Annals of Epidemiology 35 (2019) 59–65

Contents lists available at ScienceDirect

Annals of Epidemiology

Original article

The association between physical function and proximity to death in older adults: a multilevel analysis of 4,150 decedents from the Cardiovascular Health Study

Sathya Karunananthan, PhD [a, b, *], Erica E.M. Moodie, PhD [a], Howard Bergman, MD [c], Hélène Payette, PhD [d], David Wolfson, PhD [e], Paula H. Diehr, PhD [f], Christina Wolfson, PhD [a, g]

[a] Department of Epidemiology, Biostatistics and Occupational Health, McGill University, Montreal, Quebec, Canada
[b] Clinical Epidemiology Program, Ottawa Hospital Research Institute, Ottawa, Ontario, Canada
[c] Department of Family Medicine, McGill University, Montreal, Quebec, Canada
[d] Research Center on Aging, Integrated Academic Health Center and Social Services in the Eastern Townships, Faculty of Medicine and Health Sciences, University of Sherbrooke, Sherbrooke, Quebec, Canada
[e] Department of Mathematics and Statistics, McGill University, Montreal, Quebec, Canada
[f] Department of Health Services, University of Washington, Seattle
[g] Department of Medicine, McGill University, Montreal, Quebec, Canada

ARTICLE INFO

Article history:
Received 23 November 2018
Accepted 8 April 2019
Available online 18 April 2019

Keywords:
Gait speed
Grip strength
Mortality

ABSTRACT

Purpose: When examining whether poor physical function is a risk factor for imminent death in older adults, one challenge is the lack of a meaningful time origin, a time point on which the estimate of time-to-death is anchored. In this study, we overcame this challenge by discarding the traditional—and flawed—approach of survival analysis with "time since beginning of follow up" as the time variable, and instead used a novel analytic approach that uses time-to-death as a covariate to examine its association with physical function.

Methods: Physical function and other covariates were measured annually in the Cardiovascular Health Study on 4150 individuals followed up to their time of death. Using multilevel models, we estimated gait speed and grip strength in relation to two time axes: age and proximity to death.

Results: As individuals approached death, both gait speed and grip strength decreased significantly. However, after adjustment for health and lifestyle covariates, there was significant variation in the level of physical function between individuals.

Conclusion: Although physical function was significantly associated with time-to-death, there was significant variation in level of physical function between individuals at comparable proximity to death. A better understanding of these variations is needed before measures of physical function are recommended as a clinical tool for identifying individuals at high risk of death.

Introduction

Over the past few decades, researchers have reported a strong association between measures of physical function and survival in older persons. These findings have led to the recommendation that physical function serve as a clinical tool for identifying individuals at higher risk of death and targeting care accordingly [1–9].

When studying the association between physical function and survival in older adults, however, one important challenge is the lack of a meaningful time origin—a time point on which the measurement of survival is anchored. Researchers have commonly used time of entry into a longitudinal study as the time origin [1–4]. When the exposure of interest is a disease or intervention, time of entry into a study is a meaningful time point because it usually coincides with disease onset, diagnosis, or the initiation of the intervention. Survival from these time points is therefore of interest. In the case of physical function, however, decline typically starts in middle age, and rate of decline varies throughout late adulthood [10–12]. Thus, using study entry as the time origin yields

* Corresponding author: Ottawa Hospital Research Institute, 501, Smyth Road, L1255, P.O. Box 711, Ottawa, Ontario K1H 8L6, Canada.
E-mail address: sathya.karunananthan@mail.mcgill.ca (S. Karunananthan).

https://doi.org/10.1016/j.annepidem.2019.04.005
1047-2797/

estimates of survival that are adjusted for time on study and therefore have no useful interpretation and can lead to misleading conclusions [13–16].

One way of overcoming the lack of a meaningful time origin is to use an analytic approach developed in research on cognitive function and mortality, referred to as terminal decline [17–19]. This approach, aimed at examining accelerated decline in cognitive function at the end of life, limits the analytic sample to the decedents of a cohort, anchors the analysis at the time of death, and uses a time-to-death scale as a *covariate* in a regression model for a specific health outcome. Time-of-death offers a well-defined time point and a novel approach to addressing the question of poor physical function as an independent risk factor for death in older adults. The multilevel analysis also indicates whether there is significant variation between individuals once age and proximity to death are accounted for.

In the present study, we use methods developed in terminal decline research to assess whether physical function is an independent risk factor of death. We identified three previous studies where researchers examined terminal decline in physical function [20–22]. All three of the studies reported an accelerated decline in physical function at the end of life. Because these studies aimed to assess whether physical function was part of the dying process, two of them did not control for any other health characteristics considered to be part of the same process [20]. The only study that did control for health characteristics treated them as time-invariant over a follow-up of 13 years [22]. If physical function is to be used as a clinical tool in identifying older adults at higher risk of death, it is important to know whether it is a risk factor for imminent death after potential time-varying characteristics normally considered by clinicians are controlled for.

The specific objectives of this study are 1) to examine whether the time-to-death is associated with physical function in older women and men, after accounting for age and time-varying effects of health and lifestyle characteristics, and 2) to assess whether there are significant variations between individuals in level and rate of change of physical function, once age, proximity to death and other covariates are accounted for.

Methods

Sample

This study used data from the Cardiovascular Health Study (CHS), a cohort study of American adults aged 65 years and over at recruitment, initiated in 1989. Participants in the CHS were randomly sampled from the Medicare eligibility list of the Health Care Financing Administration in four geographic regions of the United States: Forsyth County, North Carolina; Sacramento County, California; Washington County, Maryland; and Pittsburgh, Pennsylvania. Details of the sampling strategy have been described elsewhere [23]. The sample for the present study comprised the original cohort of CHS participants recruited in 1989–1990, for whom a date of death was recorded by December 31, 2010, the administrative censoring date for this analysis. Seventy-five percent of women and 86% of men of the original CHS sample had died by then, yielding a sample of 4150 decedents for this study. Follow-up for vital status was 100%, so those excluded from the present study are the CHS "survivors." The CHS obtained participant informed consent and the McGill University IRB approved the current analysis.

Physical function

For this study, physical function was the outcome variable, operationalized as gait speed and grip strength. Both of these were measured annually for 10 years. Gait speed was measured as the time taken to walk a 15-foot course and converted into meters per second. Grip strength was measured on the dominant hand using a hand-held Jamar dynamometer.

Time-to-death and age

Time-to-death was the primary predictor of interest in this analysis. It was defined as the number of days between the measurement of physical function (gait speed or grip strength) and the participant's date of death, divided by 365, to convert the units into years.

Age, a second key predictor of interest, was centered at the mean age of the sample at study entry to provide an interpretable model intercept in the multilevel models.

Covariates

Additional covariates of interest were demographic, lifestyle, and health characteristics. Demographic characteristics (race, education, lifetime occupation, income, and marital status) were measured only at entry into the CHS and treated as time-invariant in the current analysis. Lifestyle covariates were smoking status, number of alcoholic beverages consumed per week, and current physical activity level compared to the previous year. Health characteristics consisted of body mass index (BMI), self-rated health, self-reported vision problems, hearing problems, depressive symptoms, cognitive function, and disease status for the following conditions: cardiovascular disease, diabetes, cancer, kidney disease, liver disease, musculoskeletal disease, and Parkinson's disease. Lifestyle and health characteristics were measured at annual CHS visits and treated as time-varying for the present study.

Analysis

Analyses were conducted separately for gait speed and grip strength. To better understand sex-specific associations, the analyses were also stratified by sex.

We first compared decedents included in this study to the survivors. Next, we graphed the study sample characteristics of the decedents at their final observation, stratified by categories of their time-to-death at the final observation.

We used multilevel models to examine within-person change in physical function (outcome variable) as a function of time (predictor). We used two different time axes: time-to-death and age. Models were fit using maximum likelihood estimation. The AIC was used to determine whether progressively more complex models provided a better fit for the data.

Seven models were fit (Supplementary Table 4): 1) the unconditional mean model, where physical function was assumed to be stable over time, so variance in physical function was partitioned and quantified across people, without respect to time; 2) the time-to-death model, where physical function was modeled as a linear function of time-to-death; 3) the nonlinear time-to-death model, where a quadratic term for time-to-death was included to assess nonlinear changes in physical function with respect to time-to-death; 4) an age model, where age was used as the time axis and change in physical function was modeled with respect to increasing age; 5) a nonlinear age model, where a quadratic term for age was included; 6) a model that included both age and time-to-death, along with their quadratic forms, to directly compare the effects of *aging* to those of *dying*, and to determine whether the inclusion of one time metric may render the other nonsignificant; and finally 7) a model with both time-to-death and age, adjusted for demographic, lifestyle, and health characteristics.

For models 1–6, where the independent variables were limited to age and time-to-death, all observed values of physical function were included in the models because there were no missing values for age or time-to-death. Model 7 was limited to observations of physical function for which all covariates were also nonmissing. We also ran model 6 on a restricted subset of observations (model 6R), corresponding to those included in model 7, so that model fit of the adjusted and unadjusted models could be compared directly.

At the second level of the models, we introduced variation in the intercept and slope between individuals and examined the statistical significance of their variance components.

Results

Compared to the CHS survivors excluded from the present study, the decedents were older and in poorer health at CHS entry (Supplementary Tables 1 and 2).

Sample characteristics of decedents at their final observation are presented in Supplementary Appendix 2. Overall, not surprisingly, participants observed very close to their time-of-death were in poorer health compared to those further away from death at their last observation. Differences were most pronounced for self-rated health, BMI, and chronic diseases with poor prognosis. Cognitive function, gait speed, and grip strength were all worse among the women and men who were closer to death at their final observation.

Tables 1–4 present the results of the multilevel modeling of gait speed and grip strength in women and men. In models 1 through 6, the AICs were consistently lower, indicating better model fit, for models of age, compared to models of time-to-death. Models that included both age and time-to-death, however, provided better fit than models with only one of the two time axes. The model adjusted for demographic, health, and lifestyle covariates (model 7) consistently had the best model fit. Overall, in the fully adjusted models, there were statistically significant effects of time-to-death on gait speed and grip strength, even after adjusting for age and all other covariates.

Among women, based on the fully adjusted models, as time-to-death decreased, both measures of physical function decreased. The magnitude of the association between time-to-death and physical function was smaller than that of age and physical function. Among men, similar results were obtained for grip strength. For gait speed however, in the fully adjusted model, the association with time-to-death was stronger than with age.

In comparing the unadjusted and adjusted models (models 6R and 7), it is also worth noting that the strength of the association between time-to-death and physical function was attenuated by the adjustment for covariates. In contrast, adjustment for covariates had little impact on the association between age and physical function.

Finally, Tables 1–4 also present the random effects for all models. The statistically significant random effects in the intercept for both sexes and both measures of physical function indicate important variation in physical function between individuals preceding death. For grip strength in women and men, there was also a significant random effect for time, indicating variation in the rates of decline in grip strength between individuals, after accounting for all the covariates.

Discussion

In this study, we sought to examine whether proximity to death was associated with level of physical function, once age and other health and lifestyle covariates were accounted for. In contrast to previous studies of physical function and survival that have used

Table 1
Multilevel models of gait speed as a function of time-to-death and/or age, in female decedents

Model	1. Unconditional means	2. Time-to-death	3. Nonlinear Time-to-death	4. Age	5. Nonlinear Age	6. Age and time-to-death	6R. Age and time-to-death‡	7. Adjusted age and time-to-death§
Fixed effects	Estimate (SE)	Estimate (SE)	Estimate (SE)	Estimate (SE)	Estimate (SE)	Estimate (SE)	Estimate (SE)	Estimate (SE)
Intercept	80.31* (0.44)	66.67* (0.58)	59.84* (0.73)	80.34* (0.41)	82.77* (0.44)	70.44* (0.87)	74.74	42.38* (7.81)
Time-to-death	—	1.53* (0.05)	3.41* (0.13)	—	—	2.27* (0.14)	1.54* (0.28)	0.65† (0.26)
(Time-to-death)^2	—	—	−0.09* (0.006)	—	—	−0.08* (0.006)	−0.04† (0.01)	−0.02 (0.01)
Age	—	—	—	−1.54* (0.04)	−1.47* (0.04)	−0.99* (0.07)	−0.99* (0.10)	−0.81* (0.10)
Age^2	—	—	—	—	−0.07* (0.005)	−0.06* (0.005)	−0.05* (0.01)	−0.04* (0.008)
Random effects	Estimate (SE)	Estimate (SE)	Estimate (SE)	Estimate (SE)	Estimate (SE)	Estimate (SE)	Estimate (SE)	Estimate (SE)
Intercept	340.69* (12.68)	314.94* (11.66)	317.56* (11.85)	292.88* (10.93)	294.08* (11.07)	280.80* (10.49)	276.91* (15.08)	171.26* (10.86)
Residual	281.01* (3.47)	261.62* (3.23)	256.51* (3.17)	261.72* (3.23)	256.54* (3.17)	253.40* (3.13)	245.42* (6.22)	240.27* (6.12)
Goodness-of-fit								
AIC	134,594.5	133,479.0	133,252.0	133,340.6	133,100.7	132,835.4	42,025.9	41,474.1

* $P < .001$.
† $P < .05$.
‡ Model 6 applied to a restricted subset of observations with no missing data for covariates.
§ Adjusted for race, lifetime occupation, income, education, smoking status, physical activity level, alcohol consumption, BMI, self-rated health, CVD, diabetes, kidney disease, liver disease, cancer, musculoskeletal disease, Parkinson's disease, cognitive function, depressive symptoms, vision problems, hearing problems, and grip strength.

Table 2
Multilevel models of gait speed as a function of time-to-death and/or age, in male decedents

Model	1. Unconditional means	2. Time-to-death	3. Nonlinear Time-to-death	4. Age	5. Nonlinear Age	6. Age and time-to-death	6R. Age and time-to-death[‡]	7. Adjusted age and time-to-death[§]
Fixed effects	Estimate (SE)	Estimate (SE)	Estimate (SE)	Estimate (SE)	Estimate (SE)	Estimate (SE)	Estimate (SE)	Estimate (SE)
Intercept	88.25* (0.44)	78.16* (0.56)	73.00* (0.68)	88.74* (0.42)	90.97* (0.45)	80.30* (0.80)	83.07* (1.24)	27.35* (8.08)
Time-to-death	—	1.34* (0.05)	3.03* (0.14)	—	—	2.19* (0.15)	1.86* (0.27)	0.90* (0.27)
(Time-to-death)^2	—	—	−0.09* (0.007)	—	—	−0.08* (0.007)	−0.06* (0.02)	−0.03† (0.02)
Age	—	—	—	−1.27* (0.05)	−1.16* (0.05)	−0.66* (0.07)	−0.74* (0.11)	−0.49* (0.11)
Age^2	—	—	—		−0.06* (0.005)	−0.05* (0.005)	−0.04* (0.01)	−0.03* (0.01)
Random effects	Estimate (SE)	Estimate (SE)	Estimate (SE)	Estimate (SE)	Estimate (SE)	Estimate (SE)	Estimate (SE)	Estimate (SE)
Intercept	296.74* (12.25)	264.84* (10.94)	267.57* (11.13)	261.82* (10.81)	261.62* (10.82)	243.76* (10.13)	247.7* (14.57)	166.71* (11.10)
Residual	289.77* (3.9)	277.04* (3.73)	272.08* (3.66)	277.10* (3.73)	273.10* (3.68)	269.93* (3.63)	271.01* (7.15)	268.75* (7.09)
Goodness-of-fit								
AIC	114,229.1	113,523.2	113,351.9	113,500.3	113,339.3	113,093.5	38,157.2	37,821.0

* $P < .001$.
† $P < .05$.
‡ Model 6 applied to a restricted subset of observations with no missing data for covariates.
§ Adjusted for race, lifetime occupation, income, education, smoking status, physical activity level, alcohol consumption, BMI, self-rated health, CVD, diabetes, kidney disease, liver disease, cancer, musculoskeletal disease, Parkinson's disease, cognitive function, depressive symptoms, vision problems, hearing problems, and grip strength.

Table 3
Multilevel models of grip strength as a function of time-to-death and/or age, in female decedents

Model	1. Unconditional means	2. Time-to-death	3. Nonlinear Time-to-death	4. Age	5. Nonlinear Age	6. Age and time-to-death	6R. Age and time-to-death[‡]	7. Adjusted age and time-to-death[§]
Fixed effects	Estimate (SE)	Estimate (SE)	Estimate (SE)	Estimate (SE)	Estimate (SE)	Estimate (SE)	Estimate (SE)	Estimate (SE)
Intercept	19.41* (0.12)	17.32* (0.15)	16.19* (0.19)	20.04* (0.11)	20.26* (0.11)	18.32* (0.23)	19.24* (0.32)	16.00* (1.71)
Time-to-death	—	0.31* (0.01)	0.63* (0.03)	—	—	0.41* (0.04)	0.29* (0.06)	0.16† (0.06)
(Time-to-death)^2	—	—	−0.02* (0.002)	—	—	−0.02* (0.002)	−0.01† (0.003)	−0.005 (0.003)
Age	—	—	—	−0.33* (0.01)	−0.33* (0.01)	−0.28* (0.02)	−0.28* (0.03)	−0.19* (0.03)
Age^2	—	—	—		−0.01* (0.001)	−0.01* (0.001)	−0.01* (0.002)	−0.005† (0.002)
Random effects	Estimate (SE)	Estimate (SE)	Estimate (SE)	Estimate (SE)	Estimate (SE)	Estimate (SE)	Estimate (SE)	Estimate (SE)
Intercept	20.14* (0.87)	22.33* (0.80)	21.06* (0.84)	19.45* (0.75)	19.40* (0.75)	19.23* (0.74)	20.21* (0.92)	16.62* (0.71)
Time	0.07* (0.007)	—	0.03* (0.006)	0.10* (0.01)	0.11* (0.01)	0.10* (0.01)	0.04† (0.02)	0.03† (0.02)
Residual	14.85* (0.22)	14.92* (0.20)	14.44* (0.20)	13.94* (0.20)	13.84* (0.20)	13.81* (0.20)	11.72* (0.34)	11.60* (0.34)
Goodness-of-fit								
AIC	78,845.7	78,307.8	78,173.6	78,120	77,945.7	77,841.1	28,627.3	27,859.7

* $P < .001$.
† $P < .05$.
‡ Model 6 applied to a restricted subset of observations with no missing data for covariates.
§ Adjusted for race, lifetime occupation, income, education, smoking status, physical activity level, alcohol consumption, BMI, self-rated health, CVD, diabetes, kidney disease, liver disease, cancer, musculoskeletal disease, Parkinson's disease, cognitive function, depressive symptoms, vision problems, hearing problems, and gait speed.

Table 4
Multilevel models of grip strength as a function of time-to-death and/or age, in male decedents

Model	1. Unconditional means	2. Time-to-death	3. Nonlinear Time-to-death	4. Age	5. Nonlinear Age	6. Age and time-to-death	6R. Age and time-to-death[§]	7. Adjusted age and time-to-death[‡]
Fixed effects	Estimate (SE)	Estimate (SE)	Estimate (SE)	Estimate (SE)	Estimate (SE)	Estimate (SE)	Estimate (SE)	Estimate (SE)
Intercept	34.34* (0.19)	29.78* (0.22)	28.48* (0.26)	34.41* (0.18)	34.68 (0.18)	31.60* (0.31)	32.50*	27.02* (2.91)
Time-to-death	—	0.65* (0.02)	1.07* (0.05)	—	—	0.68* (0.06)	0.50* (0.08)	0.27* (0.09)
(Time-to-death)^2	—	—	−0.02* (0.002)	—	—	−0.03* (0.003)	−0.02* (0.004)	−0.01† (0.005)
Age	—	—	—	−0.66* (0.02)	−0.66 (0.02)	−0.50* (0.03)	−0.51* (0.03)	−0.41* (0.04)
Age^2	—	—	—	—	−0.01 (0.002)	−0.007* (0.002)	−0.004 (0.003)	−0.002 (0.003)
Random effects	Estimate (SE)	Estimate (SE)	Estimate (SE)	Estimate (SE)	Estimate (SE)			
Intercept	54.68* (2.13)	53.08* (2.18)	53.67* (2.21)	44.99* (1.9)	44.86* (1.9)	44.10* (1.84)	43.88* (2.21)	38.93* (2.01)
Time	—	0.11* (0.02)	0.10* (0.02)	0.25* (0.02)	0.26* (0.03)	0.24* (0.02)	0.17* (0.04)	0.16* (0.04)
Residual	28.16* (0.42)	23.49* (0.38)	23.29* (0.37)	22.56* (0.36)	22.39* (0.36)	22.2* (0.35)	17.69* (0.53)	17.52* (0.53)
Goodness-of-fit								
AIC	72,924.6	71,614.1	71,524.7	71,287.0	71,248.6	71,097.2	28,144.9	27,688.1

* $P < .001$.
† $P < .05$.
‡ Model 6 applied to a restricted subset of observations with no missing data for covariates.
§ Adjusted for race, lifetime occupation, income, education, smoking status, physical activity level, alcohol consumption, BMI, self-rated health, CVD, diabetes, kidney disease, liver disease, cancer, musculoskeletal disease, Parkinson's disease, cognitive function, depressive symptoms, vision problems, hearing problems, and gait speed.

time since study entry as the time axis, our approach of anchoring the analysis on time of death provides a clinically more meaningful analysis of physical function as an independent risk factor of imminent death in older adults.

We found evidence of a positive association between grip strength and time-to-death in both men and women. The association between gait speed and time-to-death was also significant among women and men. These results provide support to the hypothesis that physical function is associated with survival. They suggest that when comparing individuals of the same age and health status, those closer to death are more likely to have a poorer physical function. Other than for gait speed in men however, the strength of the association between physical function and time-to-death was weaker than that of age and physical function.

Models of physical function including age consistently had better model fit than those of physical function including time-to-death. This suggests that age alone is a better indicator of physical function than time-to-death alone. When both age and time-to-death were included in the models, both increasing age and decreasing time-to-death were significantly associated with decreasing physical function, indicating that time-to-death provides information about physical function, even after age is accounted for. In these models, the effect estimates for time-to-death were consistently larger than those for age. However, adjustment for confounders attenuated the effects of time-to-death substantially, so that for gait speed in women and for grip strength in both sexes, the effects of time-to-death became notably weaker than those for age. This indicates that the demographic, health, and lifestyle characteristics considered in this study were important confounders in the association between time-to-death and physical function, and that these confounders were more important when looking at time-to-death and physical function, than when looking at age and physical function. These results also indicate to clinicians that once other patient characteristics are considered, there may be limited added clinical value in measuring physical function to assess the risk of mortality in older adults. According to the compression of morbidity theory [24], ideally a person's health and function would not deteriorate substantially with age but instead drop rapidly near their time of death, at any given age. In our sample, even after chronic disease and other health and lifestyle characteristics were accounted for, there was a significant decline in physical function related to increasing age, providing little support for the occurrence of compression of morbidity in this sample.

Finally, we found significant variation between individuals in the level of physical function preceding death, for both women and men. In addition, for grip strength but not gait speed, there was significant heterogeneity in the rate of change between individuals. Such variation suggests that even though there is an association between physical function and time-to-death, variability across individuals is such that a measure of physical function may not provide accurate information on how close any given individual is to their death.

The unconventional methodological approach of regressing physical function on time-to-death proposed in the literature on terminal decline in cognitive function [19] was designed to assess whether the process of dying, as measured by time-to-death, may have an effect on function. We identified three studies where researchers used these methods to investigate whether physical function undergoes similar processes of terminal decline as observed for cognitive function [20–22]. All three studies reported a significant acceleration in the rate of decline for physical function at the end of life. One of them, conducted by Diehr et al., examined terminal decline in 10 health variables among CHS participants, with follow-up for mortality up to the year 2000 [20]. Several important distinctions in the research questions and

methodological approaches of these previous studies and ours are worth noting. Researchers investigating terminal decline theorize that decline in function in relation to time-to-death is part of a dying process, which includes changes in other health characteristics as well. Because these health characteristics are considered to be components of the dying process, some researchers warn against adjusting for them as confounders [20]. However, our use of the terminal decline methodology addressed a different research question, one related to the potential use of physical function as an independent risk factor of proximal death in older persons. As such, adjustments for time-varying health characteristics were warranted. These adjustments resulted in weak associations between physical function and time-to-death. Only one previous study including 439 decedents examined whether the effects of sociodemographic characteristics and time-invariant measures of chronic disease were related to rate of decline in function preceding death and reported findings consistent with ours [22]. By conducting our study on a sample of 4135 decedents using time-varying measures of disease, our analysis provides convincing evidence of the limited value of physical function as an independent risk factor of time-to-death.

We proposed regressing physical function on time-to-death to overcome the lack of a meaningful time origin in the study of the association between physical function and survival. When time-on-study is not a meaningful time axis, another alternative is to use age as the time axis [13–15]. Although survival analysis using age represents a valid approach for assessing the age-specific incidence of death for a given level of physical function, the terminal decline approach provides a different perspective that is of value to clinicians. In the terminal decline approach, by anchoring the analysis on time of death, we assess the variability of physical function among individuals at the same proximity to death, to assess whether physical function may serve as a useful indicator of imminent death. Our findings of significant variation in physical function across individuals at the same proximity to death suggest that physical function may not be a useful clinical indicator of imminent death.

The use of both terminal decline and survival models using age should be explored further to better inform our understanding of the relationship between physical function and survival. Because we are interested in assessing the potential usefulness of physical function as an independent risk factor for death, when using either of these approaches, it is important to control for the time-varying confounding effects of other health characteristics.

Methodological limitations of our work must be acknowledged. First, limiting the analysis to individuals who died could result in selection bias, if survivors excluded from our study experience end-of-life changes in physical function that are different from the decedents. Compared to the decedents, survivors were younger and healthier at CHS entry. We therefore expect that survivors would eventually experience the same changes as observed in the decedents, but we cannot rule out the possibility of cohort effects that may alter these relationships in later born participants. Another potential limitation is the missing data in models adjusted for covariates. Missing data can result in bias if participants with missing data are different from those without missing data with respect to the value of their outcome. To examine this, we ran the model of age and time-to-death on the entire set of observations and then on the restricted sample of observations with nonmissing values for covariates. We observed very little change in the estimates for time-to-death and age and thus are confident that bias created by the missing data in these models was minimal. Finally, we cannot eliminate the possibility of residual confounding. For example, marital status and income were only measured once in the CHS, and therefore their potential time-varying effects on the association between physical function and time-to-death could not be fully adjusted for.

Conclusion

Although a few recent studies have examined terminal decline in physical function to understand the dying process [20–22], ours is, to our knowledge, the first study to use the terminal decline methodology to examine the association between physical function and survival. By using this methodology, we have provided results that are of clinical interest, demonstrating that information provided by physical function with respect to survival may be more modest than what has previously been shown, once demographic, health, and lifestyle characteristics are considered, and that there is important variation across individuals in their level of physical function preceding death. If physical function is to be used as a clinical tool, a better understanding of these variations is needed.

Acknowledgment

Disclaimer: The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Funding: Sathya Karunananthan was supported by doctoral fellowships from the Institute of Aging of the Canadian Institutes of Health Research (CIHR), Canada, the Research Institute of the McGill University Health Centre, Canada, the McGill University Faculty of Medicine, Canada, the CIHR Neuroinflammation Training Program, as well as a CIHR operating grant (TO1-120301).

This research was supported by contracts HHSN268201200036C, HHSN268200800007C, HHSN268201800001C, N01HC55222, N01HC85079, N01HC85080, N01HC85081, N01HC85082, N01HC85083, N01HC85086, and grants U01HL080295 and U01HL130114 from the National Heart, Lung, and Blood Institute (NHLBI), United States, with additional contribution from the National Institute of Neurological Disorders and Stroke (NINDS), United States. Additional support was provided by R01AG023629 from the National Institute on Aging (NIA), United States. A full list of principal CHS investigators and institutions can be found at CHS-NHLBI.

References

[1] Studenski S, Perera S, Patel K, Rosano C, Faulkner K, Inzitari M, et al. Gait speed and survival in older adults. JAMA 2011;305(1):50–8.
[2] Cooper R, Kuh D, Hardy R. Objectively measured physical capability levels and mortality: systematic review and meta-analysis. BMJ 2010;341:c4467.
[3] Celis-Morales CA, Welsh P, Lyall DM, Steell L, Petermann F, Anderson J, et al. Associations of grip strength with cardiovascular, respiratory, and cancer outcomes and all cause mortality: prospective cohort study of half a million UK Biobank participants. BMJ 2018;361:k1651.
[4] Veronese N, Stubbs B, Volpato S, Zuliani G, Maggi S, Cesari M, et al. Association between gait speed with mortality, cardiovascular disease and cancer: a systematic review and meta-analysis of prospective cohort studies. J Am Med Dir Assoc 2018;19:981–988.e7.
[5] Leong DP, Teo KK, Rangarajan S, Lopez-Jaramillo P, Avezum Jr A, Orlandini A, et al. Prognostic value of grip strength: findings from the Prospective Urban Rural Epidemiology (PURE) study. Lancet 2015;386(9990):266–73.
[6] Cesari M. Role of gait speed in the assessment of older patients. JAMA 2011;305(1):93–4.
[7] Sayer AA, Kirkwood TBL. Grip strength and mortality: a biomarker of ageing? Lancet 2015;386(9990):226–7.
[8] Granic A, Davies K, Jagger C, Dodds RM, Kirkwood TBL, Sayer AA. Initial level and rate of change in grip strength predict all-cause mortality in very old adults. Age and Ageing 2017;46(6):970–6.
[9] Buckner SL, Dankel S, Bell ZW, Abe T, Loenneke J. The association of hand grip strength and mortality: What does it tell us and what can we do with it? Rejuvenation Res 2018 [Epub ahead of print].
[10] Onder G, Penninx BWJH, Lapuerta P, Fried LP, Ostir GV, Guralnik JM, et al. Change in physical performance over time in older women: the Women's Health and Aging Study. J Gerontol A Biol Sci Med Sci 2002;57(5):M289–93.
[11] Stenholm S, Härkänen T, Sainio P, Heliövaara M, Koskinen S. Long-term changes in handgrip strength in men and women-accounting the effect of

right censoring due to death. J Gerontol A Biol Sci Med Sci 2012;67(10):1068–74.
[12] Proctor DN, Fauth EB, Hoffman L, Hofer SM, McClearn GE, Berg S, et al. Longitudinal changes in physical functional performance among the oldest old: insight from a study of Swedish twins. Aging Clin Exp Res 2006;18(6):517–30.
[13] Liestøl K, Andersen PK. Updating of covariates and choice of time origin in survival analysis: problems with vaguely defined disease states. Stat Med 2002;21(23):3701–14.
[14] Lamarca R, Alonso J, Gómez G, Muñoz A. Left-truncated data with age as time scale: an alternative for survival analysis in the elderly population. J Gerontol A Biol Sci Med Sci 1998;53(5):M337–43.
[15] Commenges D, Letenneur L, Joly P, Alioum A, Dartigues JF. Modelling age-specific risk: application to dementia. Stat Med 1998;17(17):1973–88.
[16] Hernán MA, Alonso A, Logan R, Grodstein F, Michels KB, Willett WC, et al. Observational studies analyzed like randomized experiments: an application to postmenopausal hormone therapy and coronary heart disease. Epidemiology 2008;19(6):766–79.
[17] MacDonald SWS, Hultsch DF, Dixon RA. Aging and the shape of cognitive change before death: terminal decline or terminal drop? J Gerontol B Psychol Sci Soc Sci 2011;66(3):292–301.
[18] Wilson RS, Beck TL, Bienias JL, Bennett DA. Terminal cognitive decline: accelerated loss of cognition in the last years of life. Psychosom Med 2007;69(2):131–7.
[19] Riegel KF, Riegel RM. Development, drop, and death. Dev Psychol 1972;6(2):306–19.
[20] Diehr P, Williamson J, Burke GL, Psaty BM. The aging and dying processes and the health of older adults. J Clin Epidemiol 2002;55(3):269–78.
[21] Wilson RS, Segawa E, Buchman AS, Boyle PA, Hizel LP, Bennett DA. Terminal decline in motor function. Psychol Aging 2012;27(4):998–1007.
[22] Gerstorf D, Ram N, Lindenberger U, Smith J. Age and time-to-death trajectories of change in indicators of cognitive, sensory, physical, health, social, and self-related functions. Dev Psychol 2013;49(10):1805–21.
[23] Fried LP, Borhani NO, Enright P, Furberg CD, Gardin JM, Kronmal RA, et al. The Cardiovascular Health Study: design and rationale. Ann Epidemiol 1991;1(3):263–76.
[24] Fries JF. The compression of morbidity: near or far? Milbank Q 1989;67(2):208–32.

Appendix

Appendix 1. Comparison of the cardiovascular health study decedents and survivors

Supplementary Table 1
Demographic characteristics at entry into the Cardiovascular Health Study: female and male decedents, compared with survivors

Characteristic	CHS female decedents, n (%) Total n = 2217	CHS female survivors, n (%) Total n = 745	CHS male decedents, n (%) Total n = 1933	CHS male survivors, n (%) Total n = 306
Age				
<65	47 (2.12)	51 (6.85)	25 (1.29)	12 (3.92)
65–69	605 (27.29)	416 (55.84)	468 (24.21)	173 (56.54)
70–74	682 (30.76)	227 (30.47)	629 (32.54)	101 (33.01)
75–79	553 (24.94)	46 (6.17)	449 (23.23)	18 (5.88)
80–84	240 (10.83)	4 (0.54)	258 (13.35)	2 (0.65)
>85	90 (4.06)	1 (0.13)	104 (5.38)	12 (3.92)
Race				
White	2063 (93.05)	697 (93.56)	1824 (94.36)	292 (95.42)
Black	119 (5.37)	35 (4.7)	81 (4.19)	9 (2.94)
Other	35 (1.58)	13 (1.74)	28 (1.45)	5 (1.63)
Marital status				
Married/widowed	1990 (89.88)	682 (91.54)	1823 (94.46)	292 (95.42)
Divorced/separated Never married	224 (10.12)	63 (8.46)	107 (5.54)	14 (4.58)
Missing	3		3	
Education				
0–11 years (incomplete high school)	656 (29.59)	154 (20.67)	594 (30.73)	48 (15.69)
12–16 years (high school ± vocational school)	894 (40.32)	330 (44.3)	608 (31.45)	97 (31.7)
≥17 years (college/graduate/professional)	667 (30.09)	261 (35.03)	731 (37.82)	161 (52.61)
Lifetime occupation				
Professional/technical/managerial/admin	518 (23.45)	209 (28.05)	925 (47.85)	197 (64.38)
Sales/clerical services	413 (18.7)	140 (18.79)	208 (10.76)	31 (10.13)
Craftsman/machine operator/laborer	173 (7.83)	51 (6.85)	521 (26.95)	56 (18.3)
Housewife	243 (11)	48 (6.44)		
Other	862 (39.02)	297 (39.87)	279 (14.43)	22 (7.19)
Missing	8			
Income				
Under $15,999	1037 (50.71)	225 (33.09)	586 (31.81)	47 (16.26)
$16,000–$49,999	823 (40.24)	332 (48.82)	963 (52.28)	161 (55.71)
Over $49,999	185 (9.05)	123 (18.09)	293 (15.91)	81 (28.03)
Missing	172	65	91	17

Supplementary Table 2
Health and lifestyle characteristics at entry into the Cardiovascular Health Study: female and male decedents, compared with survivors

Characteristic	CHS female decedents, n (%) Total n = 2217	CHS female survivors, n (%) Total n = 745	CHS male decedents, n (%) Total n = 1933	CHS male survivors, n (%) Total n = 306
Self-rated health				
Excellent	250 (11.29)	151 (20.3)	262 (13.59)	77 (25.25)
Very good	522 (23.58)	226 (30.38)	449 (23.29)	101 (33.11)
Good	811 (36.63)	282 (37.9)	741 (38.43)	107 (35.08)
Fair	532 (24.03)	80 (10.75)	403 (20.9)	20 (6.56)
Poor	99 (4.47)	5 (0.67)	73 (3.79)	
Missing	3	1	5	1
BMI				
Mean (SD)	26.39 (5.19)	26.60 (4.59)	26.35 (3.76)	26.54 (3.32)
Missing	5		5	2
Vision problems	188 (9.19)	26 (3.62)	98 (5.18)	8 (2.61)
Missing	171	26	40	
Hearing problems	166 (7.81)	28 (3.89)	195 (10.63)	19 (6.33)
Missing	92	26	98	6
Chronic diseases				
Cardiovascular disease	1137 (51.29)	248 (33.29)	1079 (55.82)	109 (35.62)
Missing				
Diabetes	193 (8.74)	25 (3.37)	222 (11.54)	11 (3.61)
Missing	9	4	10	1
Cancer	361 (16.31)	82 11.02	295 (15.29)	44 (14.38)
Missing	4	1	4	
Kidney	87 (3.95)	8 1.08	33 (1.72)	7 (2.3)
Missing	14	2	18	1
Arthritis	1286 (58.67)	378 51.5	871 (45.65)	109 (35.74)
Missing	25	11	25	1
Parkinson's disease	15 (0.68)	1 0.13	26 (1.35)	304 (100)
Missing	5	1	2	2
Smoking				
Never smoker	1220 (55.05)	460 (61.74)	596 (30.86)	121 (39.54)
Past smoker	682 (30.78)	224 (30.07)	1120 (58)	174 (56.86)
Current smoker	314 (14.17)	61 (8.19)	215 (11.13)	11 (3.59)
Missing	1		2	
Weekly alcoholic beverages				
Mean (SD)	1.87 (14.10)	2.01 (5.18)	3.61 (8.02)	4.54 (7.60)
0	1233 (55.92)	341 (45.83)	817 (42.49)	89 (29.18)
1–7	780 (35.37)	322 (43.28)	779 (40.51)	146 (47.87)
8–14	96 (4.35)	45 (6.05)	145 (7.54)	31 (10.16)
15–21	69 (3.13)	22 (2.96)	86 (4.47)	22 (7.21)
>21	27 (1.22)	14 (1.88)	96 (4.99)	17 (5.57)
Missing	12	1	10	1
Activity level before 65 years compared with others <65 years				
A lot less active	585 (26.45)	94 (12.65)	444 (23.02)	35 (11.44)
A little less active	911 (41.18)	288 (38.76)	827 (42.87)	129 (42.16)
About as active	565 (25.54)	302 (40.65)	499 (25.87)	106 (34.64)
A little more active	115 (5.2)	37 (4.98)	110 (5.7)	26 (8.5)
A lot more active	36 (1.63)	22 (2.96)	49 (2.54)	10 (3.27)
Missing	5	2	4	
Depression*				
Depressed (CESD >10)	298 (13.71)	52 (7.01)	146 (7.64)	8 (2.66)
Missing	43	3	21	5
Cognitive function†				
Cognitively impaired (3MS < 79)	69 (3.1)	4 (0.54)	97 (5.17)	0
Missing	52	5	56	6
Grip strength (kg), mean (SD)	20.77 (6.55)	22.87 (6.05)	36.11 (9.50)	39.27 (8.40)
Missing	81	33	84	15
Gait speed (m/s), mean (SD)	0.81 (0.21)	0.92 (0.20)	0.87 (0.21)	0.98 (0.20)
Missing	36	8	23	6

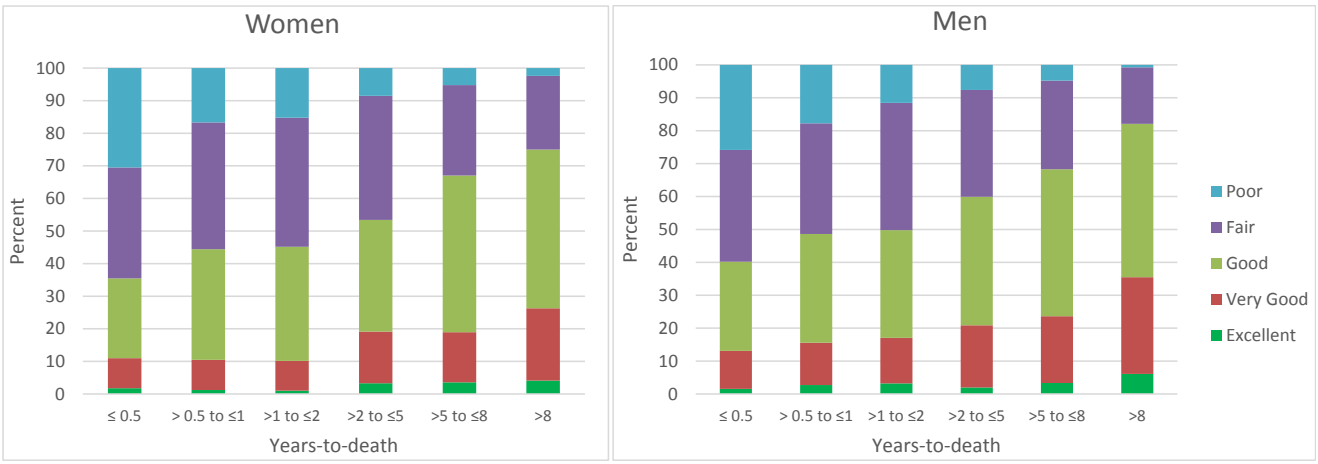
* Measured by the Centre for Epidemiologic Studies Depression Scale.
† Measured by the Modified Mini-Mental State Examination.

Appendix 2. Sample characteristics of CHS decedents

To describe the sample characteristics of decedents at their final observation, we created six strata, based on time-to-death. The widths of the time intervals for these strata were selected to have a relatively balanced number of participants in each one, resulting in shorter time intervals closer to death. This stratification was expected to create groups that were more homogeneous with respect to health status. Supplementary Table 3 presents the intervals of

Supplementary Table 3
Number of female and male decedents by strata of years-to-death at final observation

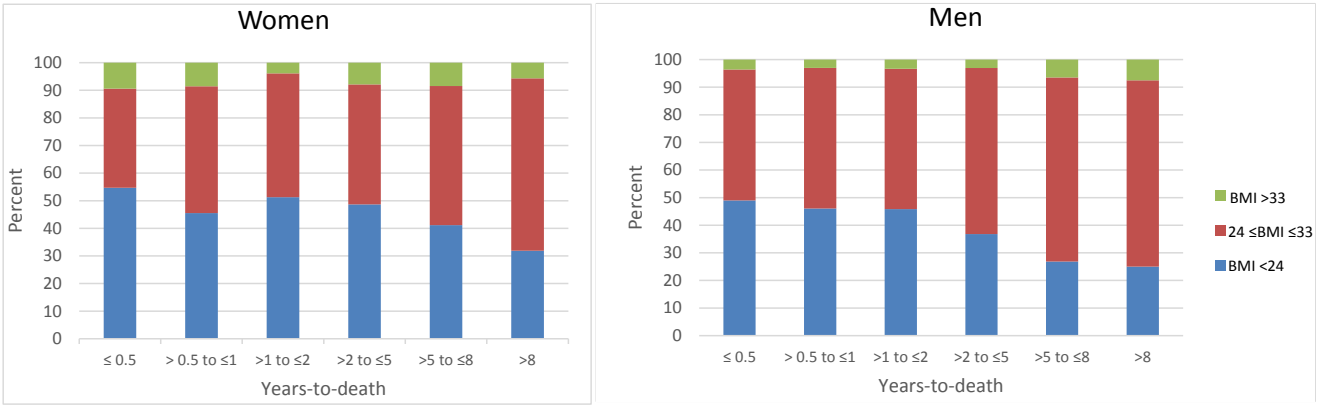
Strata of years-to-death	Female	Male
≤0.5	325	375
>0.5 to ≤1	357	421
>1 to ≤2	223	247
>2 to ≤5	457	321
>5 to ≤8	376	281
>8	479	286



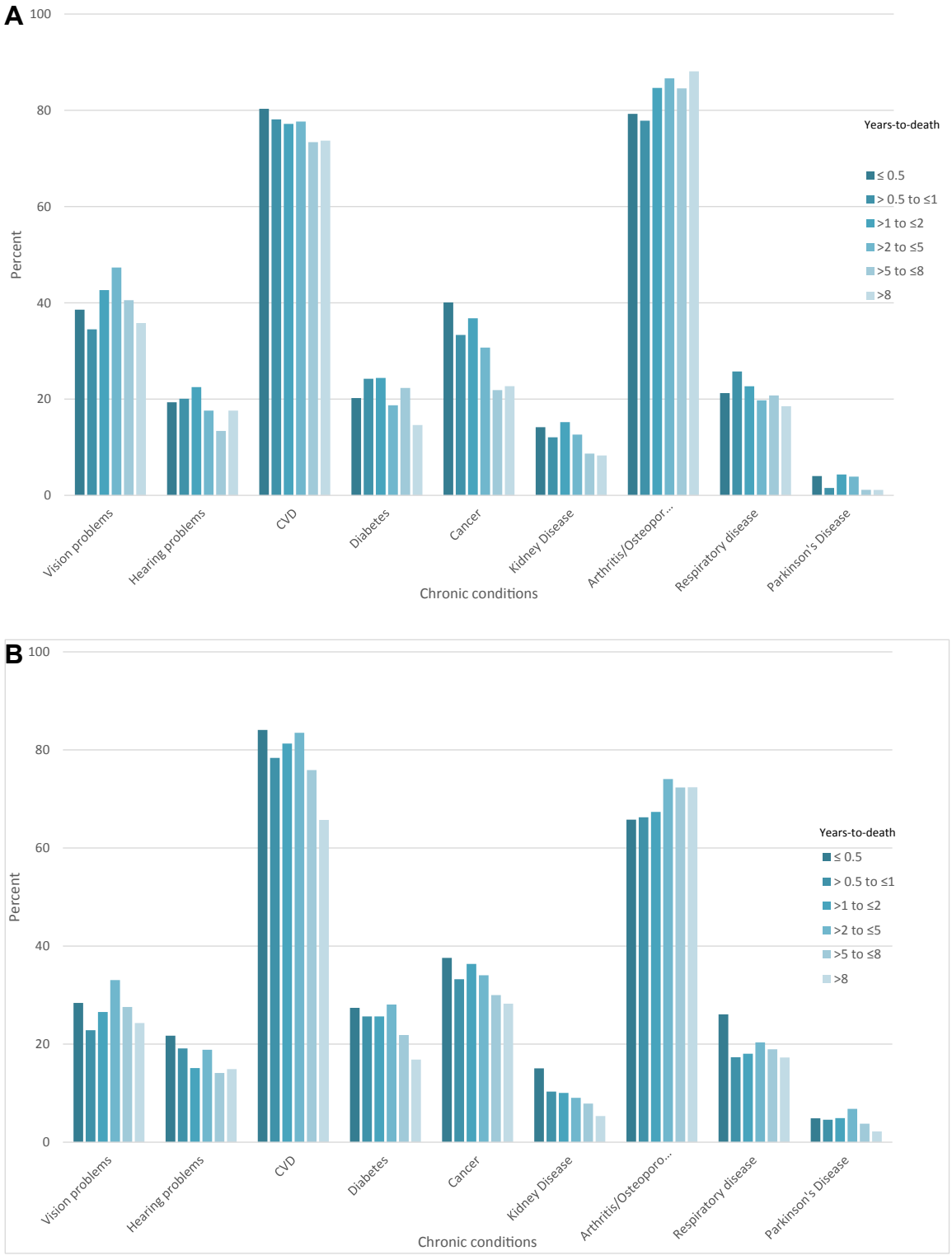
Supplementary Fig. 1. Self-rated health of female (left) and male (right) decedents at final observation, stratified by years-to-death.

time-to-death for each stratum and number of participants in each category.

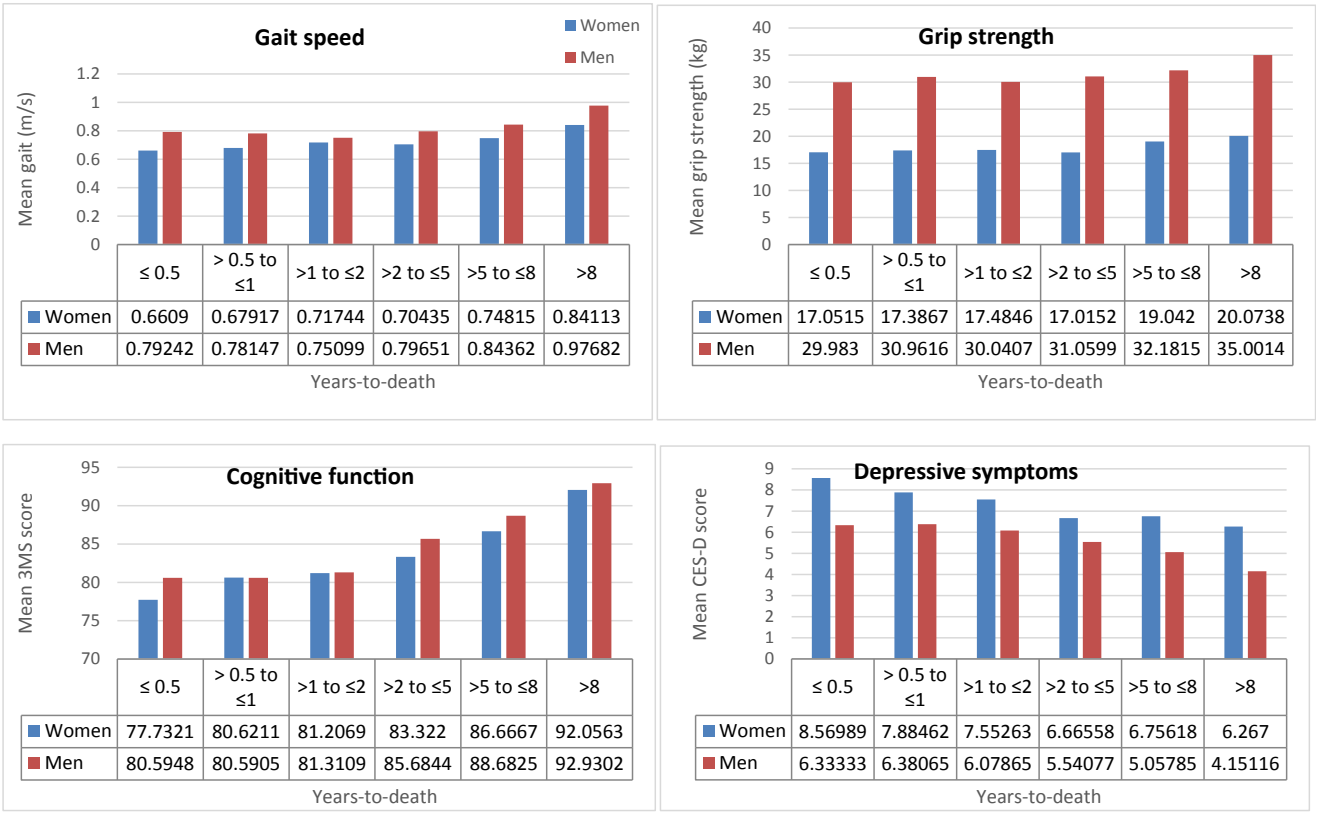
Supplementary Figures 1–4 present the health characteristics of the study sample at the final observation before death, stratified by years-to-death. In general, these indicate, as expected, that those closer to death had worse health than those further away from death. As shown in Supplementary Figure 1, the proportion of individuals with self-reported poor health is close to zero among those more than eight years from death, whereas it is at approximately 30% for those within six months of death. The proportion of individuals with a medium BMI (defined as a BMI between 24 and 33) was greatest among those furthest away from death, whereas low BMI (less than 23.9) was most prevalent among those close to death (Supplementary Fig. 2). Supplementary Figure 3, A and B show that while in general, prevalence of disease was highest among those close to death, the differences between strata were most noticeable for diseases with expected poorer short-term prognoses, such as respiratory and kidney disease. Conversely, arthritis and osteoporosis were in fact more common among those further away from time of death. The graphs in Supplementary Figure 4 display a decrease in the average gait speed, grip strength, and cognitive function and an increase in depressive symptom score with time to death. For cognitive function, there is a 14- and 13-point difference in mean scores of women and men, respectively, between the strata furthest away from death and those closest to it. The magnitude of these differences is considerable. Whereas the mean cognitive function for those over eight years from time-of-death is high, the mean for those within a year of death is very close to the cut point for cognitive impairment. Difference in mean depressive symptom scores between those furthest from death and those closest to death is two points, for women and men. Although those close to death have a higher average score for depressive symptoms, mean scores are still below the cut point (Centre for Epidemiologic Studies Depression Scale) for depression. For grip strength, the difference in mean strength between those furthest from death and those closest to death is approximately 3 kg for women and 6 kg for men. Thus, those closest to death have a grip strength that is on average 0.5 SDs below those furthest from time-of-death. Finally, for gait speed, women and men closest to death have a mean gait speed that is 0.18 m/s, or 0.86 SDs, below the mean gait speed of those who are more than eight years away from their time-of-death. Overall, these cross-sectional descriptions of health characteristics stratified by years-to-death suggest that participants observed very close to their time-of-death were in poorer health compared with those who are further away from death at their last observation. These differences were most pronounced with respect to self-rated health, BMI, and chronic diseases with poor prognosis. There are also notable differences in cognitive function, gait speed, and in grip strength, for both women and men, whereas the differences across strata in depressive symptoms are minor.



Supplementary Fig. 2. Body mass index of female (left) and male (right) decedents at final observation, stratified by years-to-death. 24 ≤ BMI ≤33; BMI >33; BMI <24.



Supplementary Fig. 3. (A): Proportion of female decedents with chronic diseases at final observation, stratified by years-to-death. (B): Proportion of male decedents with chronic diseases at final observation, stratified by years-to-death.



Supplementary Fig. 4. Mean gait speed, grip strength, 3MS score, and CESD score in female and male decedents at last observation, stratified by years-to-death.

Appendix 3. Statistical models used to assess the association of physical function with time-to-death and/or age

Supplementary Table 4
Descriptions of statistical models used to assess the association of physical function with time-to-death and/or age

Model		Description
1	Unconditional means	Stipulates no change in physical function over time
2	Time-to-death	Assesses linear changes in physical function with respect to time-to-death
3	Nonlinear time-to-death	Assesses nonlinear changes in physical function with respect to time-to-death
4	Age	Assesses linear changes in physical function with respect to age
5	Nonlinear age	Assesses nonlinear changes in physical function with respect to age
6	Age and time-to-death	Assesses the effects of both age and time-to-death when considered together and whether the effects one time metric render the other nonsignificant
6R	Age and time-to-death	Assesses the effects of both age and time-to-death (as in model 6) in a restricted subsample of observations with no missing data for covariates (subsample included in model 7)
7	Adjusted age and time-to-death	Assesses the effects of both age and time-to-death, while controlling for demographic, lifestyle, and health characteristics