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Leisure-time Physical Activity and All-cause Mortality in an Elderly Cohort

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Abstract

Background—Physical activity is one of the mainstays of secondary prevention in people with heart disease. It is not well understood, however, how the presence of heart disease or a history of habitual exercise prior to the study modify any mortality-sparing effects of leisure-time physical activity.

Methods—We analyzed data from a well-described cohort of subjects aged 54 years and older at intake (median age, 70 years) from Sonoma, CA, studied between 1993 and 2001 with mortality follow-up until 2003. A history-adjusted marginal structural model was used to obtain counterfactual excess risk estimates that were pooled across the different time points. Additive interaction was examined by comparing these excess risk estimates across strata of age, heart disease, and precohort physical activity.

Results—Estimates of the excess risk for 2-year all-cause mortality comparing Centers for Disease Control and Prevention–recommended levels of current physical activity to lower levels of activity ranged from –0.7% to –4.9% among subjects younger than 75 years of age and from –7.8% to –14.8% among older subjects. Heart disease or precohort physical activity were not found to modify the effect of leisure-time physical activity.

Conclusions—Our data are consistent with the view that the mortality-sparing effect of recent physical activity is independent of the presence or absence of underlying cardiac disease and the pattern of past physical activity.

A substantial body of data has documented the beneficial impact of physical activity on risk factors such as lipid profile,¹ morbidity,^{1–3} and mortality.^{4–11} Benefits with respect to reduced mortality have been observed in prospective studies of elderly populations.^{5–12} Physical activity is often recommended as part of a rehabilitation–prevention program for people who have recently suffered a heart attack,^{13,14} but none of these studies has assessed the extent to which reported heart disease modifies the benefits of physical activity. Likewise, with a few exceptions,⁸ virtually none of these studies has tried to determine how

lifetime patterns of physical activity prior to entry into the cohort affect the impact of more current levels of activity on health outcomes.

The Harvard Alumni Study, based on 213,000 person-years of follow-up for subjects ages 35–74 at entry, showed that reported sports activity during college did not change the magnitude of the association between increasing levels of current physical activity and decreased all-cause mortality, after adjustment for a large number of confounders.⁴ In a study of osteoporotic fractures, women who were classified as inactive at baseline but who reported becoming “moderately or highly” active at the follow-up evaluation showed a similar relative decrease in all-cause and cardiovascular mortality as those women who were classified as “moderately or highly” active at both evaluations.⁸ This finding suggests that the mortality-sparing benefits of exercise are achieved quickly and are not dependent on past levels of activity.

We used data from a well-described cohort of subjects ages 54 years and older at intake (median age, 70 years), to evaluate whether past physical activity or the presence of self-reported cardiac disease modified any beneficial effects of recent physical activity on 2-year cumulative incidence of all-cause mortality. Our analysis is based on history-adjusted marginal structural models (MSMs), a recent generalization of standard MSMs that in particular allows data to be pooled across different time points.¹⁵

METHODS

Subjects

The Study of Physical Performance and Age-Related Changes in Sonomans has been described in detail.^{16–18} Briefly, this was a community-based longitudinal cohort of 2092 persons living in and around Sonoma, CA, enrolled between May 1993 and December 1994, with participants 54 years and older at entry. The cohort was representative by age (except for percentage >85 years) and sex of the community from which it was drawn but was better educated and more health-conscious.¹⁷ Subjects were followed approximately every 2 years for 4 observation periods.^{16,19} At each evaluation, subjects completed an extensive questionnaire about their health status, exercise patterns, social arrangement, and cognitive status. Data from the present analysis were derived from the baseline and 3 subsequent evaluations (September 1995–November 1996, June 1998–October 1999, and February 2000–March 2001).

All protocols were approved by the Committee for the Protection of Human Subjects of the University of California, Berkeley.

Treatment Variable: Current Leisure-time Physical Activity

At each interview, subjects were asked about the average number of times per week that they had performed each of 22 leisure-time physical activities over the previous 12 months. Each activity was assigned a metabolic equivalent (MET) value from the compendium by Ainsworth et al^{20,21}; 1 MET corresponds to an oxygen consumption of 3.5 mL/kg/min. The exercise frequency data were then used to calculate the average METs each individual expended per week as part of leisure-time physical activity. Our treatment/exposure variable

was defined as an indicator for whether this continuous activity variable met the minimum recommendation of 22.5 METs/wk.

Effect Modifiers: Habitual Past Physical Activity, Age, and Self-reported Cardiac Events

At the baseline interview, subjects were asked whether they had performed the same set of 22 activities at least 3 times a week for 20 minutes each time for at least 1 year at ages 15–20 years, 20–39 years, and 40 years to 1 year prior to baseline. To investigate the interaction between habitual physical activity prior to cohort entry and current physical activity, we defined past habitual physical activity as an indicator variable for vigorous physical activity (defined as activities with a MET rating 6.0–6.5 in all of the time periods prior to baseline). At each interview, the presence of cardiac disease was defined as the self-report of angina, myocardial infarction, coronary artery angioplasty or bypass surgery, or congestive heart failure.

Time-independent Confounders Measured at Baseline

Past physical activity was adjusted for in the form of 6 separate variables capturing the number of moderate and vigorous activities in the age intervals noted previously (eTable 1, <http://links.lww.com/A979>). Subjects also were asked if they had changed their physical activities in the 5- or 10-year periods before the baseline interview. An indicator for participation in high school sports also was used. Other time-independent confounders included sex as well as the home-and work-specific number of years of exposure to environmental tobacco smoke reported at baseline.

Time-dependent Confounders Measured at Each Interview

Weight and height were measured based on a standard protocol at each visit, and body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared (eTable 2, <http://links.lww.com/A979>). At each survey, subjects were classified as having none or at least 1 chronic disease based on the new or past occurrence of self-reported cancer, cerebrovascular disease, diabetes mellitus, kidney disease, liver disease, or Parkinson disease. Two variables were used to describe depression: (1) a score of 16 or higher on the Center for Epidemiologic Studies Depression Scale¹⁹; and (2) current use of an antidepressant medication (direct inspection of all medications at each interview). At each survey, smoking was classified as never, current, or former.¹⁶ Subjects rated their overall health (excellent, good, fair, or poor). Living arrangements were defined for each subject as living alone, living with a spouse, or living with a nonspouse.²² An integrated index of functional limitation (NRB) was based on the replies to 10 questions related to physical functioning.¹⁸

Ascertainment of Vital Status

Mortality surveillance involved the checking of obituaries in local newspapers and quarterly receipt of listings of all deaths in Sonoma County, CA. When subjects could not be located at the time that they were scheduled for follow-up evaluation, we (1) contacted next-of-kin/friend, (2) contacted physicians/health care providers, and (3) searched the Social Security Death Index. All death certificates were reviewed by 1 of the investigators (I.B.T.).

Analysis of Data

The goal of our analysis was to estimate the causal effect of leisure-time physical activity during the year preceding a given survey on all-cause mortality in the 2 years following the survey (730 days). In particular we were interested in how this effect is modified by 3 variables: age (<75 years vs. ≥75 years), the presence of heart disease, and whether subjects used to exercise habitually in the years prior to cohort entry.

A structural assumption is needed to estimate the causal effect of a treatment variable A measured at some time point t (denoted by $A(t)$) on a subsequently measured outcome. One must assume that at time t , any measured covariates L (denoted by $L(t)$) that may confound the relationship between $A(t)$ and the outcome cannot be influenced by the treatment $A(t)$. The treatment variable physical activity was measured over the entire year preceding a given survey, which makes it possible that some of the potential confounders measured at the same interview have been influenced by the subject's physical activity level over the past year. We addressed this problem by redefining $L(t)$ as the collection of covariates measured at interview $t - 1$ rather than at interview t . In addition, we used the available information to define a collection of covariates $L(0)$ that precedes treatment at baseline (see eAppendix [p. 1], <http://links.lww.com/A979>). If we let M_t denote the time point at which interview t is conducted and let $V(t)$ denote the effect modifiers of interest (past physical activity, age, and presence of heart disease) measured at interview t , we thus have the following time ordering at each interview t : $L(t)$ and $V(t)$ precede $A(t)$, which in turn is measured over the year preceding M_t . The outcome of interest is given by the occurrence of death in the 730 days following M_t .

Our analysis is based on marginal structural models (MSMs), a relatively recent approach to causal inference that was first introduced by Robins et al.²³ This approach defines causal effects within the framework of counterfactual outcomes, that is, outcomes that we would have observed had subjects, possibly contrary to the fact, followed a particular treatment history of interest. In the context of the Sonoma study, an MSM might be used to study counterfactual mortality risks over the 2 years following the baseline interview under the hypothetical scenario in which all subjects follow a given leisure-time physical activity regimen, a , during the year preceding the baseline interview, where a can be either “low” or “high.” History-adjusted MSMs, a recent generalization of MSMs,¹⁵ allow this approach to be applied to later time points as well. Such models allow the study of counterfactual mortality risks over the 2 years following the interview at time point t under the hypothetical scenario in which all subjects follow their observed exercise history up until 1 year before that interview and then follow a given activity regimen, a , during the year immediately preceding the interview.

The counterfactual 2-year mortality risk corresponding to treatment level a at time point t is denoted by $\theta(a, t) = \Pr(T_{A(t-1)a}^- \leq M_t + 730 | T_{A(t-1)}^- > M_t)$, where $T_{A(t-1)a}^-$ denotes the survival time for a subject whose activity regimen through time point $t - 1$ corresponds to his or her observed exercise history $\bar{A}(t - 1)$ and whose physical activity at time point t is set to a . To study effect modification by $V(t)$, we can consider the same parameter in strata

defined by $V(t): \theta(a, v, t) = \Pr(T_{A(t-1)a}^- \leq M_t + 730 | T_{A(t-1)a}^- > M_t, V(t) = v)$. Each of these t -specific parameters could be estimated by fitting a corresponding MSM at time point t . If we assume that the stratum-specific effects of current leisure-time physical activity on 2-year mortality are identical for all 4 time points, we can estimate the underlying time-independent parameters with increased precision by pooling the separate t -specific parameters across time points. History-adjusted marginal structural models allow us to do just that. Specifically, we define the common counterfactual 2-year mortality risks $\beta(a, v)$ as a weighted average of the time-specific risks, with weights given by the number of observations $n(t, v)$ at each time point that are available in stratum $V(t) = v$:

$$\beta(a, v) = \frac{\sum_{t=0}^3 n(t, v) \theta(a, t, v)}{\sum_{t=0}^3 n(t, v)}.$$

Given these stratum-specific counterfactual mortality risks, one way to define the causal effect of current leisure-time physical activity on mortality in stratum v is through the excess risk $ER(v) = \beta(1, v) - \beta(0, v)$. Additive interaction between $V(t)$ and $A(t)$ can then be examined by comparing $ER(v)$ across strata of v . Multiplicative interaction could similarly be examined on the basis of corresponding relative risks, but additive interaction is typically of greater interest in the context of the counterfactual framework for causal inference.²⁴ The presence of additive statistical interaction, for example, implies that there exist members in the study population that display genuine synergism or antagonism between the effect modifier and treatment of interest, a statement that is not true for multiplicative interaction.²⁵

Counterfactual mortality risks can be estimated from the observed data under 3 fundamental assumptions: (1) The observed data on a given subject represent the counterfactual data we would have observed had the subject been assigned to the observed treatment history (consistency assumption); (2) the data set contains all covariates that are associated with treatment assignment or drop-out and have an independent causal effect on all-cause mortality (assumption of no unmeasured confounding); and (3) regardless of their observed covariate history, all subjects have a nonzero probability of choosing low or high leisure-time physical activity at each time point (assumption of experimental treatment assignment). Although a number of covariates beyond those included here might be suspected to confound the relationship of interest (diet, for example), the assumption of no unmeasured confounding is nonetheless likely to be reasonably well approximated because, with the exception of the baseline interview, we are always able to adjust for leisure-time physical activity at earlier interviews, a covariate that is highly predictive of current physical activity and likely to capture a large amount of otherwise unmeasured confounding. That is, at each time point t , effect estimates are adjusted not just for the entire history of covariates $L(0), \dots, L(t)$ available at t , but also the history of past treatment $A(0), \dots, A(t-1)$ available at $t-1$. We used a simulation-based approach to evaluate the validity of the experimental treatment assignment assumption and found that this assumption also appears to hold (see eAppendix [pp 4–6] and eTable 3, <http://links.lww.com/A979>).

Estimation of the t -specific counterfactual mortality risks $\theta(a, v, t)$ is based on Inverse-Probability-of-Treatment Weighting (IPTW).²⁶ At each time point t , the available subjects are weighted by the inverse of an estimate of the conditional probability that they would have selected their observed treatment level $A(t)$, given measured confounders; this leads to a down-weighting of observations that were likely to have selected their observed treatment level and an up-weighting of those that, instead, were unlikely to have selected their observed treatment level.²⁷ Essentially, this creates a new sample in which treatment assignment is independent of the measured confounders, which makes it straightforward to estimate counterfactual mortality risks by the observed mortality risk in this reweighted sample. We use a similar Inverse-Probability-of-Censoring Weighting (IPCW) approach to adjust for potentially informative drop-out.²⁸ Specifically, at each time point t , the available subjects are weighted by the inverse of an estimate of the conditional probability of having remained in the study population through interview t , given measured confounders. This weighting step aims to create a reweighted sample that is representative of an ideal study, in which drop-out is independent of the measured confounders. The t -specific counterfactual mortality risks can then be estimated by the observed mortality risk in a sample in which the available subjects have been weighted by the product of their IPTW and IPCW weights.²³ Estimates of $\beta(a, v)$ can be obtained as weighted averages of the t -specific estimates, using the weights given in the definition of $\beta(a, v)$. Excess risk estimates are then simply a matter of taking the difference between estimates for $\beta(1, v)$ and $\beta(0, v)$.

Bootstrap percentile confidence intervals for these excess risk estimates are reported based on 2500 resampling iterations. To examine formally the possibility of effect modification by V , we test null hypotheses of the form $H_0: (\beta(1, v_1) - \beta(0, v_1)) - (\beta(1, v_2) - \beta(0, v_2)) = 0$, where v_1 and v_2 are 2 different values for V . Specifically, we perform a 2-sided z -test based on the observation that under H_0 the estimate of this difference of excess risks will asymptotically follow a normal distribution $N(0, \sigma^2)$, where σ can be estimated by the variance of the corresponding bootstrap estimates.

The IPTW-IPCW estimator relies on consistent estimates of the conditional treatment selection and drop-out probabilities to give consistent estimates of the causal parameter of interest. Because misspecified parametric models for these nuisance parameters will lead to inconsistent estimation of the nuisance parameters and, thus, inconsistent estimation of the causal parameters of interest, we avoid the assumption of an a priori-specified functional form and, instead, use a data-adaptive model selection algorithm based on polynomial spline functions²⁹ to fit the corresponding logistic regression models (eAppendix [pp 2–4], <http://links.lww.com/A979>).

RESULTS

Table 1 summarizes the number of subjects who died and/or were lost to follow-up between surveys along with the resulting number of available subjects at each survey. Subjects younger than 75 years at a given survey contributed 62% (3838/6216) of the observations in the pooled data set but only 24% (82) of the 343 deaths (Table 2). For subjects younger than 75, more than one-half in each heart disease and precohorts exercise category reported levels of physical activity that met or exceeded current recommendations in the time interval up to

any given survey (Table 2). The pattern was less consistent for those 75 years or older. Not surprisingly, those with underlying heart disease in both age groups were more likely to rate their health as “fair” or “poor” compared with those without self-reported cardiac disease.

The logistic regression models selected to estimate the treatment selection and drop-out probabilities needed for the IPTW-IPCW weights are presented in the eAppendix (pp 2–4, <http://links.lww.com/A979>). Current physical activity at the baseline interview was predicted based on measures of precohort entry physical activity (participation in vigorous physical activity over ages 15–20 and ages 40 until cohort entry; participation in moderate physical activity over ages 40 until cohort entry), age, sex, and recent declines in physical activity were included. At later time points, current activity at earlier interviews was selected as the primary predictor, along with a measure of physical functioning, age, and BMI. Age was included in 2 of the 3 censoring models; smoking history, use of antidepressant medication, and presence of a chronic health condition appeared in the censoring model for the last follow-up interview.

Table 3 shows that point estimates for the excess risk associated with meeting the leisure-time physical activity recommendation of at least 22.5 METs/wk were smaller than zero among all subgroups of interest in which subjects were younger than 75 years (see eTable 4 for estimates of absolute 2-year mortality risks, <http://links.lww.com/A979>). Among these subgroups, point estimates ranged from –0.7% to –4.9%, but all of these excess risks were estimated rather imprecisely, most likely due to the small number of deaths (81) in this age group.

Among subjects 75 years or older, the excess risk of interest was estimated to be less than zero for those who reported neither heart disease nor habitual prior exercise (–7.8%; 95% CI = –13.0% to –3.3%), those who reported both (–14.7%; –26.8% to 0.7%), and those who reported habitual prior exercise, but no heart disease (–10.2%; –17.9% to –4.2%). The estimated excess risk among older subjects who had a history of cardiac disease but not habitual prior exercise (17.8%; –7% to 43.4%), although not very precise, seemed to suggest that higher levels of recent physical activity increased all-cause 2-year mortality in this group. This point estimate was heavily influenced, however, by 3 subjects aged 86, 90, and 94 at last interview who had very low physical functioning scores, went from no activity (2 cases) or low activity (1 case) at baseline to activity ≥ 22.5 METs, and died within 2 years of reporting the higher level of exercise. When these 3 subjects were excluded, the excess risk estimate for this group was –2.7% (–13.3% to 6.2%).

Among subjects without heart disease, current leisure-time physical activity was estimated to have a greater beneficial effect among older subjects than among younger ones (–7.8% vs. –1.5% for subjects without a history of habitual exercise; and –10.2% vs. –0.7% for subjects with a history of habitual exercise). The corresponding *P*-values for interaction (see eTable 5, <http://links.lww.com/A979>) are 0.04 and 0.01, respectively, so that these estimates provide fairly strong evidence for additive interaction between age and current leisure activity among subjects without heart disease. Among subjects who reported heart disease as well as a history of habitual activity, a similar trend was observed (–14.7% vs. –4.9%) although the corresponding *P*-value for interaction is quite large (*P* = 0.32). In 3 of 4

comparison groups, the beneficial effect of current leisure-time physical activity is estimated to be stronger among subjects with heart disease than among those without heart disease, but the corresponding *P*-values are all considerably greater than 0.20 (eTable6, <http://links.lww.com/A979>). The data similarly provide little evidence for an interaction between current activity and a history of habitual activity (eTable 7, <http://links.lww.com/A979>).

CONCLUSIONS

Our data provide evidence that current levels of leisure-time physical activity in the elderly lead to decreased all-cause mortality rates. Among subjects without heart disease, there was evidence that this beneficial effect is greater among older subjects than younger ones. There was little evidence, however, that the effect is modified by a history of habitual exercise prior to cohort entry or the presence of heart disease. This latter observation was somewhat surprising, given the expected secondary benefits attributed to exercise in people with overt cardiac disease.^{13,14} Data from many of these latter studies are not comparable to our population sample, however, in that they have included only patients with known heart disease.

Our findings agree qualitatively with earlier studies that focused only on physical activity during cohort time^{5–7,9–12} as well as with studies that specifically tried to determine if there was any interaction between past and current levels of physical activity with respect to mortality.^{4,8} The analysis reported here, however, represents a valuable contribution to this area of research because it is based on an analytic approach that provides effect estimates that have a clearer causal interpretation and that are less likely to be biased than effect estimates based on alternative approaches.

Many earlier analyses were based on Cox proportional hazards models. This approach could be used to model the hazard of mortality as a function of leisure-time physical activity, effect modifiers, and confounders as measured at baseline, thus allowing one to estimate the effect of leisure activity on mortality within strata defined by the included effect modifiers and confounders (see eTable 8 for the results of such an analysis, <http://links.lww.com/A979>). Note that a marginal structural model analysis, by contrast, provides effect estimates within strata that are defined solely by the specified effect modifiers because confounding is addressed entirely through weighting rather than through the inclusion of additional covariates in the main regression model. Moreover, in contrast to a history-adjusted MSM, such a Cox model would be restricted to the examination of interaction on a multiplicative scale and would not make use of any covariates measured after the baseline interviews.

One might address the latter issue by fitting a Cox proportional hazards model with time-dependent covariates, thus modeling the risk of all-cause mortality as a function of leisure-time physical activity, effect modifiers, and confounders at the most recent interview rather than at the baseline interview (see eTable 9 for the results of such an analysis, <http://links.lww.com/A979>). An issue with this approach is that, although the values of covariates used to model mortality risk are allowed to change over time, the actual collection of covariates included in the model is not, that is, one would only be able to make use of covariates that are available at the baseline interview. In particular, at later time points one

would not be able to adjust for current physical activity as recorded at earlier time points because such information is not available at the baseline interview. Because such a treatment history would be highly predictive of current leisure-time physical activity and thus help to adjust for a great amount of confounding, this is a major drawback. History-adjusted MSMs, by contrast, are capable of utilizing the full range of covariates, including the accumulating treatment history, available at each time point because there is no requirement that the treatment selection models fit at different time points have identical functional forms.

A third analysis approach would be based on a conventional MSM, that is, an MSM that models the risk of mortality only during the 2 years following the baseline interview. As with time-independent Cox models, however, such an approach would be wasting the information that was collected at later time points, thus leading to less precise effect estimates (as reflected in the wider confidence intervals seen in the results of such an analysis, summarized in the eTable 10, <http://links.lww.com/A979>).

This study has several limitations, some of which are unique to this study and some generic to all studies of leisure-time physical activity in general. We had relatively few deaths in the younger than 75 age group and, therefore, our estimates for this group are rather imprecise. We had to group subjects with no leisure-time physical activity with those who were active but did not report activities at the recommended levels. Grouping also had to be done for exercisers, and we could not investigate the extent to which higher-level aerobic activity might carry additional mortality-sparing benefits. We cannot be sure what biases these limitations imposed on our estimates. We did not include physical activity due to indoor activities, particularly those that relate to housework. When stratified by age groups, the percentage of subjects who reported heavy housework was nearly identical across the heart disease/precohort exercise groups. Finally, as with all studies of leisure-time physical activity based on questionnaires and without validation substudies, there is an unquantifiable amount of measurement error in the estimates of physical activity. We do not know the correlation between the errors related to physical activity and errors related to other covariates. Therefore, we cannot be sure of the direction of any bias due to such measurement errors.

In summary, based on marginal structural models, our data are consistent with the view that current levels of physical activity, at or above currently recommended levels, lead to a reduction in all-cause mortality in the elderly. We found some evidence that the mortality-sparing effect of current leisure-time physical activity was greater among older subjects than among younger ones, but no evidence that it differed between subjects with and without antecedent clinical heart disease or subjects with and without a pre-cohort history of habitual leisure-time physical activity. Although maintenance of physical activity throughout life is a desirable public health goal, our data indicate that older persons who have never exercised and are able physically to engage in recommended levels of activity, gain full benefit from such exercise.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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TABLE 1
Available Sample Size at Each Time Point and Number of Subjects Lost in Previous Interval

Interview	No.	Deaths Prior to t	Other Censoring Up to t^d		
			Lost to Follow-up	Refusal	No Leisure-time Physical Activity ^b
Entire cohort sample					
Baseline ($t = 0$)	2074 ^a	0	0	0	0
Follow-up					
$t = 1$	1748	89 ^b	7		17 213
$t = 2$	1356	139	43		8 202
$t = 3$	1098	76	14		30 138
Age 75 y					
Baseline ($t = 0$)	1432	0	0	0	0
Follow-up					
$t = 1$	1253	31	3		13 132
$t = 2$	1033	41	29		7 143
$t = 3$	880	32	10		16 95
Age >75 y					
Baseline ($t = 0$)	642	0	0	0	0
Follow-up					
$t = 1$	495	58	4		4 81
$t = 2$	323	98	14		1 59
$t = 3$	218	44	4		14 43

^a Eighteen subjects not included due to missing physical activity at the baseline interview. Each number is the number of subjects who survived to time point t . Deaths refer to all deaths between any 2 surveys without regard to occurrence within a 730-d interval after a survey.

^b Leisure-time physical activity data missing due to subjects who completed interviews by mail or telephone questionnaire that did not include the detail in the home interview or subjects who could not/would not answer all questions on the home interview. See Methods for how this censoring was addressed.

TABLE 2

Summary of Main Variables of Interest

Variable	Age <75 Y				Age 75 Y			
	Hrt ⁻ , Hab ^{-a}	Hrt ⁻ , Hab ⁺ a	Hrt ⁺ , Hab ^{-a}	Hrt ⁺ , Hab ⁺ a	Hrt ⁻ , Hab ^{-a}	Hrt ⁻ , Hab ⁺ a	Hrt ⁺ , Hab ^{-a}	Hrt ⁺ , Hab ⁺ a
Mortality								
Deaths ^b	45 (2.1%)	15 (1.2%)	13 (4.2%)	9 (4.9%)	112 (9.5%)	63 (9.8%)	61 (17.7%)	25 (12.2%)
No. observations ^c	2216	1288	312	182	1183	344	344	205
Leisure-time physical activity; %								
<22.5 METs	39.7	24.5	40.1	33.0	55.6	42.9	55.5	39.0
22.5 METs	60.3	75.5	59.9	67.0	44.4	57.1	44.5	61.0
Sex; % women	65.4	57.1	42.0	40.7	65.1	57.4	54.7	40.5
Age y; (percentiles) ^c ; %								
0th	54	54	55	55	75	75	75	75
25th	63	62	66	65	77	77	77	77
50th	67	67	70	69	80	80	81	80
75th	71	71	72	72	84	84	84	83
100th	75	75	75	75	103	98	98	95
NRB ^d (percentiles) ^c ; %								
0th	0	0	0.17	0.16	0	0	0	0
25th	0.84	0.84	0.74	0.77	0.60	0.65	0.53	0.62
50th	1	1	0.90	1	0.84	0.88	0.78	0.84
75th	1	1	1	1	1	1	1	1
100th	1	1	1	1	1	1	1	1
Self-reported health; %								
Excellent	38.5	44.4	17.6	20.9	29.3	31.7	10.5	14.6
Good	49.0	43.6	55.8	41.2	53.2	48.8	52.6	51.2
Fair	10.4	10.2	21.5	31.9	14.1	14.6	28.5	23.9
Poor	2.1	1.9	5.1	6.0	3.4	5.0	8.4	10.2

^aSee Methods for definition; NRB indicates summary measure of physical functioning over the past month; Hrt, previous self-reported cardiac event—see Methods; Hab, Exercise prior to entry into cohort—see Methods; -, absent, +, present—see Methods.

^bDeaths restricted to those that occurred 730 days since last follow-up for all surveys for subjects in category; total number of deaths = 343. This includes only those deaths that occurred within 730 days after an interview date, ie a subject whose interviews were separated by 3 years and who died 2.5 years after the preceding interview would not be counted as death in this table.

^cNumber of observations across all 4 surveys that fall into category.

TABLE 3

Estimated Excess Risk for the Effect of Physical Activity on 2-Year All-cause Mortality Based on a Marginal Structural Model Pooled Over 4 Time Points

Age	75 ^a	Cardiac Disease ^a	Habitual Activity ^a	Deaths/Population ^b	Estimated Excess Risk ^c (95% CI)
–		–	–	45/2116	–1.5% (–3.1% to 0.3%)
–		–	+	15/1288	–0.7% (–2.6% to 1.1%)
–		+	–	13/312	–2.9% (–9.0% to 2.8%)
–		+	+	9/182	–4.9% (–21.8% to 5.2%)
+		–	–	112/1183	–7.8% (–13.0% to –3.3%)
+		–	+	63/646	–10.2% (–17.9% to –4.2%)
+		+	–	61/344	17.8% (–7.0% to 43.4%) ^d
+		+	+	25/205	–14.7% (–26.8% to 0.7%)

^a As recorded at the time of a given interview; –, absent; +, present; see Methods for definitions.

^b Deaths and populations pooled across all 4 time points.

^c For each time point t , the excess risk compares the 2 hypothetical scenarios under which all study participants are allowed to follow their observed activity pattern prior to interview t before being assigned, for 1 year, to either high or low activity. The reported excess risks are weighted averages of the 4 t -specific estimates (see Methods) and compare the risk of all-cause mortality in the 730 days following a survey for physical activity 22.5 METs to the corresponding risk for physical activity <22.5 METs.

^d When 3 subjects aged 86, 90, and 94 are omitted (see text), the excess risk estimate for this group is –2.7% (95% CI = –13.3% to 6.2%).