Heterogeneity in Rate of Decline in Grip, Hip, and Knee Strength and the Risk of All-Cause Mortality: The Women's Health and Aging Study II

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OBJECTIVES: To assess the relationship between rate of change in muscle strength and all-cause mortality.

DESIGN: Prospective observational study of the causes and course of physical disability.

SETTING: Twelve contiguous ZIP code areas in Baltimore, Maryland.

PARTICIPANTS: Three hundred seven community-dwelling women aged 70 to 79 at study baseline.

MEASUREMENTS: The outcome was all-cause mortality (1994–2009); predictors included up to seven repeated measurements of handgrip, knee extension, and hip flexion strength, with a median follow-up time of 10 years. Demographic factors, body mass index, smoking status, number of chronic diseases, depressive symptoms, physical activity, interleukin-6, and albumin were assessed at baseline and included as confounders. The associations between declining muscle strength and mortality were assessed using a joint longitudinal and survival model.

RESULTS: Grip and hip strength declined an average of 1.10 and 1.31 kg/year between age 70 and 75 and 0.50 and 0.39 kg/year thereafter, respectively; knee strength declined at a constant rate of 0.57 kg/year. Faster rates of decline in grip and hip strength, but not knee strength, independently predicted mortality after accounting for baseline levels and potential confounders (hazard ratio (HR) = 1.33, 95% confidence interval (95% CI) = 1.06–1.67, HR = 1.14, 95% CI = 0.91–1.41, and 2.62, 95% CI = 1.43–4.78 for every 0.5 standard deviation increase in rate of decline in grip, knee, and hip strength, respectively).

CONCLUSION: Monitoring the rate of decline in grip and hip flexion strength in addition to absolute levels may greatly improve the identification of women most at risk of dying. **J Am Geriatr Soc 58:2076–2084, 2010.**

Key words: handgrip strength; hip strength; knee strength; mortality; older women

Age-related decline in muscle strength has been attributed to the loss of muscle mass and muscle quality referred to as sarcopenia. Such changes begin in midlife[1–3] and often result in significant functional and clinical consequences, including greater risk of falling, physical disability, and frailty in older adults.[4–7] Several studies have also shown that weaker muscle strength is associated with all-cause mortality,[8–14] and muscle strength as an indicator of muscle quality is a more-important predictor of mortality risk than muscle mass.[13,14]

Epidemiological research aimed at characterizing age-related changes in muscle strength and their effects on adverse health outcomes has primarily relied on cross-sectional measurements of strength. From a single measurement, it is impossible to distinguish whether the measurement represents an individual's usual "normal" level or an already compromised level relative to his or her past peak strength. The magnitude and nature of the change in muscle strength can only be determined in a longitudinal setting. Data on longitudinal changes in muscle strength are limited, and consist mostly of measurements at two different points in time.[15]

Upper (e.g., grip) and lower (e.g., knee extension) extremity strength have been associated with mortality risk. Although lower extremity strength is deemed to be of great importance in daily functioning in real life and therefore is commonly measured in clinical trials,[16] grip strength is typically favored over knee or hip strength in epidemiological

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studies because of its ease of measurement, higher reliability, and high correlation with other strength measures.[9] However, strength may decline at different rates, contemporaneously or not, for different muscle groups because of factors such as "local" diseases affecting specific musculoskeletal regions, differences in amount of muscle tissue and muscle mass, absolute strength at baseline, and frequency and intensity of use. To the authors' knowledge, neither the correlations between individual-level changes in grip, knee, and hip strength over time nor their relative predictive ability for all-cause mortality has been examined in older adults.

Using data from the Women's Health and Aging Study (WHAS) II with up to seven measurements of muscle strength over 10 years, this study aimed to characterize individual and population average trajectories of age- and aging-related changes in grip, knee, and hip strength over time; the interrelationships between individual rates of change in grip, knee, and hip strength over time; the effects of absolute strength and rate of change in strength on all-cause mortality; and potential mediating effects of health characteristics on the association between strength and mortality.

METHODS

Study Population

WHAS II is a prospective cohort study of 436 women aged 70 to 79 recruited from an age-stratified sample of Medicare beneficiaries in 12 contiguous ZIP codes of Baltimore City and County, Maryland. Study eligibility criteria included no functional difficulty or self-reported difficulty in one of four domains of physical function: mobility, upper extremity, high functioning, and self-care tasks and a Mini-Mental State Examination score of 24 or higher.[17] Thus, participants were representative of the two-thirds highest-functioning community-dwelling women aged 70 to 79. Interviews and physical examinations were conducted at baseline, beginning in 1994, and at six follow-up examinations ($\sim$ 18 months apart except for the interval between the third and the fourth examination, which was, on average, 3 years). Median follow-up time was 10 years between 1994 and 2009. The Johns Hopkins University institutional review board approved the study. The analytical sample for this study consisted of 307 women with baseline data available on all covariates and at least three measurements on grip, knee, and hip strength before death, at study dropout, or by the end of the follow-up period. The 91 women who were excluded from the analysis because they had two or fewer measurements of grip, knee, and hip strength were older and more likely to be African American and have a lower level of education, a higher prevalence of obesity, a lower level of physical activity, and a higher level of interleukin (IL)-6 than the study sample. There was no significant difference in disease burden; smoking status; albumin level; or grip, knee, or hip strength between the two groups at baseline. The 38 women who were excluded because of missing blood samples (n = 37) or body mass index (BMI) values (n = 1) at baseline on average had greater hip strength but were otherwise comparable with the study sample (Table 1). As a sensitivity analysis, the analyses were rerun including the 36 of the 38 women with complete information on age, race, education, and BMI. The results were similar to those of the minimally adjusted model reported in Table 3.

Measures of Muscle Strength

Isometric grip strength was measured in kilograms using a JAMAR hand dynamometer (Model #PC 5030J1, J.A. Preston Co., Jackson, MI). The test was performed three times on each hand with the participant in a sitting position with the arm to be tested pressing against her side at a right angle. Study participants were instructed to grab the metal handles of the dynamometer and squeeze as hard as they could. The maximum measurement in the nondominant hand was used in the analyses. The nondominant hand was selected because it is less subject than the dominant hand is to the variable "non-whole body" influences of trauma, repetitive use syndromes, or strengthening from daily activities.

Maximal isometric strength of the hip flexion and knee extensor muscles was measured using a handheld dynamometer (Nicholas Manual Muscle Tester: Model #01160, Lafayette Instrument, Inc., Lafayette, IN).[18] The tests were performed twice on each side with the participant in a sitting position with knee extended 75° from the horizontal position for the knee strength test and with hips and knees flexed at 90° for the hip strength test. During testing, participants were coached to increase the force gradually to the greatest possible level while the tester was opposing. Strength is expressed as kilograms of force the examiner had to apply to break the isometric contraction. The maximum of left and right hip and knee strength was used in the analyses.

Grip and knee strength were assessed at baseline and at each follow-up examination for a maximum of seven measurements per study participant; hip strength was assessed at each of the first five follow-up examinations for a maximum of six measurements per study participant. Using the results of the three trials of the handgrip test and the two trials of the hip and knee tests, conducted in sequence by the same examiner with only a few seconds between trials, the intrarater reliability coefficient was calculated and averaged 0.90, 0.89, and 0.86 across examinations for grip, knee, and hip strength tests, respectively.

Total Mortality

Data on all-cause mortality were obtained through follow-up interviews with proxies, obituaries, and matching with the National Death Index, with the most recent update completed on January 28, 2009.

Covariates

To assess the independent effect of muscle strength decline on total mortality, age, race, education, BMI, and the following covariates were included in multivariate-adjusted analyses.

Chronic Diseases

Physicians adjudicated presence or absence of 14 major chronic diseases and conditions at baseline (angina pectoris or myocardial infarction; congestive heart failure; peripheral arterial disease; hip fracture; osteoarthritis of the hip, knee, or hand; Parkinson's disease; rheumatoid arthritis; osteoarthritis; stroke; pulmonary disease; diabetes mellitus; cancer; spinal stenosis; and disc disease) based on predefined criteria.[19] The number of "definite" conditions, out of 14, was used as a summary measure of disease burden.

Table 1. Summary of Demographic and Health Characteristics of Women's Health and Aging Study II Samples at Baseline (N = 436)

Characteristic	Analytical Sample (n = 307)	Excluded Because of Missing Strength Measurements (n = 91)*	Excluded Because of Missing Covariates (n = 38)†
Age, mean ± SD	73.6 ± 2.8	74.7 ± 2.6	74.2 ± 2.8
Race, %			
Caucasian	83.7	72.5	79.0
African American	16.3	27.5	18.4
Other	0	1.1	2.6
Education, years, mean ± SD	12.9 ± 3.2	11.4 ± 3.6	12.2 ± 3.3
Number of diseases, mean ± SD§	1.5 ± 1.0	1.6 ± 1.1	1.6 ± 1.1
Body mass index, kg/m^2, %‡			
<18.5	3.6	3.3	0
18.5–24.9	38.4	25.3	36.8
25.0–29.9	39.4	31.9	36.8
≥30.0	18.6	38.5	23.7
Physical activity, %‡			
Inactive	5.9	14.2	2.6
Insufficient	33.9	44.0	26.3
Recommended	60.3	39.6	68.4
Smoking status, %‡			
Never	52.7	55.0	65.8
Former	38.1	27.5	26.3
Current	9.1	15.4	5.3
Geriatric Depression Scale score ≥10, %	7.5	12.1	5.3
Albumin, g/dL, mean ± SD	4.28 ± 0.27	4.23 ± 0.29	—
Interleukin-6, pg/mL, median (range)	2.96 (2.20–3.86)	3.60 (2.60–5.44)	—
Grip strength, kg, mean ± SD	23.5 ± 5.0	23.0 ± 4.6	22.9 ± 4.5
Knee strength, kg, mean ± SD	21.8 ± 5.9	21.1 ± 5.1	23.3 ± 4.8
Hip strength, kg, mean ± SD	18.7 ± 6.7	19.5 ± 6.7	21.8 ± 6.7

* The subset of those who had two or fewer measurements of grip, knee, and hip strength.
† The subset of those who had missing demographic, health characteristics, or blood samples at baseline.
‡ Percentages may not add up to 100% because of missing data.
§ Presence of "definite" diseases (angina pectoris or myocardial infarction; congestive heart failure; peripheral artery disease; hip fracture; osteoarthritis of the hip, knee, or hand; Parkinson's disease; rheumatoid arthritis; osteoarthritis; stroke; pulmonary disease; diabetes mellitus; cancer; spinal stenosis; and disc disease).
SD = standard deviation.

Health Habits

Smoking status was classified based on self-report into current smoker, former smoker, and never smoker. Physical activity was assessed through self-report of total minutes per week spent in six moderate-intensity activities (walking for exercise, heavy household chores, heavy outdoor work, regular exercise, dancing, and bowling) using a modified version of the Minnesota Leisure Time Physical Activity Questionnaire.[4] Women were classified as being inactive or having insufficient or recommended levels of physical activity if they reported 0, 0 to 149, or 150 min/wk or more of activity, respectively. The cutoff of 150 min/wk corresponds to Centers for Disease Control and Prevention and American College of Sports Medicine recommendations of 30 minutes or more of moderate intensity physical activity on most (5) days of the week.[20]

Mental Health

Depressive symptomatology was assessed using the 30-item Geriatric Depression Scale (GDS). Women with scores of 10 or above were considered to have high depressive symptoms.

Biomarkers of Inflammation and Malnutrition

Blood samples were collected from 391 (90%) women at baseline by venipuncture between 9 a.m. and 2 p.m. in a nonfasting state, processed, and stored at −70°C until analysis. Plasma IL-6 was measured in duplicate using enzyme-linked immunosorbent assay (High Sensitivity Kit, R&D Systems, Inc., Minneapolis, MN) from frozen specimens, and the average of the two measures was used. The lower detection limit was 0.1 pg/mL, and the interassay coefficient of variation was 7%. Albumin was measured using dye-binding bromocresol green.

Data Analysis

To describe change in grip, knee, and hip strength over time, for each strength measure, a random sample of 10 individual trajectories of strength within each decile group of strength was plotted at study baseline. The population average trajectories of changes in strength were examined using smooth splines with four degrees of freedom for identification of potential nonlinear trends. Knee strength declined at a steady, linear rate over 10 years, but rates of decline (i.e., slopes) differed before and after age 75 for grip and hip strength. Linear random effects growth curve models (REGCM) were used to assess population average rates of change in strength over time (fixed effects) by including age centered at 70 in the models as a time-dependent covariate. To account for the nonlinear time trends in changes of grip and hip strength, a two-piece linear spline was used in the REGCM with one knot fixed at age 75 (see details in Appendix 1). The knot was identified using a profile likelihood approach. Race, education, BMI, physical activity, and IL-6, which were predictive of early dropout in the model, were also included as covariates to minimize the effect of nonignorable missing data.[21] To account for between-person heterogeneity in terms of individual deviation from the population mean trajectory, intercept (strength at age 70) and age slope (for knee) or age slope before age 75 (for grip and hip) were modeled as random effects with an unstructured variance–covariance matrix.

Next, rates of decline across muscle groups were compared by analyzing the three strength measures jointly in a multivariate REGCM (see details in Appendix 1). Measure-specific strength at age 70 and rates of decline were included as population means and as random effects to model individual differences. This multivariate modeling approach allowed mean differences in standardized rates of decline to be compared and tested directly across muscle groups.

To assess the effects of baseline and change in grip, knee, and hip strength over time on the risk of mortality, individual specific strength at age 70 and rate of change in strength were first estimated from the REGCM with only intercept and age slope in the model as both fixed and random effects. The Kaplan-Meier survival curves were then plotted according to tertile of strength at age 70 and median split of rate of change in strength. The tertile or median cutoffs were selected to achieve a reasonable balance between adequate number of survival events in each strength category for valid representation of the data and minimal loss of power due to categorization.

Finally, joint analysis of the repeated measurements of strength and time-to-death was performed by explicitly modeling the dependency between the time trends of strength change and the survival time using a mixed-effects model (see details in Appendix 1).[22] In the joint model, log survival time was entered as the response variable, and individual-specific strength at age 70 and individual-specific age slope estimated from the REGCM were entered as main effects; baseline age centered at 70, race, education, BMI, smoking status, number of diseases, GDS, physical activity level, IL-6, and albumin were also included as potential confounders. To assess the degree to which change in muscle strength improved the prediction of mortality beyond baseline level, the Maddala likelihood-based R^2_M statistic,[23,24] which approximates the coefficient of determination (R^2) as in linear regression and therefore can be interpreted as explained variation for the dependent variable (survival time), was calculated. Analyses were conducted in SAS version 9.1 (SAS Institute, Inc., Cary, NC) and SPLUS version 2000 (Insightful, Inc., Seattle, WA).

RESULTS

Table 1 summarizes the demographic and health characteristics of the study sample at baseline. At baseline, mean

Table 2. Grip, Knee, and Hip Strength According to Study Visit in the Women's Health and Aging Study II

	n, Mean ± Standard Deviation		
Study Visit	Grip Strength, kg	Knee Strength, kg	Hip Strength, kg
Baseline	306, 23.5 ± 5.0	302, 21.8 ± 5.9	302, 18.7 ± 6.7
Year 1.5	292, 22.3 ± 4.6	286, 20.0 ± 5.5	285, 15.8 ± 5.8
Year 3	295, 18.5 ± 3.9	284, 19.1 ± 4.8	283, 12.9 ± 4.6
Year 6	244, 18.7 ± 4.6	244, 19.1 ± 5.0	241, 12.3 ± 4.3
Year 7.5	204, 17.4 ± 4.7	229, 16.7 ± 4.8	231, 12.9 ± 4.4
Year 9	206, 17.1 ± 4.9	202, 15.4 ± 4.8	204, 12.5 ± 4.4
Year 10.5	122, 17.7 ± 4.2	123, 15.6 ± 4.8	—*

*These data were not collected in Year 10.5.

grip strength ± standard deviation in the nondominant hand was 23.5 ± 5.0 kg, mean knee strength was 21.8 ± 5.9 kg, mean and hip strength was 18.7 ± 6.7 kg.

More than 70% of the 307 women in this study had five or more measurements of grip, knee, and hip strength, with a median follow-up time of 9.4, 9.3, and 9.0 years, respectively, before study dropout or death. Attrition due to study withdrawal was minimal over the first three examinations (8.7%, n = 38 at Examination 2; 2%, n = 8 at Examination 3) and increased at Examinations 4 (14%, n = 55), 5 (11%, n = 37), 6 (17%, n = 51), and 7 (21%, n = 52). Twenty-nine percent of the 307 women died during the study, with an incidence rate of 24.6 per 1,000 person-years.

As shown in Table 2, there was in general a declining trend in mean grip, knee, and hip strength over time. Figure 1A displays a representative sample of individual trajectories of change in grip, knee, and hip strength with age. The absolute value and the rate of change in strength appear to be heterogeneous among different study participants, and the average trends denoted by thick lines underestimated the individual-level changes. The random-effects model estimated that mean grip, knee, and hip strength at age 70 would be 26.5, 23.4, and 21.7 kg, respectively. Grip strength declined an average of 1.10 kg/year (range 0.59–1.83 kg/year) between age 70 and 75 ($P<.001$) and 0.50 kg/year (range −0.01–1.23) thereafter, knee strength declined at a constant rate of 0.57 kg/year (range 0.15–1.00 kg/year), and hip strength declined an average of 1.31 kg per year (range 0.59–2.17 kg/year) between age 70 and 75 ($P<.001$) and 0.39 kg/year (range −0.33–1.25 kg/year) thereafter. Moreover, regardless of baseline value of strength, all study participants experienced a significant decline in grip, knee, and hip strength between age 70 and 75. Figure 1B compares the standardized estimates of average rates of decline in grip, knee, and hip strength after adjusting for race, education, BMI, IL-6, and physical activity. Grip strength declined at the fastest rate between age 70 and 75, followed by hip strength. Although knee strength showed the slowest but a steady decline initially, the rate of decline for grip and hip slowed significantly after age 75, with the decline being much more attenuated in hip than grip and knee after age 75.

Having seen evidence of uniform decline in all three muscle groups at a population mean level, it would be interesting to see whether the changes occurred simultaneously across muscle groups within a person. It was found

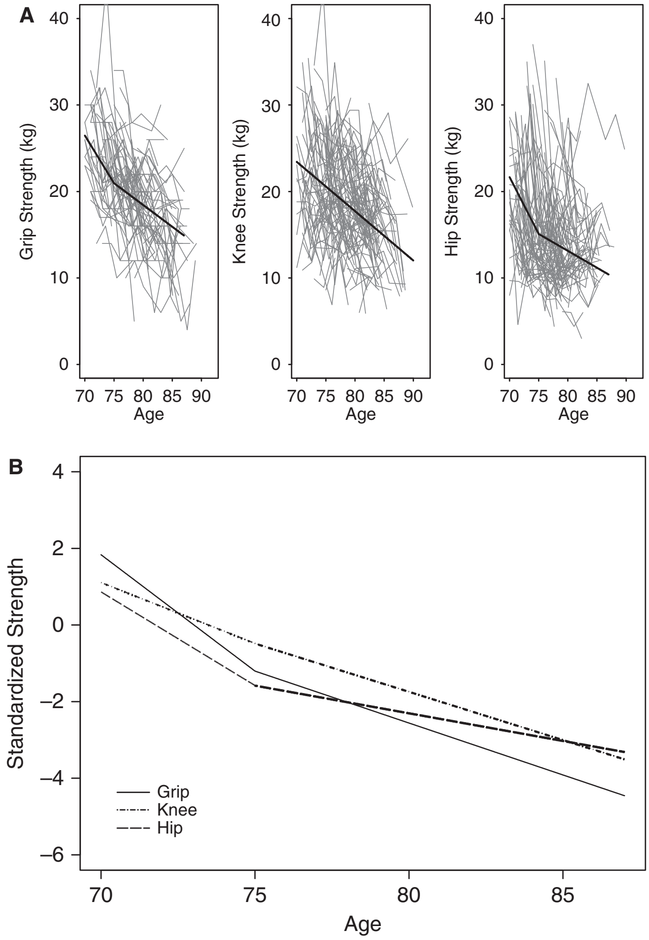

Figure 1. (A) Trajectories of grip, knee, and hip strength over time in the Women's Health and Aging Study (WHAS) II (N = 307); thin lines represent individual trajectories, and thick lines represent population-average trends estimated from linear random effects models. (B) Estimated population-average trajectories of change in grip, knee, and hip strength over time in Caucasian women with 12 years of education, body mass index between 18.5 and 24.9 kg/m^2, interleukin-6 less than 2.5 pg/mL (bottom tertile), and more than 150 min/week of physical activity in WHAS II. The estimates of strength plotted on the Y-axis were standardized to facilitate comparisons across muscle groups.

that individual estimates of grip, knee, and hip strength at age 70 were positively correlated, with correlation between knee and hip being the strongest (Pearson correlation coefficient (r) = 0.67). Although there was positive correlation in rate of decline between hip and knee ($r = 0.51$) within a person, the correlation between grip and knee ($r = 0.10$) and between grip and hip ($r = 0.17$) was much weaker.

Next, whether absolute strength and change in strength over time are associated with all-cause mortality was examined. Mortality risk increased in a stepwise fashion as absolute levels of grip, knee, and hip strength decreased (Figure 2A–C), although the crude associations were not statistically significant, possibly because of weakened power as a result of categorization of the absolute strength. Figure 2D–F compares Kaplan-Meier survival curves of faster and slower decliners (below vs above median rate of decline). Because few women in the bottom (or upper) tertile of knee or hip strength at age 70 experienced rate of decline greater (or less) than 0.56 kg/year in knee strength or 1.29 kg/year in hip strength, the comparison was limited to women in the middle tertile groups of strength at age 70. As shown in Figure 2D–F, the groups of women experiencing faster decline in grip or hip strength had a significantly greater risk of total mortality ($P < .05$); there was no significant effect of rate of decline in knee strength on total mortality ($P = .44$).

The joint longitudinal and survival analyses showed that greater grip, knee, and hip strength at age 70 were significantly associated with lower risk of mortality after adjusting for age, race, education, and BMI at study baseline. Specifically, risk of mortality was 1.4 (95% confidence interval (95% CI) = 1.2–1.7, $P = .001$), 1.4 (95% CI = 1.1–1.7, $P = .004$), and 3.8 (95% CI = 2.2–6.6, $P = .001$) times as high for every 0.5 SD decrease in grip (1.9 kg), knee (2.3 kg), and hip (2.7 kg) strength at 70, respectively. Furthermore, the risk of mortality was 1.4 (95% CI = 1.1–1.8, $P = .003$) and 3.2 (95% CI = 1.8–5.7, $P = .001$) times as high for every 0.5 SD increase in the rate of decline in grip (0.07 kg/year) and hip strength (0.14 kg/year), respectively, and the associations were independent of grip and hip strength at age 70. The results remained essentially unchanged after further adjustment for disease burden, physical activity, GDS, smoking, albumin, and IL-6 (Table 3). For hip and grip strength, including change in muscle strength as a predictor in addition to baseline level explained an extra 20% of total variance in survival time in addition to the model with the baseline level alone; there was no meaningful gain in percentage variance explained by including change in knee strength (<2%). Older age, greater number of chronic diseases, and higher levels of IL-6 were also independently associated with higher risk of total mortality.

DISCUSSION

The study provides the first longitudinal evidence linking aging-associated loss of skeletal muscle strength with all-cause mortality over 10 years in initially high-functioning older women living in the community. Specifically, it was found that rate of change in grip and hip flexion strength was independent of absolute strength in predicting mortality and that the associations were independent of age, disease burden, lifestyle, nutritional status, inflammation, and mental well-being. A previous analysis using data from a sample of moderately to severely disabled women aged 65 and older showed that grip strength was associated with all-cause mortality and cardiovascular mortality after adjusting for demographic and health characteristics similar to those used in the current study.[9] The fact that the current study reached the same conclusion using the least-disabled women strengthens the argument that there may be an independent pathway other than disability linking strength and mortality that is not clearly understood. Because declines in strength are a central component of frailty and a predictor of development of frailty itself,[6] frailty may be in the causal pathway. The current study also confirms the findings from earlier studies, in that muscle mass cannot fully explain the association between strength and mortality. Although BMI is a rather crude measure of muscle mass, and separate measures of lean and fat mass of the upper and lower extremities as well as the whole body were not

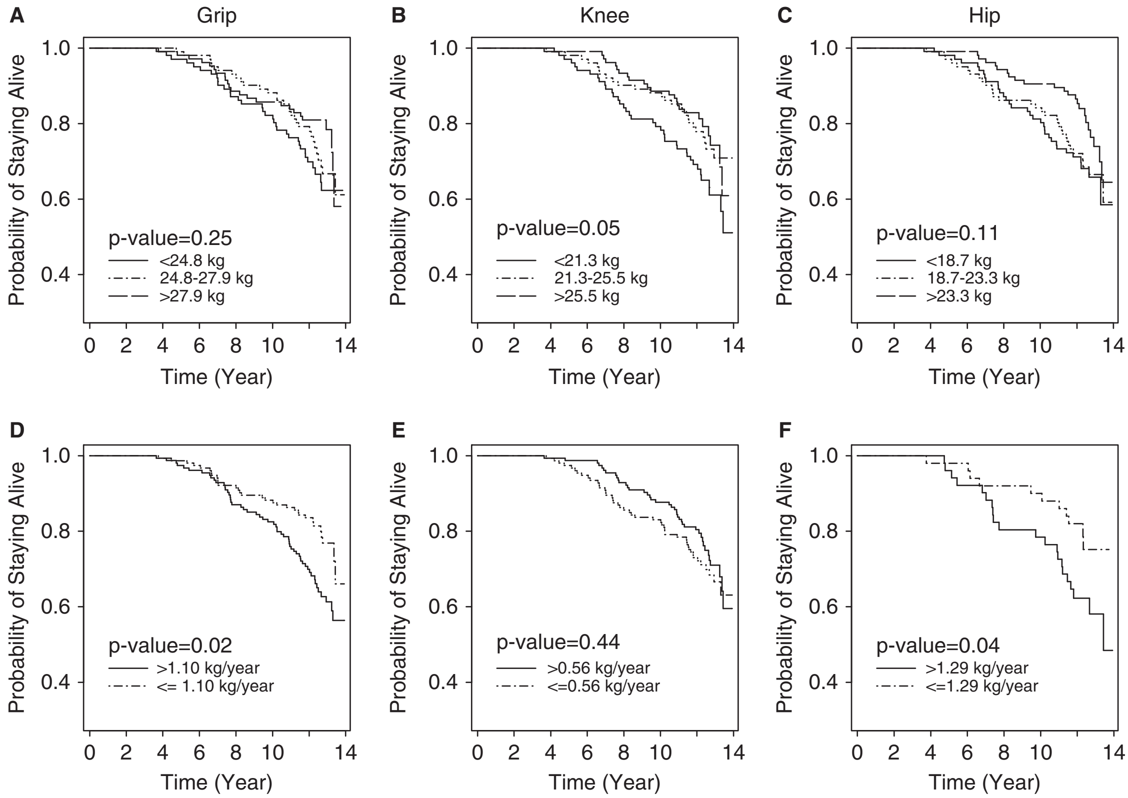

Figure 2. Unadjusted Kaplan–Meier survival curves according to tertiles of estimated strength at age 70 (A–C) and median split of the estimated annual rate of decline in strength (D–F), with the latter restricted to the subset of women in the middle tertile of strength at age 70. *P*-values were based on log-rank tests of the differences between the survival curves.

available in WHAS, a previous study found little difference in the association between strength and mortality regardless of whether BMI or measures of lean and fat mass or muscle and fat areas were used.[13] Therefore, it is unlikely that the selection of measures of body composition could meaningfully alter the independent effect of strength on mortality.

Table 3. Associations Between Knee and Hip Strength at Age 70, Rate of Decline Over Time, and Total Mortality in the Women's Health and Aging Study II (N = 307)

	HR (95% Confidence Interval) *P*-Value	
Measure	**Minimally Adjusted Model***	**Fully Adjusted Model†**
Strength at age 70, kg‡		
Grip	1.42 (1.18–1.70) <.001	1.34 (1.13–1.59) .001
Knee	1.36 (1.11–1.67) .004	1.35 (1.10–1.66) .005
Hip	3.77 (2.15–6.61) <.001	3.11 (1.75–5.50) <.001
Rate of decline§		
Grip	1.41 (1.13–1.77) .003	1.33 (1.06–1.67) .01
Knee	1.17 (0.92–1.48) .20	1.14 (0.91–1.41) .26
Hip	3.17 (1.76–5.72) <.001	2.62 (1.43–4.78) .002

* Adjusted for age, race, education, and body mass index.

† Additionally adjusted for number of diseases, smoking status, depressive symptoms, physical activity, albumin, and interlukin-6.

‡ Hazard ratio (HR) estimates for 0.5–standard deviation (SD) unit decrease in grip (1.9 kg), knee (2.3 kg), and hip (2.7 kg) strength at age 70.

§ HR estimates for 0.5-SD unit increase in annual rate of decline in grip (0.07 kg/year), knee (0.08 kg/year), and hip (0.14 kg/year) strength.

An argument could be made that the reason that rate of strength decline was a strong predictor of mortality is that declining strength may be part of the dying process, such that measurements taken closer to the time of death might have overly influenced the overall rate of decline. Of the 88 women in the study who died, the time between the last measurement and death ranged from 2 weeks to 9.2 years (median 2.3 years); 19 (22%) women died within 1 year of the last measurement of strength. As a sensitivity analysis, the analyses were rerun excluding these 19 women; the results remained unchanged. Therefore, it is unlikely that declining strength close to death determined the significant effect of declining strength on mortality.

The fact that lower and declining hip strength were more strongly associated with mortality than lower and declining grip strength suggests that the former may be more strongly influenced by or contribute to mobility or catastrophic events such as falls that account for significant mortality; experimental and observational studies have shown that poorer muscle strength, especially of the lower limbs, is one of the most important risk factors for falls.[7,25] The current study found that absolute knee extension strength, but not loss of knee strength, was predictive of mortality, although it may be premature to conclude that the rate of change in knee strength is not an important clinical target. Future studies are needed to validate these findings.

Consistent with findings from earlier studies, rate of decline in strength varies across people,[10,15,26] and the current analyses showed that such heterogeneity persisted even after accounting for age and health characteristics. Initial evidence was also found that population-average strength declined at different rates in different muscle groups, with grip strength declining the fastest. In addition, it was found that the decline was, on average, slower in grip and hip after age 75 than it was between age 70 and 75, suggesting that strength plateaus may occur in older age. The slowing rate of decline may indicate important thresholds beyond which external and internal compensatory mechanisms may be activated in an attempt to restore homeostasis, albeit at a suboptimal level. For example, some people may compensate for underlying functional decrements associated with loss of strength by adapting to a modified daily routine (e.g., cutting back on physical activities) to maintain a basic level of performance in real life, thereby retarding subsequent decline. To investigate whether the slow-down occurred predominantly in women survivors over the course of the study, trajectories of change in grip and hip strength were analyzed stratified according to survival status. Although the rate difference remained statistically significant and of comparable magnitude in grip strength in those who died, it was no longer statistically significant in hip strength despite a 45% reduction in average rate of decline after age 75 (results not shown). More research is warranted to assess the generalizability of these findings.

This study confirmed the findings of earlier studies that cross-sectional measurements of grip, knee, and hip strength are highly correlated. Although women experiencing a faster rate of decline in hip strength were also more likely to exhibit a faster rate of decline in knee strength and vice versa, the association between grip and knee or between grip and hip appears to be much weaker. Such discordance in the rate of change in strength between upper and lower body muscle groups warrants further investigation. One hypothesis is that body composition may have a greater effect on lower body strength changes than upper body strength changes, possibly because of disproportionate body mass overload on the lower body. For example, individuals may become less mobile because of obesity, exacerbating declines in strength, perhaps more so in the lower extremities than the upper extremities. Testing of this hypothesis is beyond the scope of this work.

Strengths of this study include its prospective design, long-term follow-up, and its initially high-functioning women. In addition, the statistical methodology employed in this study greatly facilitated the inference concerning the effects of individual trends in strength change (a time-dependent covariate) on all-cause mortality while simultaneously accounting for measurement error in the repeated measurements of strength and mortality-dependent study dropout. One limitation of the study is missing data—as in any epidemiological study with long-term follow-up, particularly those involving older adults. The varying degrees of missing data on strength among study participants were arguably informative (nonignorable missing[21]) rather than random. The degree to which the missing data may bias a given analysis depends on the analytical method used and the degree to which those with observed data represent those in the population targeted by sampling.[27] By including indicators of health risks (race, education, BMI, level of physical activity, and inflammation) that were associated with study dropout in the longitudinal models as covariates, it was hoped that a reasonable approximation to the missing at random assumption would be achieved,[21] providing at least partial protection against biased inference that informative dropout unaccounted for by mortality risk would otherwise induce. Alternatively, given that there was an overall decline in grip, knee, and hip strength over time, it is likely that selective loss of the oldest and most cognitively and physically impaired participants resulted in conservative estimates of true decline and its effect on total mortality, although the magnitude of such selection bias is hard to quantify without additional modeling assumptions that can be neither confirmed nor refuted based on the observed data.

An overwhelming body of observational and experimental evidence suggests that aging-related decline in muscle strength is reversible through progressive resistance strength training (PRT) even in very old people.[16] A recent Cochrane review of 73 trials on this topic found a moderate to large beneficial effect of PRT on lower-limb extensor muscle strength, with a standardized mean difference of 0.84 (95% CI = 0.67–1.00) over 8 to 12 weeks between PRT and non-PRT groups.[16] Although the leg extensor group of muscles was the most frequently evaluated in the PRT studies,[16] grip strength as a prognostic nutritional parameter was often assessed in the nutritional intervention studies.[28–30] A trial of 80 middle-aged and older malnourished adults with benign digestive disease, reported a 0.48-SD improvement in grip strength after 3 months of treatment with protein- and energy-rich supplements, compared with a 0.1-SD improvement in controls.[29] An 8-week oral nutrition supplementation given to 136 people aged 75 and older after hospital discharge was also found to be associated with a 0.39-SD increase in grip strength, compared with a 0.12-SD increase in nonsupplemented controls.[28] The fact that the current study found an average decline of approximately 0.2 SDs per year in grip and hip strength between age 70 and 75 gives a sense of hope and optimism for the future of exercise and nutritional therapies.

In summary, muscle strength is an important marker and a potential cause of mortality in old women. Monitoring the rate of decline in grip and hip flexion strength in addition to absolute levels may greatly improve the identification of women most at risk of dying. In addition, because of observed limited heterogeneity in the rate of decline among women with extreme high or low strength at age 70, the results from this study may be most relevant for women with values at the middle of the strength distribution, where individual differences in rate of change could be most predictive of future mortality. Despite the benefits of PRT and nutritional intervention for preventing, delaying, and reversing muscle strength decline in older adults, it is unknown whether better muscle strength translates into better performance of daily tasks,[31–33] because the latter may involve a number of other factors (e.g., home environment, psychological, social support) that may be independent of or interact with muscle strength. These findings raise the question of whether there are critical points in decline in muscle strength where interventions would be most effective and should be targeted for intervention.

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APPENDIX 1

To assess the effects of baseline and change in grip, knee, and hip strength over time on the risk of mortality, joint analysis of the repeated measurements of strength and time-to-death were performed by explicitly modeling the dependency between the time trends of strength change and the survival time using a nonlinear mixed-effects model.[34] Specifically, the joint model consists of two submodels: linear random effects growth curve model (REGCM) for the longitudinal process of change in strength (termed "longitudinal submodel") and accelerated failure time model (AFT) for the survival process (termed "survival submodel"). Suppose that the ith person had grip strength measurements $y_{i1}, \ldots, y_{in_i}$ over n_i successive examinations ($i = 1, \ldots, n$), the REGCM characterizes the trajectory of grip strength as:

$$y_{ij} = \beta_0 + \beta_1 t_{ij} + b_{i0} + b_{i1} t_{ij} + \varepsilon_{ij}, \qquad (1)$$

where t_{ij} is the time in years of person i's jth evaluation since age 70 ($j = 1, \ldots, n_i$); $\beta_0 + \beta_1 t_{ij}$ is the population mean trajectory by which grip strength changes over time (fixed effects), and $b_{i0} + b_{i1} t_{ij}$ is the deviation of person i's trajectory from the mean trajectory (random effects), such that $\beta_0 + b_{i0}$ and $\beta_1 + b_{i1}$ can be interpreted as the individual-level grip strength at age 70 and the annual rate of decline in grip strength, respectively, for person i. Model (1) typically assumes that $(b_{i0}, b_{i1}, \varepsilon_{ij})$ are normally distributed with mean 0 and that the residual errors ε are independent of (b_{i0}, b_{i1}). The REGCM differs from the conventional mean effects regression in that it describes the extent to which individual baseline and rate of change vary about the population mean (between-person heterogeneity) through the random effects. The degree and significance of the heterogeneity can be assessed based on the variances of b_{i0} and b_{i1}. To account for the nonlinear time trends in changes of grip and hip strength, a two-piece linear spline was used in the REGCM with one knot fixed at age 75:

$$y_{ij} = \beta_0 + \beta_1 t_{ij} + \beta_2 I(t_{ij} - 5) + b_{i0} + b_{i1} t_{ij} + \varepsilon_{ij}, \qquad (2)$$

where $I(t_{ij} - 5)$ is a binary indicator (1 if $t_{ij} > 5$, 0 otherwise); b_{i0} and b_{i1} are the random intercept and random slope before age 75, respectively. $\beta1$ and $\beta1+\beta2$ are the rates of change in strength before and after age 75, respectively. It was not possible to estimate random effect for age slope after age 75, which could mean that there was no additional significant between-person variability in age slope after age 75 after controlling for the between-person heterogeneity before age 75 or that the sample size or the cluster size (number of repeated measurements within a subject) were too small to estimate reliably.

The validity of the REGCM relies on the assumption of data missing at random;[21] race, education, body mass index, physical activity, and interleukin-6, which were predictive of early dropout in the model, were included as covariates in models (1) and (2) to minimize the effect of nonignorable missing data, a statistical adjustment technique commonly used in the missing data literature. Because the main interest of the study was to assess the independent association between change in muscle strength and mortality, the covariates adjusted in the longitudinal submodel bear little scientific interest.

The survival submodel is specified as

$$\log(\mu_i(st)) = z_i\alpha + \gamma_1 b_{i0} + \gamma_2 b_{i1}, \qquad (3)$$

where survival time (st; time to death since study baseline) was assumed to follow a Weibull distribution $(k, \mu_i(st))$, with shape parameter k and mean survival time $\mu_i(st)$ for person i. The fact that the relationship between $\log(-\log(S(st))$, where $S(st)$ is the Kaplan–Meier estimate of the survival function, and $\log(st)$ can be approximated using a straight line supports the validity of the Weibull distribution assumption. In (3), z_i denotes the confounders (e.g., age at study baseline) of the association between strength and mortality; b_{i0} and b_{i1}, respectively, are individual-specific absolute strength at age 70 and rate of decline estimated from the longitudinal submodel (1) for knee strength and submodel (2) for grip and hip strength, with corresponding regression coefficients γ_1 and γ_2 representing the effects of individual trajectory of strength on log survival time. For ease of model interpretation, the regression coefficients $\gamma = (\gamma_1, \gamma_2)$ estimated from the model (3) were converted using the formula $\exp(-k\gamma)$ to permit the usual hazard ratio interpretation, as in the conventional Cox proportional hazard model. The parameters for the two submodels were estimated jointly using maximum likelihood using SAS PROC NLMIXED (SAS Institute, Inc., Cary, NC), as detailed previously.[34]

Goodness-of-fit criteria, including log likelihood ratio, the Akaike Information Criterion, and the Bayesian Information criterion, were used for model selection. To assess global goodness-of-fit of the joint model, the observed population average trajectories of strength and time to death were visually compared with the model-based estimates. The close agreement between the observed and the fitted estimates indicated that the joint longitudinal and survival model fit the data reasonably well (results not shown).

To compare the rates of decline in grip, hip, and knee strength, the univariate REGCM (1) was extended to a multivariate REGCM as follows:

$$\begin{aligned} y_{ij} = {} & \beta_{01} + \beta_{02} I_{\text{knee}} + \beta_{03} I_{\text{hip}} + \beta_{11} t_{ij} + \beta_{12} t_{ij} I_{\text{knee}} \\ & + \beta_{13} t_{ij} I_{\text{hip}} + b_{i01} + b_{i02} I_{\text{knee}} + b_{i03} I_{\text{hip}} \\ & + b_{i11} t_{ij} + b_{i12} t_{ij} I_{\text{knee}} + b_{i13} t_{ij} I_{\text{hip}} + \varepsilon_{ij}, \end{aligned} \qquad (4)$$

where I_{knee} and I_{hip} are binary indicators with a value of 1 if y_{ij} is a measurement of the type of strength denoted by the subscript of I and 0 otherwise, β_{01} represents population average grip strength at age 70, β_{02} (β_{03}) is the difference between population mean grip strength and knee (hip) strength at age 70, β_{11} is population average rate of change in grip strength, β_{12} (β_{13}) is the difference between the population average rate of change in grip and that of knee (hip), and $(b_{i01}, b_{i02}, b_{i03})$ and $(b_{i11}, b_{i12}, b_{i13})$ denote random effects that follow a multivariate normal distribution with an unstructured variance-covariance matrix. The nonlinear age effect on changes in grip and hip strength was accommodated by including in (4) a linear spline for age, as in Model (2).