adjusted associations are likely closer to the true associations, which were likely be underestimated by multivariable adjustments of baseline cardiovascular risk factors or mediators that may have been affected by prior physical activity [19].

Findings from the current study suggest that older adults beginning low (1–499 MET-minutes) level of physical activity at or after age 65 years may be able to significantly reduce their risk of incident AMI, stroke and cardiovascular mortality. Although there seems to be no additional reduction in the risk of incident AMI and stroke with higher levels of physical activity, the risk for cardiovascular mortality seems to reduce further with higher levels of physical activity. Additionally, high level of physical activity was also associated with the lower risk of non-cardiovascular death. Finally, high level of physical activity (> 1000 MET-minutes; which is equivalent to greater than 300 minutes (5 hours) of moderate-intensity activity or 150 minutes (2.5 hours) of vigorous-intensity physical activity per week) also seemed to reduce the risk of incident HF. Findings from a recent mechanistic study based on CHS suggest that the cardiovascular benefit of physical activity may be mediated by prevention of neurohormonal activation and cardiac injury [4].

The cardiovascular benefits of physical activity in general have been well described [7, 20, 21]. Several previous studies reported the associations between physical activity and reduction in the risk of incident HF [1–4, 22, 23]. However, to the best of our knowledge, this is the first study of the association of baseline physical activity as quantified by MET-minutes per week with HF and other cardiovascular events in community-dwelling older adults. MET is the ratio of the rate of energy expended during an activity to the rate of energy expended at rest [5]. MET-minute is a useful unit for describing the energy expenditure of a specific physical activity and to compare total amount of physical activity across various persons and types of activities. According to the U.S. Department of Health and Human Services 2008 Physical Activity Guidelines for Americans, medium level of physical activity (500 to 1,000 MET-minutes per week) can be accomplished by 150–300 minutes of moderate-intensity physical activity per week, 75–150 minutes of vigorous-intensity physical activity per week, or an equivalent combination of moderate and vigorous-intensity physical activity [5].

Limitations

Our study has several limitations. Despite attempts to adjust for confounding risk factors using multivariate modeling, residual bias and bias due to unmeasured confounders are possible. Further, we were not able to account for the duration and severity of many risk

factors in the study population both prior to baseline and during follow-up. Although the Minnesota Leisure Time Physical Activity questionnaire has been well validated with direct measures of physical activity, it may not have adequately captured subject's level of physical activity over the duration of follow-up in the older population. In addition, the questionnaire is self-reported and may over- or under-estimate physical activity. Finally, we had no data on left ventricular ejection fraction for those with incident HF, which limited our ability to study whether level of physical activity may have any differential effect on incident systolic versus diastolic HF.

In conclusion, in community-dwelling older adults, all levels of physical activity were associated with lower risk of incident AMI, stroke, and cardiovascular mortality. However, high level of physical activity was also associated with additional health benefit of lower risk of incident HF and non-cardiovascular mortality.

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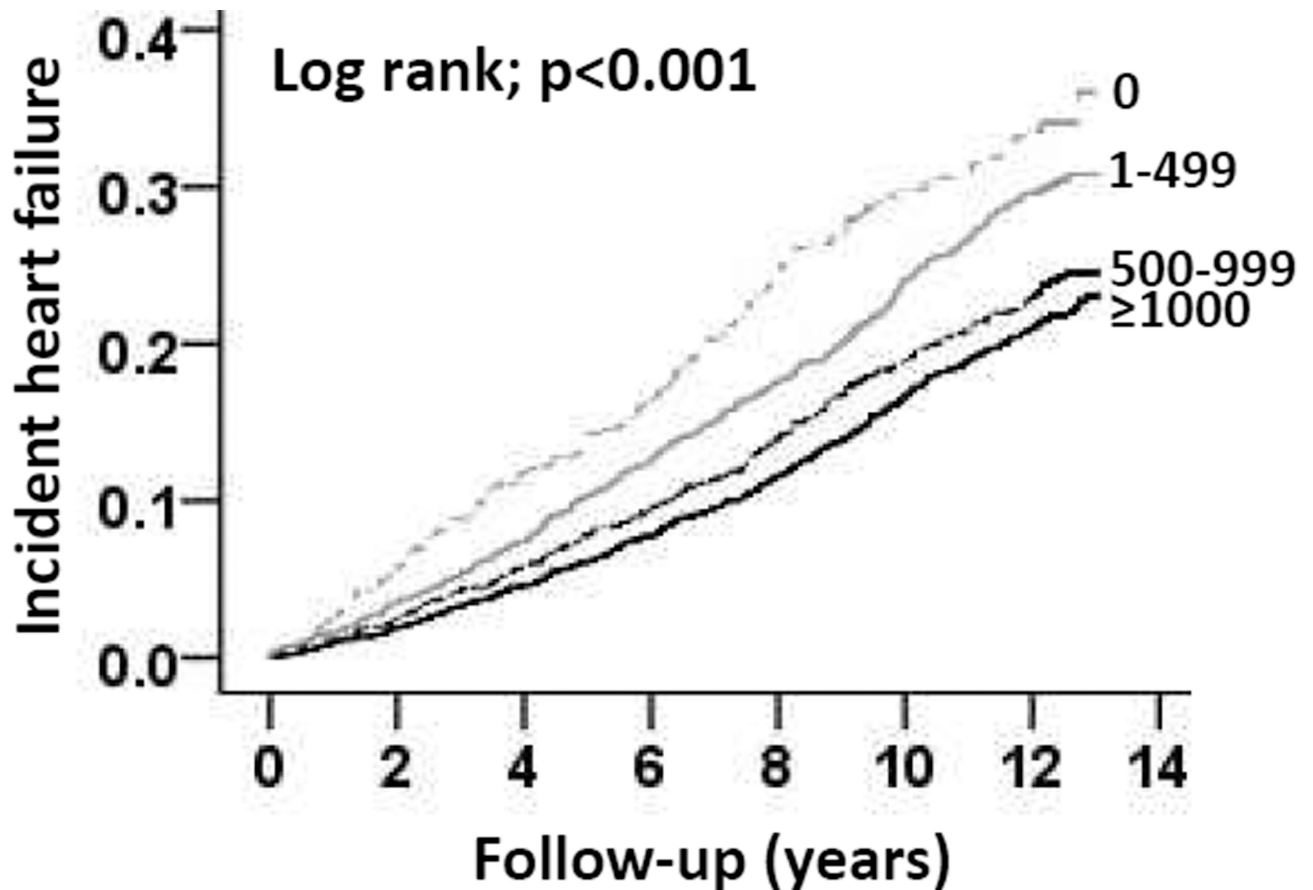
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The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [24].

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Number at risk by MET-minutes per week

0	489	434	370	313	257	182	148
1-499	1458	1351	1225	1068	918	615	511
500-999	1086	1035	954	863	745	567	490
≥ 1000	2470	2382	2237	2054	1851	1496	1290

Figure 1.

Kaplan-Meier plot displaying unadjusted association of physical activity levels by metabolic equivalent task-minutes (MET-minutes) per week categories and incident heart failure in the Cardiovascular Health Study (CHS)

Table 1

Baseline characteristics by physical activity categories

Mean (\pm SD) or n (%)	Physical Activity in MET-minutes/week				P value for linear trend
	0 (n=489)	1-499 (n=1458)	500-999 (n=1086)	1000 (n=2470)	
Age, years	75 (\pm 6)	74 (\pm 6)	73 (\pm 5)	73 (\pm 5)	<0.001
Female	316 (65%)	877 (60%)	612 (56%)	1375 (56%)	<0.001
African American	103 (21%)	358 (25%)	154 (14%)	225 (9%)	<0.001
Education higher than high school	186 (38%)	577 (40%)	475 (44%)	1130 (46%)	<0.001
Income >25K	157 (32%)	477 (33%)	401 (37%)	1012 (41%)	<0.001
Alcohol, drinks per week	2.0 (\pm 6.5)	2.3 (\pm 6.6)	2.6 (\pm 6.6)	2.6 (\pm 6.2)	0.134
Smoke, pack-years	19 (\pm 31)	18 (\pm 26)	18 (\pm 27)	17 (\pm 26)	0.277
Never eat chicken skin	325 (67%)	942 (65%)	733 (68%)	1799 (73%)	<0.001
Body mass index, kg/m ²	27 (\pm 4)	28 (\pm 4)	27 (\pm 4)	26 (\pm 4)	<0.001
Systolic blood pressure, mmHg	140 (\pm 23)	138 (\pm 22)	136 (\pm 21)	135 (\pm 21)	<0.001
Diastolic blood pressure, mmHg	72 (\pm 12)	72 (\pm 11)	71 (\pm 11)	70 (\pm 11)	<0.001
Medical problems					
Coronary heart diseases	111 (23%)	272 (19%)	183 (17%)	393 (16%)	<0.001
Acute myocardial infarction	52 (11%)	122 (8%)	84 (8%)	184 (7%)	0.032
Angina pectoris	96 (20%)	231 (16%)	147 (14%)	321 (13%)	<0.001
Hypertension	326 (67%)	923 (63%)	636 (59%)	1330 (54%)	<0.001
Diabetes mellitus	106 (22%)	272 (19%)	165 (15%)	315 (13%)	<0.001
Stroke	42 (9%)	65 (4%)	35 (3%)	71 (3%)	<0.001
Atrial fibrillation	16 (3%)	36 (2%)	17 (2%)	46 (2%)	0.038
Left ventricular hypertrophy by electrocardiogram	37 (8%)	69 (5%)	42 (4%)	91 (4%)	0.001
Left ventricular systolic dysfunction by echocardiogram	44 (9%)	111 (8%)	90 (8%)	165 (7%)	0.070
Arthritis	306 (63%)	773 (53%)	548 (51%)	1228 (50%)	<0.001
Chronic obstructive pulmonary disease	81 (17%)	200 (14%)	140 (13%)	265 (11%)	<0.001
Cancer	67 (14%)	230 (16%)	161 (15%)	335 (14%)	0.208
Geriatric problems					
Activity of daily living	0.39 (\pm 0.9)	0.15 (\pm 0.5)	0.08 (\pm 0.4)	0.06 (\pm 0.3)	<0.001
Instrumental activity of daily living	0.86 (\pm 1.2)	0.43 (\pm 0.8)	0.30 (\pm 0.6)	0.18 (\pm 0.5)	<0.001

Mean (\pm SD) or n (%)	Physical Activity in MET-minutes/week				P value for linear trend
	0 (n=489)	1-499 (n=1458)	500-999 (n=1086)	1000 (n=2470)	
Blocks walked last week	13 (\pm 30)	20 (\pm 32)	38 (\pm 46)	56 (\pm 66)	<0.001
Time to walk 15 ft	6.9 (\pm 3.1)	6.1 (\pm 2.4)	5.7 (\pm 1.8)	5.4 (\pm 2.0)	<0.001
Mini mental state examination score	26.8 (\pm 3.4)	27.3 (\pm 3.0)	27.8 (\pm 2.4)	27.8 (\pm 2.4)	<0.001
Depression score	6.0 (\pm 5.3)	5.2 (\pm 4.7)	4.5 (\pm 4.3)	4.1 (\pm 4.2)	<0.001
Loss of balance	150 (31%)	377 (26%)	237 (22%)	502 (20%)	<0.001
Frequent fall	35 (7%)	54 (4%)	34 (3%)	57 (2%)	<0.001
Orthostatic dizziness	149 (31%)	317 (22%)	235 (22%)	425 (17%)	<0.001
Laboratory measures					
Serum cholesterol, mg/dL	219 (\pm 42)	211 (\pm 40)	211 (\pm 38)	212 (\pm 38)	0.001
Serum triglyceride, mg/dL	152.7 (\pm 96.4)	141.3 (\pm 70.8)	142.0 (\pm 82.5)	134.7 (\pm 72.8)	<0.001
Serum creatinine, mg/dL	1.01 (\pm 0.46)	0.98 (\pm 0.45)	0.95 (\pm 0.39)	0.93 (\pm 0.31)	<0.001
Serum potassium, mEq/L	4.1 (\pm 0.40)	4.1 (\pm 0.39)	4.2 (\pm 0.37)	4.2 (\pm 0.37)	0.001
Serum glucose, mg/dL	116 (\pm 42)	115 (\pm 40)	111 (\pm 38)	107 (\pm 32)	<0.001
Serum albumin, g/dL	4.0 (\pm 0.3)	4.0 (\pm 0.3)	4.0 (\pm 0.3)	4.0 (\pm 0.3)	0.176
Serum uric acid, mg/dL	6.0 (\pm 1.7)	5.8 (\pm 1.5)	5.7 (\pm 1.5)	5.5 (\pm 1.4)	<0.001
Serum C-reactive protein, mg/dL	5.7 (\pm 7.8)	5.6 (\pm 9.3)	4.4 (\pm 8.0)	4.0 (\pm 7.3)	<0.001
Serum interleukin-6, pg/mL	2.6 (\pm 1.7)	2.4 (\pm 1.9)	2.1 (\pm 1.6)	2.0 (\pm 1.8)	<0.001
Serum insulin, μ U/mL	18.8 (\pm 25.3)	18.9 (\pm 29.6)	16.1 (\pm 20.7)	15.2 (\pm 21.6)	<0.001
Fibrinogen, mg/dL	337 (\pm 74)	331 (\pm 69)	320 (\pm 65)	316 (\pm 62)	<0.001
Serum coagulation factor-VII, %	129 (\pm 33)	124 (\pm 29)	124 (\pm 28)	122 (\pm 29)	<0.001
Hemoglobin, g/dL	13.9 (\pm 1.38)	13.9 (\pm 1.43)	14.1 (\pm 1.29)	14.1 (\pm 1.31)	<0.001
Platelet count, $10^3/\mu$ L	260 (\pm 89)	250 (\pm 72)	245 (\pm 69)	252 (\pm 76)	0.001

Abbreviation: MET, metabolic equivalent task; SD, standard deviation

Table 2

Association of physical activity across MET-minutes/week categories with incident heart failure

MET-minutes/week	% (events/total)	Hazard ratio (95% confidence interval)		
		Unadjusted	Age-sex-race-adjusted	Multivariable-adjusted*
0	26 (128/489)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
1–499	23 (338/1458)	0.79 (0.64–0.97); p=0.022	0.87 (0.71–1.06); p=0.170	0.97 (0.79–1.20); p=0.807
500–999	20 (213/1086)	0.61 (0.49–0.75); p<0.001	0.68 (0.54–0.85); p=0.001	0.86 (0.69–1.08); p=0.201
1000	19 (458/2470)	0.53 (0.44–0.65); p<0.001	0.60 (0.49–0.74); p<0.001	0.79 (0.64–0.97); p=0.026
P trend#	<0.001	<0.001	<0.001	0.003

Abbreviation: MET, metabolic equivalent task

* Adjusted with age, sex, race, education, income, alcohol, smoking, body mass index, coronary artery disease, acute myocardial infarction, hypertension, diabetes, stroke, atrial fibrillation, left ventricular hypertrophy, left ventricular systolic dysfunction, systolic blood pressure, diastolic blood pressure, depression score, Mini-mental state examination score, serum cholesterol, serum albumin, serum creatinine and serum C-reactive protein

Median value for each category: 0 = 0, 1–499 = 253.00, 500–999 = 729.50, 1000 = 2054.50

Table 3

Association of physical activity across MET-minutes/week categories with other incident cardiovascular events

MET-minutes/week	% (events/total)	Hazard ratio (95% confidence interval)		
		Unadjusted	Age-sex-race-adjusted	Multivariable-adjusted**
Acute myocardial infarction* (n=5061)				
0	15 (67/437)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
1–499	11 (146/1336)	0.63 (0.48–0.85); p=0.002	0.63 (0.47–0.85); p=0.002	0.68 (0.51–0.91); p=0.010
500–999	11 (107/1002)	0.57 (0.42–0.78); p<0.001	0.56 (0.41–0.76); p<0.001	0.65 (0.47–0.89); p=0.007
1000	12 (266/2286)	0.60 (0.46–0.78); p<0.001	0.58 (0.44–0.76); p<0.001	0.68 (0.51–0.91); p=0.008
P trend#	0.331	0.065	0.038	0.361
Angina pectoris* (n=4708)				
0	22 (88/393)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
1–499	19 (230/1227)	0.75 (0.59–0.96); p=0.021	0.74 (0.58–0.95); p=0.017	0.79 (0.62–1.01); p=0.062
500–999	19 (176/939)	0.70 (0.54–0.91); p=0.007	0.68 (0.53–0.88); p=0.004	0.79 (0.61–1.03); p=0.079
1000	19 (406/2149)	0.67 (0.54–0.85); p=0.001	0.66 (0.52–0.83); p<0.001	0.79 (0.62–1.01); p=0.056
P trend##	0.347	0.018	0.013	0.459
Stroke* (n=5290)				
0	19 (84/447)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
1–499	14 (188/1393)	0.64 (0.50–0.83); p=0.001	0.71 (0.55–0.92); p=0.011	0.76 (0.59–0.99); p=0.042
500–999	12 (127/1051)	0.53 (0.40–0.70); p<0.001	0.60 (0.46–0.80); p<0.001	0.68 (0.52–0.91); p=0.008
1000	14 (323/2399)	0.56 (0.44–0.72); p<0.001	0.66 (0.52–0.85); p=0.001	0.75 (0.58–0.96); p=0.022
P trend###	0.060	0.006	0.096	0.376

Abbreviation: MET, metabolic equivalent task

* Exclude prevalent disease events

** Adjusted with age, sex, race, education, income, alcohol, smoking, body mass index, coronary artery disease, acute myocardial infarction, hypertension, diabetes, stroke, atrial fibrillation, left ventricular hypertrophy, left ventricular systolic dysfunction, systolic blood pressure, diastolic blood pressure, depression score, Mini-mental state examination score, serum cholesterol, serum albumin, serum creatinine and serum C-reactive protein

Median value for each category: 0 = 0, 1–499 = 254.00, 500–999 = 725.45, 1000 = 2061.63

Median value for each category: 0 = 0, 1–499 = 255.89, 500–999 = 729.73, 1000 = 2051.98

Median value for each category: 0 = 0, 1–499 = 254.17, 500–999 = 724.50, 1000 = 2051.65

Table 4

Association of physical activity across MET-minutes/week categories with mortality

MET-minutes/week	% (events/total)	Hazard ratio (95% confidence interval)		
		Unadjusted	Age-sex-race-adjusted	Multivariable-adjusted*
All-cause mortality				
0	59 (286/489)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
1–499	48 (703/1458)	0.73 (0.64–0.84); p<0.001	0.82 (0.71–0.94); p=0.005	0.89 (0.77–1.02); p=0.094
500–999	43 (471/1086)	0.60 (0.52–0.70); p<0.001	0.69 (0.59–0.80); p<0.001	0.79 (0.68–0.92); p=0.002
1000	39 (966/2470)	0.50 (0.44–0.57); p<0.001	0.59 (0.51–0.67); p<0.001	0.67 (0.59–0.77); p<0.001
P trend [#]	<0.001	<0.001	<0.001	<0.001
Cardiovascular mortality				
0	28 (136/489)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
1–499	19 (270/1458)	0.59 (0.48–0.73); p<0.001	0.67 (0.54–0.82); p<0.001	0.76 (0.62–0.94); p=0.011
500–999	17 (181/1086)	0.49 (0.39–0.61); p<0.001	0.56 (0.45–0.70); p<0.001	0.72 (0.57–0.91); p=0.006
1000	16 (390/2470)	0.43 (0.35–0.52); p<0.001	0.50 (0.41–0.61); p<0.001	0.65 (0.52–0.79); p<0.001
P trend [#]	<0.001	<0.001	<0.001	0.001
Non-cardiovascular mortality				
0	31 (149/489)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
1–499	29 (429/1458)	0.86 (0.71–1.03); p=0.099	0.96 (0.79–1.15); p=0.641	1.00 (0.83–1.21); p=0.984
500–999	27 (289/1086)	0.71 (0.58–0.86); p=0.001	0.81 (0.66–0.99); p=0.037	0.86 (0.70–1.06); p=0.149
1000	23 (575/2470)	0.57 (0.48–0.68); p<0.001	0.67 (0.55–0.80); p<0.001	0.71 (0.59–0.86); p<0.001
P trend [#]	<0.001	<0.001	<0.001	<0.001

Abbreviation: MET, metabolic equivalent task

* Adjusted with age, sex, race, education, income, alcohol, smoking, body mass index, coronary artery disease, acute myocardial infarction, hypertension, diabetes, stroke, atrial fibrillation, left ventricular hypertrophy, left ventricular systolic dysfunction, systolic blood pressure, diastolic blood pressure, depression score, Mini-mental state examination score, serum cholesterol, serum albumin, serum creatinine and serum C-reactive protein

[#] Median value for each category: 0 = 0, 1–499 = 253.00, 500–999 = 729.50, 1000 = 2054.50