Published in final edited form as:

Med Sci Sports Exerc. 2012 February ; 44(2): 253–259. doi:10.1249/MSS.0b013e31822cf717.

Cardiorespiratory Fitness as a Predictor of Dementia Mortality in Men and Women

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Abstract

There is evidence that physical activity may reduce the risk of developing Alzheimer's disease and dementia. However, few reports have examined the physical activity-dementia association with objective measures of physical activity. Cardiorespiratory fitness (hereafter called fitness) is an objective reproducible measure of recent physical activity habits.

Purpose: We sought to determine whether fitness is associated with lower risk for dementia mortality in women and men.

Methods: We followed 14,811 women and 45,078 men, ages 20-88 at baseline, for an average of 17 years. All participants completed a preventive health examination at the Cooper Clinic in Dallas, Texas during 1970-2001. Fitness was measured with a maximal treadmill exercise test, with results expressed in maximal metabolic equivalents (METs). The National Death Index identified deaths through 2003. Cox proportional hazards models were used to examine the association between baseline fitness and dementia mortality, adjusting for age, sex, examination year, body mass index, smoking, alcohol use, abnormal ECGs, and health status.

Results: There were 164 deaths with dementia listed as the cause during 1,012,125 person-years of exposure. Each 1-MET increase in fitness was associated with a 14% lower adjusted risk of dementia mortality (95% confidence interval, CI 6%-22%). With fitness expressed in tertiles, adjusted hazard ratios (HRs) for those in the middle and high fitness groups suggest their risk of dementia mortality was less than half that of those in the lowest fitness group (respectively: HR 0.44, CI 0.26-0.74; HR 0.49, CI 0.26-0.90).

Conclusion: Greater fitness was associated with lower risk of mortality from dementia in a large cohort of men and women.

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Conflict(s) of Interest: None

Keywords

physical fitness; cognitive function; Alzheimer's disease; vascular dementia; metabolic equivalents (METs)

Introduction

Alzheimer's disease (AD) and related disorders are the sixth leading cause of death in the United States (8), and the fifth leading cause for ages 65 and older (1). While mortality attributed to several major causes of death including heart disease, breast cancer, stroke is decreasing, mortality attributed to AD has increased dramatically over the last 15 years (1). Between 2002 and 2006, the total number of deaths attributed to AD increased by nearly 46.1% (1), making AD a major public health concern.

Increasing evidence from observational epidemiologic studies suggests that physical activity may reduce the risk of developing AD and related disorders (18,28,30). In a meta-analysis of 16 prospective epidemiologic studies on the effect of physical activity and risk of neurodegenerative disease, physical activity was found to be associated with a reduced risk of both dementia and AD by 28% and 45%, respectively (18). The effects of increased physical activity and cardiorespiratory fitness (CRF) on cognitive function in healthy adults have also been examined in randomized controlled trials (RCTs). However, results were mixed. While some RCTs reported that exercise programs maintained or improved cognitive function compared with controls, others found no benefit of exercise for cognitive function (28). A Cochrane review (3) evaluated 11 RCTs examining the effectiveness of aerobic exercise interventions aimed at improving CRF for healthy older adults, specifically to enhance cognitive function. The review found suggestive evidence of potential improvements in cognitive capacity in 8 of these studies, with the most promising results for cognitive speed, motor function, and auditory and visual attention; however, the majority of comparisons were not statistically significant. Another recent review of RCTs in this area found little evidence of an association between activity and cognitive outcomes, but noted that almost all studies in this area have serious methodological limitations (30). Nonetheless, given the strength of the evidence from observational studies and animal models, the Physical Activity Guidelines Advisory Committee and the American College of Sports Medicine recently concluded that cardiovascular fitness and higher levels of physical activity reduce the risk of cognitive decline and dementia, and that physical activity in previously sedentary older adults can improve cognitive performance, particularly for complex tasks requiring executive control (9,25).

Despite similar beneficial outcomes reported across prospective epidemiologic studies, study designs and findings vary greatly (18). A major source of variation involves assessment of physical activity. A substantial proportion of previous epidemiologic studies might not have accurately quantified physical activity levels (18,28). Physical activity has most often been self-reported, and therefore subject to reporting bias (12,28). CRF is an objective reproducible measure that correlates strongly with habitual physical activity, and is more highly correlated with many health outcomes than self-reported physical activity (7). Consistent evidence has suggested an inverse relationship between CRF and both cardiovascular disease and all-cause mortality (7,16,31). This evidence suggests that CRF may also be associated with lower dementia risk, because vascular damage is a notable risk factor for developing AD and VaD (19). One way to examine this possible relationship is to study deaths for which dementia has been assigned as a contributory cause (hereafter called "dementia mortality"). Only one prospective study, by Middleton and colleagues, has suggested potential benefits of self-reported physical activity for reducing dementia

mortality (24). The goal of the present study is to investigate the association between CRF and dementia mortality in a large prospective cohort of adults, thus improving on previous research by using an objective measure of individuals' physical activity habits.

Methods

Study Sample

Participants were 14,811 women and 45,078 men, ages 20 to 88 years, who had a baseline physician examination and clinical assessment at the Cooper Clinic in Dallas, Texas, during 1970 to 2001. Individuals were included in the study if they met the following criteria: 1) enrollment in the Aerobics Center Longitudinal Study (ACLS); 2) completion of a maximal treadmill exercise test, achieving at least 85% of their age-predicted maximal heart rate ($220 - \text{age in years}$); and 3) completion of at least 1 year of follow-up. The majority of participants were white, well-educated, and typically employed or formerly employed in professional positions. Participants completed a written informed consent, indicating that they agreed to participate in the clinical examination and the follow-up study. The Cooper Institute Institutional Review Board annually reviewed and approved the study protocol.

Clinical Examination

The baseline examination was conducted following an overnight fast. Published reports have described the examination in detail (7,16). In brief the examination consisted of an extensive self-reported personal and family medical history, a questionnaire on demographic information and health habits, blood chemistry tests, and other clinical measurements. Body mass index (kg/m^2) was computed from measured height and weight on a standard physician's balance beam scale and stadiometer. Resting blood pressures were recorded as the first and fifth Korotkoff sounds, using standard auscultation methods. Hypertension was defined by measured resting systolic (≥ 140 mm Hg) or diastolic (≥ 90) blood pressure, or a history of physician diagnosis. Serum samples were analyzed for lipids and glucose using standardized automated bioassays. Diabetes was defined as fasting plasma glucose concentration of ≥ 7.0 mmol/L (126 mg/dL), a history of physician diagnosis, or insulin use. Health status was based on presence of physician-diagnosed conditions (myocardial infarction, stroke, or cancer). Smoking habits and alcohol intake were obtained from a standardized questionnaire.

CRF was assessed by a maximal symptom-limited treadmill exercise test following a modified Balke protocol (5). Patients began walking at 88 m/min without elevation. After the first minute, elevation was increased to 2%, and thereafter increased 1% per minute until the 25th minute. After 25 minutes, elevation did not change while speed was increased by 5.4 m/min for each minute increment until test termination. Patients were encouraged to give maximal effort. The test endpoint was volitional exhaustion or termination by the physician for medical reasons. Exercise duration on this protocol is highly correlated with measured maximal oxygen uptake in men (26) ($r = 0.92$) and women (27) ($r = 0.94$). Thus, CRF in this study is equivalent to maximal aerobic power. We estimated maximal metabolic equivalents (METs, 1 MET = 3.5 ml O_2 uptake/kg/min) from the final treadmill speed and grade (2). Patients were grouped into tertiles based on their MET values. We classified the least-fit tertile as low fit, the next third as middle fit, and the upper tertile as high fit. Maximal MET values for the three fitness categories were: low, <9.9 ; middle, 9.9 to 12.2; and high, ≥ 12.2 . Abnormal exercise electrocardiogram (ECG) responses included rhythm and conduction disturbances and ischemic ST-T wave abnormalities (16). In a previous study, three physicians who read a random sample of 357 patient records agreed with 90% of the ECG interpretations (16).

Mortality Surveillance

All participants were followed for mortality from their baseline visit through December 31, 2003. The National Death Index (NDI) was the primary data source for mortality surveillance. The underlying cause of death was determined from the NDI report or by a nosologist's review of official death certificates obtained from the department of vital records in the decedent's state of residence. VaD mortality was defined by International Classification of Diseases, Ninth Revision (*ICD-9*) code 290 before 1999 and *Tenth Revision (ICD-10)* codes F01 and F03 during 1999-2003. AD mortality was defined by *ICD-9* code 331.0 before 1999 and *ICD-10* code G30 during 1999-2003. Total dementia included VaD and AD. We computed person-years of exposure as the sum of follow-up time among decedents and survivors. In a mean 17 years of follow-up, 4,047 deaths were identified, 164 of which were dementia mortality (72 vascular dementia and 92 Alzheimer's disease).

Statistical Analyses

Baseline characteristics of the population were estimated separately for survivors and decedents, and also specifically for dementia decedents. Differences in covariates between survivors and decedents were tested using Student *t* tests for continuous variables and chi-square tests for categorical variables. Cox proportional hazards models were used to estimate adjusted hazard ratios (HRs), 95% confidence intervals (CIs), mortality rates (deaths/10,000 person-years of follow-up), and linear trends for VaD, AD, and total dementia mortality for each fitness category. When calculating HRs, the low fitness group was used as the reference category. METs were also entered into the model as a continuous variable.

Cumulative hazard plots grouped by exposure suggested no appreciable violations of the proportional hazards assumption. We excluded events that occurred during the first year of follow-up to reduce potential confounding caused by procedure-related deaths and the influence of undetected subclinical disease at baseline. To examine potential modifying effects of selected variables on the fitness-dementia association, we conducted Cox regression analyses according to strata of age (<55 vs. ≥55 years), sex (female vs. male), BMI (<25 vs. ≥25 kg/m²), and chronic medical conditions (presence/absence). Tests for multiplicative interaction between a variable representing METs in 1-MET increments and other risk factors in relation to total dementia risk were performed by likelihood ratio tests, which compared the models with and without interaction terms. All *P* values are based on two sided tests, with an alpha level of 0.05. All statistical analyses were performed using SAS statistical software, version 9.1 (SAS Inc., Cary, NC).

Results

Table 1 presents participants' selected baseline demographic, clinical, and health habit characteristics, by vital status. The mean age of the cohort (*n* = 59,889) was 43.5 (SD, 10.0) years. Approximately 25% of participants were women. Compared with survivors, participants who died were older, had lower CRF, and had less favorable risk factor profiles for cardiovascular diseases. There were 164 dementia deaths (72 VaD, 92 AD) during 1,012,125 person-years of exposure.

Table 2 shows the relationship between CRF levels and the risk of VaD, AD, and total dementia mortality. After adjusting for age and sex, and compared to those in the low fitness category, participants in the middle and high fitness categories had significantly lower HRs for VaD mortality (respectively: HR 0.27, CI 0.12-0.60; HR 0.46, CI 0.21-0.99) and total dementia mortality (respectively: HR 0.49, CI 0.31-0.78; HR 0.59, CI 0.35-0.99), *P*-trend <

0.01 for each. The lower risks of dementia mortality for those with higher CRF levels remained significant after additional adjustment for BMI, current smoking, alcohol intake, abnormal exercise ECG responses, and other medical conditions. The results for AD mortality were not statistically significant. Adjusting for blood pressure, lipids and glucose as continuous scores did not materially change the results (data not shown).

We next examined the relationship between CRF and each of the three mortality outcomes representing maximal METs as a continuous variable (Table 3). Adjusted for age, sex, and examination year, the HR for VaD mortality associated with each 1-unit increment in maximal METs was 0.84 (95% CI = 0.75-0.95). CRF remained inversely associated with VaD death risk after additional adjustment for other risk factors ($P = 0.01$). The magnitudes of the inverse associations were similar between CRF and the risk of AD and total dementia mortality (Model 2, respectively: HR 0.87, CI 0.76-0.99; HR 0.86, CI 0.78-0.94). Similar results were obtained when blood pressure, lipids and glucose were adjusted for as continuous scores (data not shown).

Finally, we examined whether other risk predictors modified the association between CRF and total dementia mortality (Table 4). Multivariable analyses showed that each 1-MET increment of maximal exercise was associated with a 9 to 34 percent lower dementia mortality risk in these groups, with the greatest benefit of higher CRF in those having chronic medical conditions ($P < 0.05$ for most strata). The consistency in the direction and magnitude of association between CRF and dementia mortality suggested that there was little effect modification across risk factor categories. A possible exception to this generalization may be a greater effect of CRF for those at ages <55 at baseline, compared to their older counterparts. The test for interaction between age and fitness was significant (P for interaction = 0.02, not shown in the table).

Figure 1 depicts the modifying effect of baseline age on the association between CRF and dementia mortality. As in Table 4, age was grouped into two categories (<55 years and ≥ 55 years). After adjusting for all the covariates, there was a significant reduction in risk of total dementia death in the top two tertiles of CRF for ages <55 , compared to the lowest CRF category (P -trend = 0.0001). Although there was no suggestion of a gradient of declining risk for ages ≥ 55 , those in the two higher CRF groups had lower risk of dementia mortality than those in the low-fitness group. The figure suggests that the greatest reduction in dementia mortality may have occurred between the low and middle tertiles of CRF, where the HR dropped by two-thirds.

Discussion

In this large, prospective study of men and women followed for an average of 17 years, individuals with higher levels of CRF had significantly lower mortality for both VaD and total dementia. The association remained after adjustments for potential confounding variables including age, sex, examination year, BMI, smoking status, alcohol intake, abnormal ECG responses, and baseline medical conditions. The association was particularly strong for VaD mortality; persons in the middle and high fitness categories had a 73% and 69% lower mortality risk for vascular dementia, respectively, compared with those in the low CRF category. No beneficial effect of CRF on AD mortality risk was detected in the analysis of CRF tertiles.

When CRF was evaluated using continuous variables, an approach with greater statistical power than the tertile analysis, each 1-unit increase in maximal MET expenditure was associated with reductions in VaD, AD, and total dementia mortality of 18%, 13%, and 14%, respectively, after accounting for potential risk factors. Our findings are consistent

with those reported by Barnes et al. (6) In their longitudinal study of healthy older adults, higher baseline fitness was positively associated with preservation and enhancement of cognitive function over a 6-year follow-up period.

A strong inverse trend in the adjusted risk of dementia mortality was observed across the three CRF categories in the younger group (<55 years). The adjusted risk of dementia mortality was the lowest in the high CRF group and the highest in the low CRF group. The beneficial effect of greater CRF was approximately equal when comparing younger and older individuals in the middle fitness category to those in the low fitness category. For both age groups, the risk for those in the middle fitness category was more than 60% lower than the corresponding risk for those in the lowest fitness category. Younger individuals appeared to receive more protective benefit from being in the high fitness category than did older individuals. It is possible that the latter finding results from physical activity over more years of follow-up for participants who were younger at baseline, or more intense, frequent, or lengthy periods of activity during follow-up; we do not have CRF measures for participants during the follow-up period. This result may also be an artifact of the relatively small number of individuals age 55 or older in the high fitness category at baseline (n = 1,144). Additional research in this area is warranted.

Cardiorespiratory fitness may preserve cognitive function through a variety of plausible cellular and molecular mechanisms, including increasing cerebral blood flow and oxygen delivery (10), enhancing neuronal plasticity (13), inducing fibroblast growth factors in the hippocampus and cerebellum (17), reducing oxidative stress and inflammation (20), increasing brain volume (11), and stimulating neuronal creation and survival (13). Fitness may also lower the risk of several medical conditions, such as cardiovascular disease, cerebrovascular disease, hypertension, and diabetes, all of which are important risk factors linked to cognitive decline (4,21). In addition, results from randomized trials suggest that increasing the level of physical activity may enhance cognition in older adults at risk for AD (22). Participating in physical activity may also provide an enriched social environment. Individuals may benefit from both the activity itself and the social interaction. Animal studies have shown that mice exposed to an “enriched environment” have significantly lower levels of amyloid deposits, which are associated with AD, compared to animals raised under normal conditions (23). Results from longitudinal studies also suggest that socially isolated older adults are at higher risk of all-cause mortality (29) and dementia (14), compared to those with close social ties or better social support.

The current study has several strengths. First, the use of standardized and objective measurements of fitness reduced the likelihood of exposure misclassification, compared to self-reported measures of physical activity. No previous studies have examined the association between physical activity and dementia mortality using CRF as their fitness measurement. Second, the extensive and standardized baseline covariate measurement minimized potential confounding due to undetected subclinical diseases at baseline. Lastly, the prospective study design, with a mean follow-up of 17 years, provided a sufficiently large number of dementia mortality cases to enable us to examine the association between CRF and both AD and VaD.

Several limitations of this study should be considered. First, the generalizability of our findings may be limited due to the homogeneity of our study population. Participants were predominately white, well-educated, had middle to upper socioeconomic status (SES), and were physically able to complete a fitness test. Whether similar findings would be obtained in adults from different ethnic or SES backgrounds or with functional limitations is not clear. On the other hand, the homogeneity of participants strengthens the study’s internal validity by minimizing potential confounding attributable to income, education, or SES

differences. Second, there were no baseline or longitudinal data on cognitive performance. It is possible that some individuals in the study had preclinical or early-stage disease at baseline, although the average 17 years of follow-up limits that possibility. Third, there was insufficient information on medication use, menopausal status, family history of dementia, or dietary habits to control for these factors. These unmeasured factors may have introduced residual confounding. However, it seems unlikely that these factors would explain all of the observed association between CRF and dementia mortality. It should also be noted that the analysis of dementia mortality may be affected by the fact that we studied an incomplete cohort, one in which the majority of participants remained alive. Because the dynamics of dementia mortality could differ at older ages, estimates of dementia mortality will remain uncertain until most or all of the cohort has died. The relatively small number of participants and dementia deaths in the middle and high fitness groups for ages 55 and over may have affected the results. Thus, it will be useful to continue to follow this cohort to completion. In terms of exposure assessment, CRF was assessed only at baseline. We were unable to explore changes in fitness that may have occurred during follow-up. It is possible that low-fit individuals increased their fitness levels at some point during the follow-up, or that high-fit individuals decreased their fitness levels. Misclassification associated with changing levels of physical activity would likely underestimate the magnitude of the association observed in the present study. In addition, other relevant health behaviors and other time varying covariates were not measured during the years of follow-up. It is possible that these factors changed over time. Such changes may introduce residual confounding. Finally, the ascertainment of dementia mortality may be limited by variation in diagnosis or inconsistent reporting of dementia as the underlying or contributory cause of death on death certificates (15). Again, the high SES and homogeneity of our sample may help to ameliorate this concern. Given their high SES, study participants were likely to have had accessible health care of relatively high quality, which may contribute to more reliable diagnoses. Participants' homogeneity similarly may have been associated with relatively non-differential reporting of dementia diagnoses on death certificates.

This study found that higher levels of CRF were associated with lower risk of AD mortality, VaD mortality, and total dementia mortality, in a large cohort of women and men. CRF is an objective measure of physical activity habits. The results persisted after adjustment for clinical variables. Clinicians should encourage patients to maintain an active lifestyle. These findings support physical activity promotion campaigns by public health organizations and nonprofit organizations such as the Alzheimer's Association, and should encourage individuals to be physically active. Following current physical activity recommendations (32) will keep most individuals out of the low-fitness category, and may therefore reduce dementia mortality. Consistent with current physical activity recommendations, results also suggest that having even more activity than the recommended level may bring added benefits.

Acknowledgments

The study was supported by National Institutes of Health Grants AG06945, HL62508, and R21DK088195. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health, nor constitute endorsement by ACSM.

The authors thank the Cooper Clinic physicians and technicians for collecting the baseline data, and staff at the Cooper Institute for data entry and data management.

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FIGURE 1. Multivariate-adjusted total dementia mortality hazard ratios (and 95% confidence intervals, CIs), by cardiorespiratory fitness (CRF) level and age groups.*

*The number of individuals (and total dementia deaths) in the low, middle, and high CRF groups were 16,518 (37), 15,369 (11), and 19,573 (5) among those <55 years; and 5,336 (83), 1,949 (12), and 1,144 (13) among those ≥ 55 years.

TABLE 1

Baseline Characteristics of Survivors and Decedents, Aerobics Center Longitudinal Study, 1970-2001.

Characteristic	Total (n=59,889)	Survivors (n=55,842)	Decedents (n=4,047)	Dementia decedents (n=161)	P Value*
Age (years)	43.5±10.0	42.9±9.7	51.1±10.7	58.4 ±8.4	<0.0001
Female (%)	24.7	25.5	14.2	24.2	<0.0001
Body Mass Index (kg/m ²)	25.6±4.1	25.5 ±4.1	26.2 ±4.3	25.3 ±4.1	<0.0001
Maximal METs	11.1 ±2.6	11.2 ±2.6	9.6 ±2.4	8.9 ±2.2	<0.0001
Treadmill time (m)	16.7 ±5.4	16.9 ±5.3	13.6 + 5.1	12.1 ±4.8	<0.0001
Lipids, mmol/L					
Total cholesterol	5.4 ± 1.1	5.4 ± 1.1	5.8 + 1.1	6.0 ±1.0	<0.0001
HDL-C	1.3 ±0.4	1.3 ±0.4	1.2 ±0.4	1.2 ±0.3	<0.0001
Triglycerides	1.4 ±1.3	1.4 ±1.3	1.7 ±1.6	1.6±0.9	<0.0001
Fasting blood glucose (mmol/L)	5.5 ±3.3	5.5 ±3.4	5.9 ±1.6	5.7 ±1.2	<0.0001
Blood pressure, mean (SD), mmHg					
Systolic	120 ±14	119 + 14	127 ±17	127 ±18	<0.0001
Diastolic	80 ±10	80 ±10	83 ±11	81 ±10	<0.0001
Current smoker (%)	15.6	15.1	23.6	10.6	<0.0001
Alcohol intake (5 drinks per week) (%)	32.5	31.9	41.8	31.7	<0.0001
Abnormal ECG during exercise (%)	5.2	4.6	13.8	20.5	<0.0001
Chronic medical conditions (%)					
Myocardial infarction	1.0	0.7	4.5	3.7	<0.0001
Stroke	0.2	0.2	0.4	0	0.001
Diabetes mellitus	2.6	2.3	5.5	5.6	<0.0001
Hypertension	13.4	12.7	23.6	16.8	<0.0001

Data shown as Means ± SD unless specified otherwise.

Abbreviations: METs, maximal metabolic equivalents; HDL-C, high-density lipoprotein cholesterol; ECG, electrocardiogram.

*
Difference between survivors and decedents

TABLE 2

Rates and Hazard Ratios for Dementia Mortality by CRF Groups in Women and Men.

	Low CRF	Middle CRF	High CRF	<i>P</i> value for Trend
Death due to vascular dementia				
No. of cases	57	7	8	
No. of person-years	379,388	294,851	337,757	
Rate *	1.2	0.3	0.5	
Age-, sex- adjusted HR (95% CI)	1.00 (Referent)	0.27 (0.12-0.60)	0.46 (0.21-0.99)	0.003
Multivariate HR (95% CI) [†]	1.00 (Referent)	0.27 (0.11-0.65)	0.31 (0.12-0.84)	0.002
Death due to Alzheimer's disease				
No. of cases	66	16	10	
No. of person-years	379,388	294,851	337,757	
Rate *	1.1	0.8	0.8	
Age-, sex- adjusted HR (95% CI)	1.00 (Referent)	0.72 (0.41-1.27)	0.73 (0.36-1.47)	0.25
Multivariate HR (95% CI) [†]	1.00 (Referent)	0.59 (0.30-1.14)	0.66 (0.30-1.43)	0.15
Total dementia mortality[‡]				
No. of cases	120	23	18	
No. of person-years	379,388	294,851	337,757	
Rate *	2.2	1.1	1.3	
Age-, sex-adjusted HR (95% CI)	1.00 (Referent)	0.49 (0.31-0.78)	0.59 (0.35-0.99)	0.005
Multivariate HR (95% CI) [†]	1.00 (Referent)	0.44 (0.26-0.74)	0.49 (0.26-0.90)	0.002

Abbreviations: HR, Hazard ratio; CI, Confidence interval; CRF, cardiorespiratory fitness.

* Rate is expressed per 10,000 person-years, adjusted for age and sex.

[†] Adjusted for age, sex, examination year, body mass index (kg/m²), current smoking (yes or not), alcohol intake (≥ 5 drinks/wk, or not), abnormal exercise electrocardiogram responses (present or not), hypertension (present or not), diabetes (present or not), hypercholesterolemia (present or not), and health status (myocardial infarction, stroke, or cancer).[‡] Total dementia included vascular dementia and Alzheimer's disease.

TABLE 3

Hazard Ratios of Dementia Mortality per 1-MET Increment in Results of Maximal Treadmill Exercise Test in Women and Men.

	Model 1 [*]			Model 2 [†]		
	HR	95% CI	P value	HR [†]	95% CI	P value
Vascular dementia						
Maximal METs	0.84	0.75-0.95	0.005	0.82	0.71-0.96	0.01
Alzheimer's disease						
Maximal METs	0.90	0.81-1.00	0.056	0.87	0.76-0.99	0.03
Total dementia						
Maximal METs	0.88	0.81-0.95	0.001	0.86	0.78-0.94	0.001

Abbreviations: METs, maximal metabolic equivalents; HR, Hazard ratio; CI, Confidence interval.

^{*} Model 1 results adjusted for age, sex and examination year.

[†] Model 2 results adjusted for covariates included in Model 1, plus body mass index (kg/m²), current smoking (yes or not), alcohol intake (5 drinks/wk, or not), abnormal exercise electrocardiogram responses (present or not), hypertension (present or not), diabetes (present or not), hypercholesterolemia (present or not), and health status (myocardial infarction, stroke, or cancer).

TABLE 4

Risk of Total Dementia Mortality per 1-MET Increment in Results of Maximal Exercise Test within Strata of Other Personal Characteristics.

Characteristic	N	Deaths with Dementia	HR (95% CI)	P value
Age, years [*]				
<55	51,460	53	0.66 (0.56-0.77)	<0.0001
55	8,429	108	0.87 (0.78-0.96)	0.007
Sex [*]				
Female	14,811	39	0.80 (0.64-0.99)	0.04
Male	45,078	122	0.88 (0.80-0.97)	0.009
Body mass index, kg/m ² [*]				
18.5-24.9	32,889	99	0.85 (0.77-0.94)	0.002
25	27,000	62	0.93 (0.80-1.09)	0.37
Chronic medical conditions ^{*†}				
No	50,307	126	0.91 (0.83-1.00)	0.04
Yes	9,582	35	0.76 (0.63-0.92)	0.005

Abbreviations: HR, hazard ratio; CI, confidence interval; ECG, electrocardiogram.

^{*} Adjusted for examination year and the other variables in the table.

[†] Chronic medical conditions including diabetes, hypertension, stroke, myocardial infarction or cancer.