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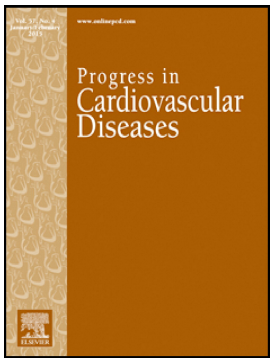

Temporal changes in personal activity intelligence and mortality: Data from the aerobics center longitudinal study

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Temporal Changes in Personal Activity Intelligence and Mortality: Data from the Aerobics Center Longitudinal Study

Brief title: Changes in PAI and mortality

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Abstract

Background: Personal activity intelligence (PAI) is a metric developed to simplify a physically active lifestyle for the participants. Regardless of following today's advice for physical activity, a PAI score ≥100 per week at baseline, an increase in PAI score, and a sustained high PAI score over time were found to delay premature cardiovascular disease (CVD) and all-cause mortality in a large population of Norwegians. However, the association

between long-term temporal change in PAI and mortality in other populations have not been investigated.

Objective: To test whether temporal change in PAI is associated with CVD and all-cause mortality in a large population from the United States.

Methods: We studied 17 613 relatively healthy participants who received at least two medical examinations in the Aerobics Center Longitudinal Study between 1974 and 2002. The participant's weekly PAI scores were estimated twice, and adjusted hazard ratios (AHR) and 95% confidence intervals (CI) for CVD and all-cause mortality related to changes in PAI between baseline and last examination were assessed using Cox proportional hazard regression analyses.

Results: During a median follow-up time of 9.3 years [interquartile range, 2.6-16.6; 181,765 person-years], there were 1144 deaths, including 400 CVD deaths. We observed an inverse linear association between change in PAI and risk of CVD mortality (P=0.007 for linear trend, and P=0.35 for quadratic trend). Compared to participants with zero PAI at both examinations, multivariable-adjusted analyses demonstrated that participants who maintained high PAI scores (≥100 PAI at both examinations) had a 51% reduced risk of CVD mortality [AHR, 0.49: 95% CI, 0.26-0.95)], and 42% reduced risk of all-cause mortality [AHR, 0.58: 95% CI, 0.41-0.83)]. For participants who increased their PAI scores over time (PAI score of zero at first examination and ≥100 at last examination), the AHRs were 0.75 (95% CI, 0.55-1.02) for CVD mortality, and 0.82 (95% CI, 0.69-0.99) for all-cause mortality. Participants who maintained high PAI score had 4.8 (95% CI, 3.3-6.4) years of life gained. For those who increased their PAI score over time, the corresponding years gained were 1.8 years (95% CI, 0.1-3.5).

Conclusion: Among relatively healthy participants, an increase in PAI and maintaining a high PAI score over time was associated with reduced risk of CVD and all-cause mortality.

Keywords: physical activity, mortality, cardiovascular disease, exercise, activity metric.

Condensed Abstract

Our objective was to investigate the association between temporal changes in PAI and mortality in a large population from the United States. In this prospective cohort study of 17,613 relatively healthy participants at baseline, maintaining a high PAI score and an increase in PAI score over an average period of 6.3 years was associated with a significant reduction in CVD and all-cause mortality. Based on our results, clinicians can easily recommend that patients obtain at least 100 PAI for most favourable protection against CVD- and all-cause mortality, but can also mention that significant benefits also occur at maintaining low-to-moderate PAI levels.

Abbreviations and acronyms

ACLS = Aerobics Center Longitudinal Study
BMI = body mass index
BP = blood pressure
CI = confidence interval
CVD = cardiovascular disease
DBP = diastolic blood pressure
HR = hazard ratio
PA = physical activity
PAI = personal activity intelligence
QoL = quality of life
SBP = systolic blood pressure

Introduction

Population growth, aging and the increase in non-communicable diseases (NCDs) around the world are amongst the primary drivers of healthcare costs [1, 2]. It is projected that global healthcare spending will continue to increase [3], with societies struggling to afford the mounting costs [4]. This has caused a shift of focus away from “sick”, “reactive” care to one of

"health", "proactive" care, where the emphasis is placed on disease prevention and promotion of overall well-being, and implementation of forecasting analytics that may help to optimize healthcare spending, and improve government and private sector actions to promote population health [5, 6].

Physical activity (PA) is crucial in healthcare promotion [7, 8]. The World Health Organization (WHO) appropriately identifies insufficient PA as one of the leading risk factors for NCDs and death, and adequate levels of PA may serve as a low-cost non-prescription therapy for prevention of hypertension, overweight, and obesity, and for improvement of mental health and quality of life (QoL) [9, 10]. Regular exercise may also improve immune function across the lifespan [11]. Unfortunately, more than 1.4 billion people around the world are not sufficiently physically active, which puts them at risk of developing or worsening inactivity related diseases [12]. As one of the nine global targets to improve the prevention and treatment of NCDs, the WHO member countries agreed to work on reducing physical inactivity by 10% by the year 2025 [13], but sadly that goal is not likely to materialise [12]. Lack of time and inability to self-manage are often reported as barriers to PA participation [14-17].

New technologies have the potential to revolutionize health care delivery, remote patient monitoring, and health management. Ideally, they would also improve equitable access to quality health care. However, it is challenging to identify the best use of technology to ensure that it can deliver real patient/consumer benefit and support its adoption [18]. With patients and consumers taking more active roles in their own healthcare, the healthcare providers with an understanding of what patients/consumers expect from new emerging health technologies (such as wearables promoting physically active lifestyle) will likely be better positioned to

develop sustainable patient/consumer engagement strategies and ultimately lead them to better informed healthcare decisions [18].

Personal activity intelligence (PAI) is a metric developed to simplify a physically active lifestyle for the patient/consumer. PAI takes into account individual's age, sex, resting and maximal heart rate, and heart rate response to PA, in order to translate it into a simple to understand score (0 PAI = inactive, and 100 PAI = active enough) [19]. The score informs the patient/consumer if they have performed sufficient PA to prevent NCDs, and reduce risk for premature death as well as increased functional capacity and QoL. A PAI score of 100 can be obtained through a combination of PA of different volume and intensity, as per individual preference, as long as the heart rate is elevated above a certain threshold. PAI has been integrated into a self-assessment heart rate device and/or Health-Apps and translates heart rate variations over the course of a week into a simple and easily understandable score [19, 20].

Previous studies on PAI in relatively healthy populations have shown that, compared to inactive individuals, those who attained a weekly score of at least 100 PAI had lower risk of cardiovascular (CVD) and all-cause mortality, regardless of whether the PA recommendations were met [20, 21]. Similar findings were reported in those with CVD [22]. Importantly, improvement in PAI score over time was associated with reduced risk of CVD and all-cause mortality in an apparently healthy Norwegian cohort [23]. However, to date, the association between change in PAI and mortality is investigated in a relatively homogenous population of Norwegians, as such, generalization of the findings to other settings and populations is currently limited [23]. Therefore, the aim of the current study was to examine the association between change in weekly PAI score over time and both CVD and all-cause mortality in a

large United States (US) population from the Aerobics Center Longitudinal Study (ACLS) cohort at the Cooper Clinic (Dallas, Texas, USA) [24, 25].

Methods

Study Population

The ACLS is a population based observational study of mostly Caucasian men and women, from middle to upper socioeconomic strata, who underwent preventive medical examinations during 1974-2002 at the Cooper Clinic (Dallas, Texas, USA) [24]. Study participants came to the clinic for periodic preventive health examinations and for counselling regarding diet, exercise, and other lifestyle factors associated with increased risk of chronic diseases. The majority of the participants were sent by their employers, some were referred by their personal physicians, and others were self-referred.

To examine the association between change in PAI and both CVD and all-cause mortality, we included ACLS participants who received at least two medical examinations (n=22,006). For those attending more than two examinations, we used the first and last examinations, and followed participants for subsequent mortality after the last examination (baseline for follow-up). The aim of this study was to follow-up individuals with varying health phenotypes at baseline, therefore, our exclusion criteria included: 1) a history of cancer (n=893) or CVD (n=360); 2) a body mass index (BMI) below 18.5 $kg.m^{-2}$ (n=417); 3) participants with less than 1 year of follow-up (n=939); and 4) participants with missing data on PA (n=1784). In total, data on 17 613 participants (14 371 men, 3242 women) was included for mortality analyses (**Figure 1**). All participants signed informed consent, and the Cooper Institute Institutional Review Board approves the study protocol annually.

Clinical Characteristics: Measurements and Questionnaire-Based Information

All participants underwent measurements after an overnight fast. Measurements included height and weight, blood pressure (BP), blood chemistry, physical examination, and a detailed questionnaire on medical history. Resting systolic BP (SBP) and diastolic BP (DBP) were measured after at least 5 minutes of seated rest using standardized auscultation method. Average of at least two BP readings, separated by 2 minutes, was recorded. Hypertension was defined as history of hypertension or SBP/DBP ≥140/90 mmHg. Automated bioassays in the Cooper Clinic laboratory were used to analyse blood chemistry. Hypercholesteremia was defined as total cholesterol ≥240mg/dl or history of hypercholesterolemia. Diabetes was defined as history of diabetes, current treatment for diabetes or fasting glucose ≥126 mg/dl.

Personal Activity Intelligence

Self-reported questionnaires were used to record information on leisure time or recreational PA. The questionnaire was based on 10 specific activities: 1) walking; 2) treadmill exercise; 3) jogging; 4) running 5) cycling: 6) stationary cycling; 7) racquet sports; 8) swimming; 9) aerobic dance; and 10) other sports-related activities (e.g. soccer or basketball). Study participants were asked to provide information on activity frequency and duration, as well as speed (time per mile) for activities such as walking, running, treadmill exercise and cycling. Intensity of PA was estimated using speed-specific or activity-specific metabolic equivalence of task (MET) available from the Compendium of Physical Activities [26, 27]. Responses from PA questionnaire on duration, frequency, and intensity were used to calculate PAI score for each participant [19, 20]. The major assumptions underlying the PAI metric have robust scientific background, and include a threshold of exercise intensity after which PAI can be accumulated as very low intensity does not contribute to increased cardiorespiratory fitness, non-linear

scaling of exercise intensity as fewer exercise sessions of higher intensities are associated with similar or improved health benefits compared with frequent sessions at low intensity activity where it is easier to earn first 50 PAI vs next 50 PAI because of exercise induced lowering of resting as well as submaximal or maximal heart rates, and the evidence that moving from an inactive state to an active one is associated with a relatively larger reduction in mortality [20]. To calculate the PAI, weekly minutes spent performing PA were obtained by multiplying the average frequency with the average duration, and reported PA intensity was translated into relative PA intensity (% of heart rate reserve). Exercise volumes were then combined with intensity of exercise using heart rate reserve to estimate the weekly PAI score. For example, a score of 100 PAI can be obtained by combining 60 weekly minutes of brisk walking, 40 weekly minutes of cycling, 50 weekly minutes of swimming, 30 weekly minutes of dancing/aerobics, and 20 weekly minutes of running. Furthermore, performing 150 weekly minutes at light intensity exercise (~44% heart rate reserve) contributes to approximately 38 PAI. The recommended amount of 100 PAI can be achieved by a minimum of 40 weekly minutes of vigorous intensity exercise (~85-90% heart rate reserve), or a combination of exercises at varying intensities according to personal preferences [20].

Assessment of Outcomes

Study participants were followed from baseline to the date of death or 31st December 2003, whichever came first. National Death Index (NDI), an accurate method of ascertaining death in observational studies with high sensitivity (86%) and specificity (100%) was used as a basis of mortality surveillance [28]. The primary endpoint was mortality caused by CVD (International Classification of Diseases, 9th revision (ICD-9) codes 390 to 449.9 before 1999,

and 10th revision (ICD-10) codes I00 to I78 during 1999-2003, and the secondary endpoint was all-cause mortality.

Statistical Analyses

Descriptive data are reported as mean (SD) for continuous variables and number (%) for categorical variables. To compare baseline characteristics of study participants, chi square test and regression analyses were used for categorical and continuous variables, respectively. To assess the association between change in PAI and mortality, we used the following categories of change between the first and last examinations: 0 PAI at both time points, 0 PAI to 1-99 PAI, and 0 PAI to ≥100 PAI from time point 1 to time point 2, respectively; 1-99 at both time points, 1-99 PAI to 0 PAI, and 1-99 PAI to ≥100 PAI from time point 1 to time point 2, respectively; and ≥100 PAI at both time points, ≥100 PAI to 0 PAI, and ≥100 PAI to 1-99 PAI from time point 1 to time point 2, respectively. The choice of these cut points was made "*a priori*" based on previous reports [19, 23], and further extended to investigate the association between change in PAI and mortality. We used Cox proportional hazard regression analyses to assess the association between PAI score change and mortality. The basic model was adjusted for age, number of clinical visits and number of years between the first and last examination, and stratified by sex (interaction test for sex: *P*-value for CVD death = 0.86, *P*-value for all-cause death = 0.84). The model was further adjusted for combination pattern of changes in BMI, smoking status, hypertension, diabetes, and hypercholesterolemia between the first and last examination, and parental history of CVD (yes/no) at last examination. The final model was further adjusted for PAI score at first examination. We defined four combination patterns of BMI (<25 and<25, <25 and ≥25, ≥25 and <25, or ≥25 and ≥25 $kg.m^{-2}$), smoking (remained non-smokers, became smokers, became non-smokers, or

remained smokers), and three combination patterns of each medical condition (e.g., remained normotensive, became hypertensive, or remained hypertensive) at the two examinations [29]. Proportional hazard assumption was tested and satisfied using Schoenfeld residuals, and by addition of time interactions with the covariates.

In a separate analysis, we estimated the change in PAI as continuous variable as the difference between the first and last examinations, divided by the number of years between the two examinations, and included the squared value of PAI change to assess the nonlinear trend. The time intervals between the two examinations varied among our participants; therefore, we used change in PAI per year as our exposure variable for these analyses. To allow visual assessment of the trend, we used the following categories of change in PAI: a decrease of greater than 25 PAI, a decrease between 6 and 25 PAI, a change from −5 to 5 PAI, an increase between 6 and 25 PAI, and an increase of greater than 25 PAI. We also used Laplace regression [30, 31], adjusted for sex to estimate the years of life gained as the difference in survival years associated with the different PAI change groups.

We conducted several stratified analyses to investigate whether the association of change in PAI with mortality could be modified by other factors. For instance, we assessed the potential effect modification by sex, age (dichotomized at the age of 60 years), BMI (<25, ≥25 $kg.m^{-2}$), smoking status (yes, no), diabetes (yes, no), hypertension (yes, no), hypercholesterolemia (yes, no), and parental history of CVD (yes, no).

Results were reported as adjusted hazard ratios (AHR) with 95% confidence intervals (CI) as precision estimates. We also calculated the rate of death per 1000 person-years. All statistical tests were two-sided, and $P<0.05$ was considered statistically significant. We used

Stata statistical software (version 15.1, StataCorp, College Station, TX, USA) for all statistical analyses.

Results

The characteristics of study participants according to temporal changes in PAI are presented in **Table 1**. Participants who increased their PAI or maintained high PAI scores between both time points were younger (mean age 48.5 years for those who maintained ≥100 PAI and 50.4 years for those who increased their PAI over time), and appeared to be healthier (i.e., low BMI, lower percentage of hypertension, diabetes, hypercholesterolemia, and current smoking status) compared with participants with low PAI scores. Men tended to maintain higher PAI scores (63% vs 55.2%) or increase in PAI (25.6% vs 17%) between two time points compared to women.

During a median follow-up time of 9.3 years [interquartile range, 2.6-16.6; 181,765 person-years], there were 1144 deaths including 400 deaths caused by CVD. Compared with participants with zero PAI at both examinations, multivariable-adjusted analyses demonstrated that participants who maintained high PAI scores (≥100 PAI at both examinations) had a 51% reduced risk of CVD mortality (AHR, 0.49: 95% CI, 0.26-0.95), and 42% reduced risk of all-cause mortality (AHR, 0.58: 95% CI, 0.41-0.83). For participants who increased their PAI scores over time (PAI score of zero at first examination and ≥100 at last examination), the AHRs were 0.75 (95% CI, 0.55-1.02) for CVD mortality, and 0.82 (95% CI, 0.69-0.99) for all-cause mortality. Participants who maintained a PAI score between 1 and 99 at both examinations had a 45% (AHR, 0.55: 95% CI, 0.32-0.97) reduced risk of CVD

mortality, and 28% (AHR, 0.72: 95% CI, 0.53-0.99) reduced risk of all-causes compared to inactive participants at both examinations (**Table 2**).

In the analyses using PAI as a continuous variable, we found an inverse linear association between change in PAI and risk of CVD mortality ($P = 0.007$ for linear trend and $P = 0.35$ for quadratic trend). Compared to participants with an increase of greater than 25 PAI between first and last examinations, participants with a change from −5 to 5 PAI and a decrease of greater than 25 PAI had a 34% (AHR, 1.34: 95% CI, 1.00-1.80) and 87% (AHR, 1.87: 95% CI, 1.13-3.10) increased risk of CVD mortality, respectively (**Figure 2**).

Compared with the inactive participants at both examinations, those who maintained high PAI score (≥100 PAI at both examinations) had 4.8 (95% CI, 3.3-6.4) years of life gained (**Figure 3**). For those who increased their PAI score over time (PAI score of zero at first examination and ≥100 at last examination), the corresponding years gained were 1.8 years (95% CI, 0.1-3.5). For participants who were 60 years or older at first examination, both an increase in PAI and sustaining high PAI scores at both examinations were associated with 4.1 (95% CI, 1.0-7.2) and 6.6 (95% CI, 4.1-9.2) years of life gained, respectively (data not shown).

In separate stratified analyses, the results were not substantially different from the main analyses. These analyses are presented in **sTable 1** and **sFigures 1 to 5** in the Supplemental Material.

Discussion

In this prospective study of apparently healthy men and women from a large US cohort, we found that maintaining a high PAI score and an increase in PAI score over time was

associated with a significant reduction in CVD and all-cause mortality. Moreover, the association between change in PAI and CVD mortality was linear suggesting that an increase in PAI over time was associated with reduced mortality.

The results of our study strengthened the knowledge about PAI and mortality by showing that change in PAI score over time is strongly associated with health and longevity. The main findings of the study that an increase in PAI and maintaining a high PAI score over time was associated with reduced mortality are in line with previous reports [23], indicating that PAI is relevant in diverse settings. In a prospective cohort study of 24 880 healthy Norwegians [23], sustaining ≥100 PAI at both time points was associated with 32% reduced risk of CVD mortality and 20% reduced risk of all-cause mortality. The mortality reduction benefits associated with an increase in PAI score over time were 13% for CVD mortality and 14% for all-cause mortality [23]. Our findings relating to continuous change in PAI and mortality are consistent with the earlier reports investigating temporal changes in PA and mortality [32-35]. For instance, long term increases in PA energy expenditure ($kJ.kg^{-1}.day^{-1}$) were inversely associated with mortality, irrespective of past PA levels and established risk factors [33].

Overwhelming evidence supports the role of regular PA for health outcomes [9, 10]. Unfortunately, a significant percentage of the global population remains physically inactive and leads a sedentary lifestyle [36]. In this context, main barriers to participation in PA have been extensively studied, and research indicates two leading reasons for most of the people not to be physically active on most days of a week: lack of time and inability to self-manage [14-16], making it difficult to meet the PA recommendations from health authorities around the world. The PAI provides individuals with readily available feedback to track their activity

levels using a single, easy-to-understand activity metric. The algorithm also incorporates the fact that the higher the intensity of the activity, the shorter the time needed to obtain 100 PAI. In practical terms, it is an important contribution to the PA science because earlier reports have shown that fewer activity sessions performed at higher intensities provide similar or larger health benefits compared with frequent, low intensity activity of longer durations [10, 37, 38]. However, a recent analysis [39] showed no significant association between step intensity and mortality after adjusting for total daily steps, contradicting the findings of earlier reports that higher walking speeds were associated with lower mortality risk [40, 41]. Of note, total daily steps in the study of US adults [39] were positively correlated with step intensity, suggesting that individuals who took more steps per day tended to have higher step intensity. Nonetheless, future prospective and randomized studies are warranted to investigate the role of PAI and other PA metrics of varying intensities for the CVD risk reduction.

Modern technologies in the healthcare sector have the potential to revolutionize health management now and in the future [18]. According to International Data Corporation, year over year growth of worldwide shipments of wearables (wristbands, smartwatches) has increased by approximately 50% in third quarter of 2019 [42]. The PAI metric is integrated into wearable devices with a downloadable application (compatible with most Bluetooth enabled heart rate monitors), and is freely available worldwide. The PAI data may be shared between clinicians and patients/consumers, and provides an opportunity for the clinicians to track the activity levels of their patients and motivate them to obtain at least 100 PAI for most favourable protection against CVD and all-cause mortality.

Strength and Limitations

A relatively large population-based cohort of healthy men and women from the US, information on a broad range of confounding factors, a large set of major outcomes studied, and long-term follow-up time are the main strengths of the present study. Moreover, we minimized the likelihood of underlying subclinical disease by excluding participants with a history of CVD and cancer, those with a BMI less than 18.5 kg/m^2, and those who died during the first year of follow-up. The study, however, also has some limitations. The ACLS study population is comprised mostly of well-educated, non-Hispanic whites from middle to upper socioeconomic strata, and therefore, may have some similarities with the Norwegian population from which PAI was developed. However, physiologic characteristics of participants from the ACLS were similar with the representative population groups [43] and other large studies from the US [44, 45]. Moreover, socioeconomic homogeneity may reduce the spurious effects of income, education and ethnicity. Nonetheless, the generalizability of the PAI metric in different races, ethnicities across different socioeconomic strata with varying CVD risk still warrants additional investigations. Furthermore, data used to estimate PAI was self-reported and, therefore, prone to information bias. However, the nature of misclassification in prospective studies is most likely to be non-differential in relation to future disease, and therefore likely to yield underestimates of the true effects. Although, analyses were conducted in a relatively healthy population and were controlled for possible known confounders, we acknowledge that unknown underlying factors and lack of data especially about diet and medications use may have introduced some residual and unmeasured confounding.

Clinical Recommendations and Impact

Considering the high prevalence of CVD and the relative lack of effective PA and exercise training in most Westernized populations, these data from a large United States cohort support assessing PAI in clinical practice, as well as efforts to increase PAI or maintain high levels of PAI with PA and exercise training, for the primary prevention of CVD – and all-cause mortality. Clinicians can recommend PAI recommendations and thresholds in their PA prescriptions, mentioning that significant benefits also occur at maintaining 'low-to-moderate PAI' levels. This strategy may be particularly useful in transitioning those who are sedentary to some level of PA that have favourable protection against all-cause and CVD mortality [36, 46].

Conclusion:

In this prospective study of relatively healthy participants from a large US cohort, an increase in PAI and maintaining a high PAI score over time was associated with reduced risk of all-cause and CVD mortality.

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Conflict of interest: Professor Wisløff is the inventor of PAI, and scientific advisor of a company (PAI Health Inc.) that holds the IP rights for PAI and develops applications that utilize data from diverse heart rate monitors to display PAI for users. Due to the potential conflict of interest, Professor Wisløff was not involved in the data acquisition and statistical analyses of the data in the current study. There are no further disclosures or potential conflicts of interest to report.

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Central Illustration. PAI and your Health

Figure 1. Selection of Participants for the Study.

ACLS, Aerobics Center Longitudinal Study; CVD, cardiovascular disease: BMI, body mass index

Figure 2. Death from Cardiovascular Disease by Changes in PAI.

The data markers indicate the hazard ratios and the error bars indicate the 95% confidence intervals. CVD, cardiovascular disease.

[a]Deaths/1000 person-years.

[b]Adjusted for age, number of clinical visits between the first and last examinations, parental cardiovascular disease, combination pattern of changes in confounders (BMI, smoking status, hypertension, diabetes, and hypercholesterolemia) between the first and last examinations, PAI score at first examination, and stratified by sex.

Figure 3. Survival Curves by Changes in Personal Activity Intelligence.

Table 1. Characteristics of study participants according to changes in Personal Activity Intelligence[a]

PAI 1st exam	**0**			**1-99**			**≥100**		
PAI last exam	**0**	**1-99**	**≥100**	**0**	**1-99**	**≥100**	**0**	**1-99**	**≥100**
	(n=4725)	(n=1583)	(n=2006)	(n=997)	(n=1070)	(n=979)	(n=1494)	(n=883)	(n=3876)
Age, mean (SD), y	50.6 (11.1)	53.1 (10.6)	50.4 (10.6)	51.8 (10.8)	52.5 (9.9)	50.2 (10.3)	50.6 (11.1)	52.1 (10.2)	48.5 (9.4)
Female sex, No (%)	993 (21.0)	304 (19.2)	264 (13.2)	228 (22.9)	243 (22.7)	194 (19.8)	291 (19.5)	164 (18.6)	561 (14.5)
Body mass index, No. (%)									
18.5-24.9	1784 (37.8)	614 (38.8)	975 (48.6)	359 (36.0)	432 (40.4)	456 (46.6)	648 (43.4)	358 (40.5)	2039 (52.6)
25.0-29.9	2113 (44.7)	710 (44.8)	849 (42.3)	441 (44.2)	478 (44.7)	427 (43.6)	674 (45.1)	397 (45.0)	1559 (40.2)
≥30.0	828 (17.5)	259 (16.4)	182 (9.1)	197 (19.8)	160 (14.9)	96 (9.8)	172 (11.5)	128 (14.5)	278 (7.2)
Systolic BP, mean (SD), mmHg	121.6 (15.4)	122.7 (15.5)	121.8 (14.7)	122.6 (15.9)	122.1 (14.7)	120.9 (15.1)	122.6 (14.7)	123.2 (16.2)	121.3 (13.9)
Diastolic BP, mean (SD), mmHg	80.9 (9.7)	81.3 (9.6)	80.2 (9.5)	81.7 (10.1)	80.9 (9.40	79.9 (9.4)	81.2 (9.7)	81.7 (9.3)	80.6 (9.2)
Hypertension status, No. (%)[b]									
No	3305 (70.0)	999 (63.1)	1404 (70.0)	667 (66.9)	734 (68.6)	711 (72.6)	1085 (72.6)	582 (65.9)	2862 (73.8)
Yes	1420 (30.0)	584 (36.9)	602 (30.0)	330 (33.1)	336 (31.4)	268 (27.4)	409 (27.4)	301 (34.1)	1014 (26.2)
Smoking status, No. (%)									
Never	2958 (62.6)	990 (62.5)	1195 (59.6)	745 (74.7)	735 (68.7)	667 (68.1)	1163 (77.8)	637 (72.2)	2636 (68.0)
Former	1050	408	622	175	246	237	222	191	931

	(22.2)	(25.8)	(31.0)	(17.6)	(23.0)	(24.2)	(14.9)	(21.6)	(24.0)
Current	717 (15.2)	185 (11.7)	189 (9.4)	77 (7.7)	89 (8.3)	75 (7.7)	109 (7.3)	55 (6.2)	309 (8.0)
Fasting glucose, mean (SD), mmol/L									
	5.6 (1.1)	5.6 (1.3)	5.5 (0.9)	5.5 (0.9)	5.5 (0.9)	5.4 (0.8)	5.4 (0.8)	5.4 (0.8)	5.3 (0.7)
Diabetes, No (%)[c]									
No	4442 (94.0)	1485 (93.8)	1929 (96.2)	927 (93.0)	1004 (93.8)	926 (94.6)	1425 (95.4)	829 (93.9)	3753 (96.8)
Yes	283 (6.0)	98 (6.2)	77 (3.8)	70 (7.0)	66 (6.2)	53 (5.4)	69 (4.6)	54 (6.1)	123 (3.2)
Total cholesterol, mean (SD), mmol/L									
	5.4 (1.5)	5.3 (1.0)	5.2 (1.0)	5.2 (1.0)	5.3 (1.0)	5.2 (0.9)	5.1 (1.0)	5.2 (1.6)	5.1 (0.9)
Hypercholesterolemia, No. (%)[d]									
No	3403 (72.0)	1107 (69.9)	1510 (75.3)	732 (73.4)	729 (68.1)	717 (73.2)	1134 (75.9)	614 (69.5)	2985 (77.0)
Yes	1322 (28.0)	476 (30.1)	496 (24.7)	265 (26.6)	341 (31.9)	262 (26.8)	360 (24.1)	269 (30.5)	891 (23.0)
Parental cardiovascular disease, No. (%)[e]									
No	3603 (76.3)	1153 (72.8)	1455 (72.5)	788 (79.0)	809 (75.6)	731 (74.7)	1204 (80.6)	672 (76.1)	2938 (75.8)
Yes	1122 (23.7)	430 (27.2)	551 (27.5)	209 (21.0)	261 (24.4)	248 (25.3)	290 (19.4)	211 (23.9)	938 (24.2)

PAI, Personal Activity Intelligence; BP, blood pressure.
[a]For all of the trend comparisons, the *P*-values were <0.01 unless otherwise indicated. For linear trend, regression analyses were used for continuous variables; chi2 tests were used for proportions of categorical variables.
[b]Defined as systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg and/or history of hypertension. [c]Defined as fasting glucose ≥126 mg/dl (7.0 mmol/L), current therapy with insulin, or history of diabetes. [d]Defined as total cholesterol ≥240 mg/dl (6.3 mmol/L) or history of hypercholesterolemia. [e]Parental history of premature coronary heart disease and/or stroke.

PAI 1st exam	**0**			**1-99**			**≥100**		
PAI last exam	**0**	**1-99**	**≥100**	**0**	**1-99**	**≥100**	**0**	**1-99**	**≥100**
All-cause deaths	473	138	161	50	47	55	59	33	128
Rate/1000	8.1	8.2	6.5	5.7	5.2	5.7	4.9	5.4	3.5
AHR (95% CI)[a]	1.00 (Reference)	0.90 (0.75-1.10)	0.78 (0.65-0.93)	0.74 (0.55-0.99)	0.70 (0.52-0.95)	0.80 (0.61-1.06)	0.73 (0.56-0.96)	0.75 (0.52-1.07)	0.57 (0.47-0.70)
AHR (95% CI)[b]	1.00 (Reference)	0.92 (0.76-1.11)	0.82 (0.68-0.99)	0.79 (0.59-1.06)	0.74 (0.55-1.01)	0.87 (0.66-1.16)	0.81 (0.62-1.07)	0.85 (0.59-1.21)	0.65 (0.53-0.80)

AHR (95% CI)[c]	1.00 (Reference)	0.92 (0.76-1.11)	0.82 (0.69-0.99)	0.77 (0.57-1.04)	0.72 (0.53-0.99)	0.85 (0.63-1.13)	0.73 (0.50-1.07)	0.76 (0.49-1.18)	0.58 (0.41-0.83)
CVD deaths	181	47	54	19	14	17	21	11	36
Rate/1000	3.1	2.8	2.2	2.2	1.6	1.8	1.7	1.8	1.0
AHR (95% CI)[a]	1.00 (Reference)	0.81 (0.58-1.12)	0.69 (0.50-0.93)	0.69 (0.43-1.11)	0.51 (0.30-0.88)	0.64 (0.39-1.05)	0.68 (0.43-1.07)	0.65 (0.35-1.20)	0.42 (0.29-0.60)
AHR (95% CI)[b]	1.00 (Reference)	0.81 (0.58-1.12)	0.74 (0.55-1.02)	0.71 (0.44-1.15)	0.56 (0.32-0.96)	0.69 (0.42-1.14)	0.78 (0.50-1.24)	0.75 (0.41-1.39)	0.51 (0.35-0.73)
AHR (95% CI)[c]	1.00 (Reference)	0.81 (0.58-1.12)	0.75 (0.55-1.02)	0.71 (0.43-1.16)	0.55 (0.32-0.97)	0.69 (0.41-1.15)	0.77 (0.40-1.47)	0.74 (0.34-1.60)	0.49 (0.26-0.95)

PAI, Personal Activity Intelligence; AHR, adjusted hazard ratio; CI, confidence interval; CVD, cardiovascular disease

[a]Adjusted for age, number of clinical visits and number of years between the first and last examinations, and stratified by sex.

[b]Adjusted for age, number of clinical visits and number of years between the first and last examinations, parental cardiovascular disease, combination pattern of changes in confounders (BMI, smoking status, hypertension, diabetes, and hypercholesterolemia) between the first and last examinations, and stratified by sex.

[c]Adjusted for age, number of clinical visits and number of years between the first and last examinations, parental cardiovascular disease, combination pattern of changes in confounders (BMI, smoking status, hypertension, diabetes, and hypercholesterolemia) between the first and last examinations, PAI score at first examination, and stratified by sex.

Interaction test for sex: *P*-value for all-cause death = 0.84, *P*-value for CVD death = 0.86.

Table 2. Hazard ratios of death by changes in Personal Activity Intelligence

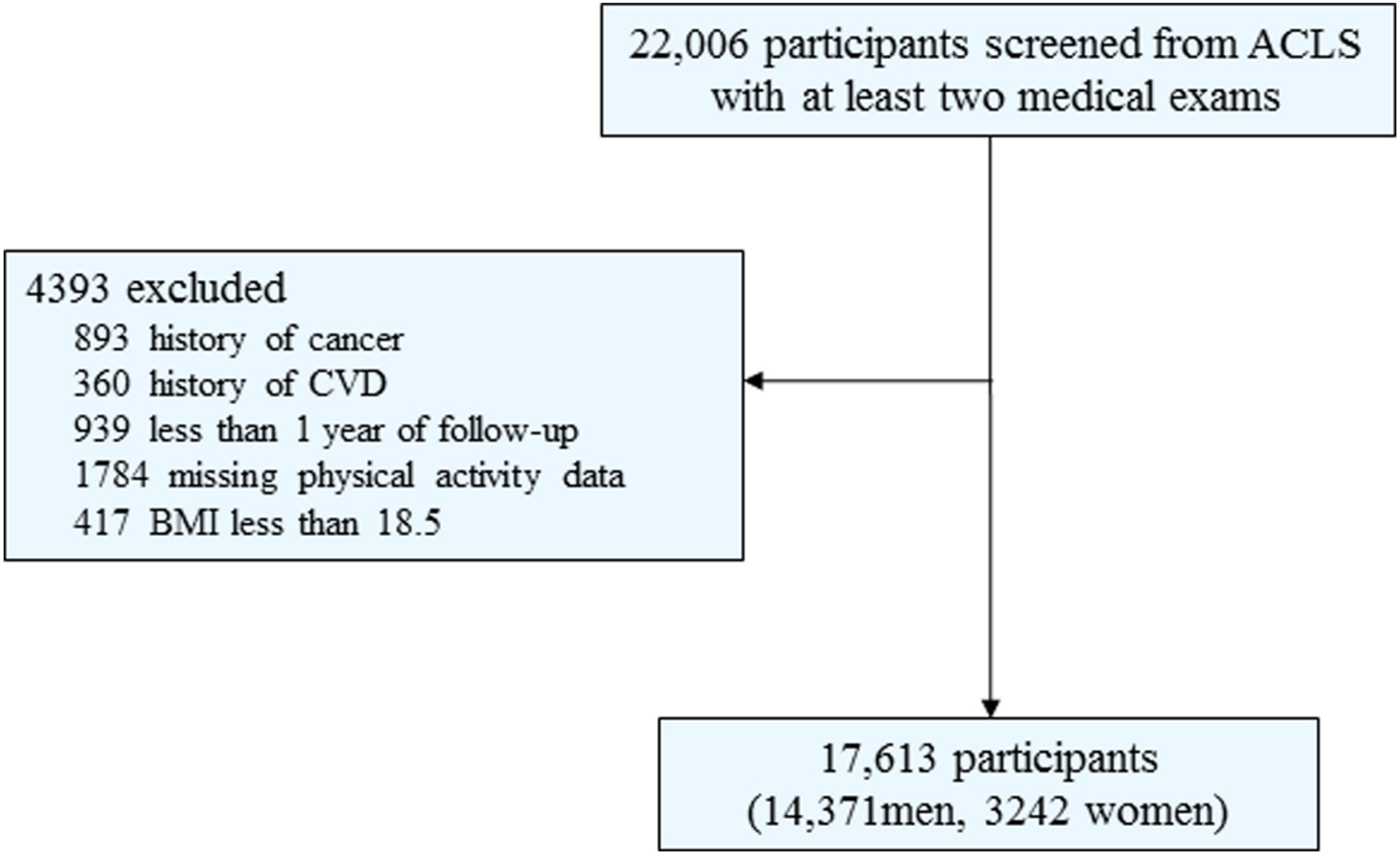
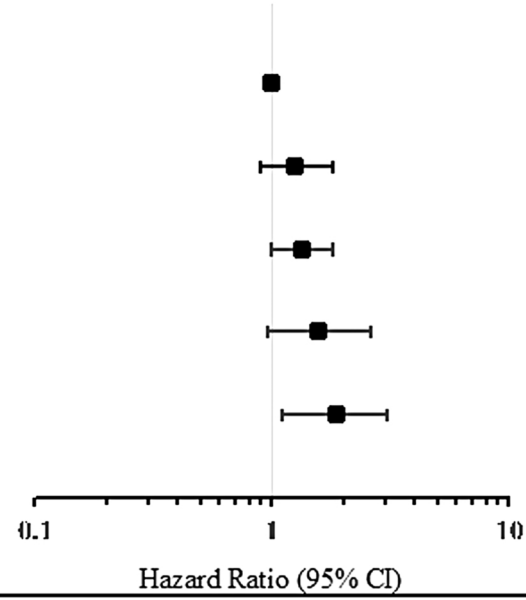

22,006 participants screened from ACLS with at least two medical exams
4393 excluded
893 history of cancer
360 history of CVD
939 less than 1 year of follow-up
1784 missing physical activity data
417 BMI less than 18.5
17,613 participants
(14,371men, 3242 women)

Figure 1

Change in PAI	CVD Deaths	Rate[a]	Hazard Ratio (95 % CI)[b]
>25	61	1.5	1.00 (Reference)
6 to 25	58	2.2	1.25 (0.86-1.81)
- 5 to 5	219	2.8	1.34 (1.00-1.80)
- 6 to - 25	30	1.8	1.58 (0.96-2.60)
<- 25	32	1.6	1.87 (1.13-3.10)



The data markers indicate the hazard ratios and the error bars indicate the 95% confidence intervals. CVD, cardiovascular disease

[a]Deaths/1000 person-years.

[b]Adjusted for age, number of clinical visits between the first and last examinations, parental cardiovascular disease, combination pattern of changes in confounders (BMI, smoking status, hypertension, diabetes, and hypercholesterolemia) between the first and last examinations, PAI score at first examination, and stratified by sex.

Figure 2

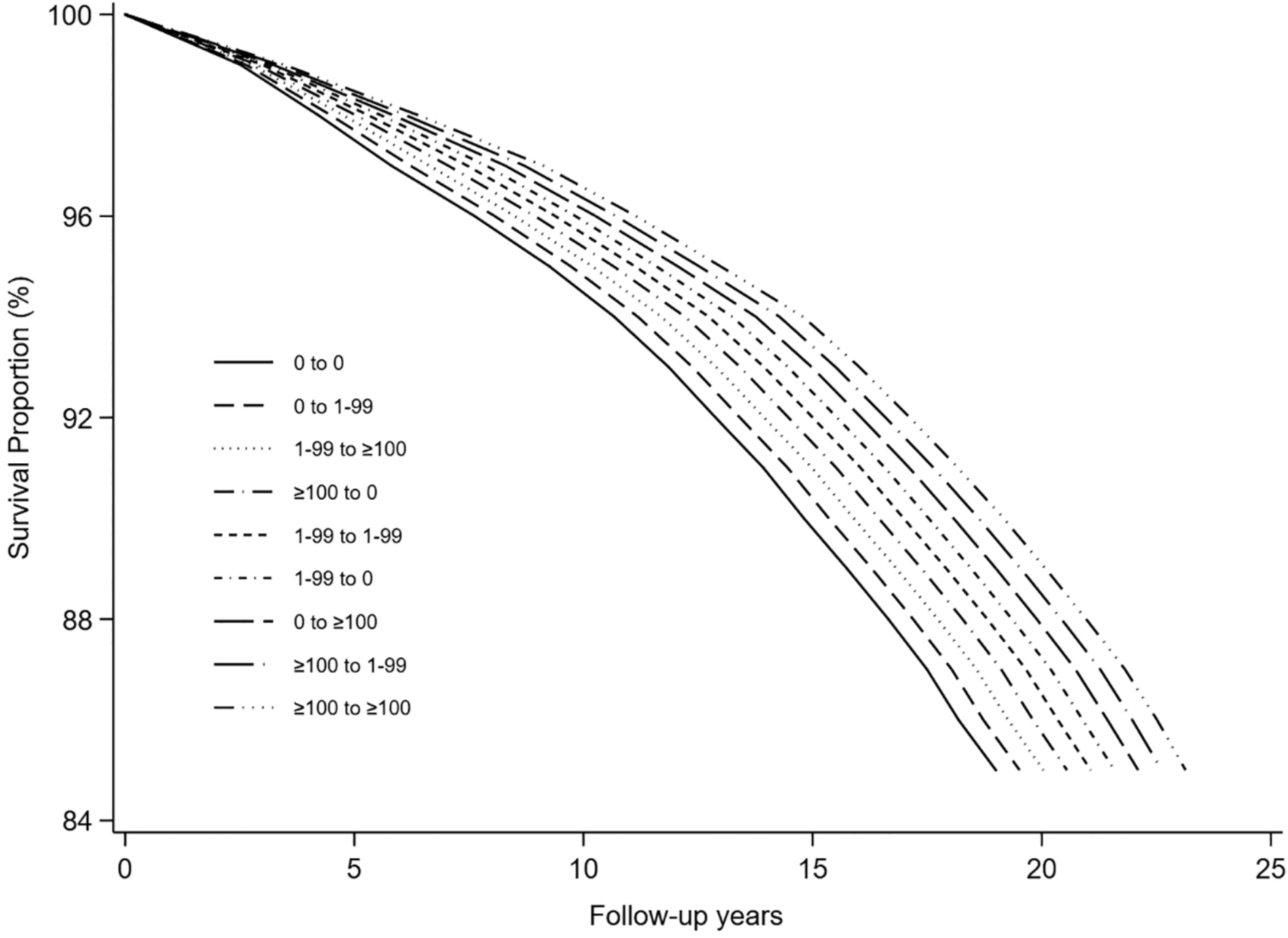

100
96
92
88
84
Survival Proportion (%)
0
5
10
15
20
25
Follow-up years
0 to 0
0 to 1-99
1-99 to ≥100
≥100 to 0
1-99 to 1-99
1-99 to 0
0 to ≥100
≥100 to 1-99
≥100 to ≥100

Figure 3