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IMPACT OF PHYSICAL FUNCTION ON HEALTH OUTCOMES IN OLDER COMMUNITY-DWELLING WOMEN

by

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IMPACT OF PHYSICAL FUNCTION ON HEALTH OUTCOMES

IN OLDER COMMUNITY-DWELLING WOMEN

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ABSTRACT

In previous epidemiologic studies, poor physical function has been associated with increased risks of nursing home placement, hospitalization, and mortality in older adults. However, these associations are subject to confounding and misclassification. Studies to date do not adequately account for these biases; previous studies have evaluated only cross-sectional associations, followed participants for less than ten years, or inadequately controlled for confounders by using only baseline values of characteristics that vary over time.[5,75,106] In addition, no study has finely controlled for age, the strongest predictor of both physical function and health outcomes such as mortality and institutionalization in older adults. This dissertation is comprised of three studies that evaluated the associations between physical performance and skeletal health, respectively, with mortality and long-term nursing home residence while utilizing age-based risk set sampling, evaluating mediation by osteoporotic fractures, and controlling for death as a competing risk.

All studies in this dissertation use data from the Study of Osteoporotic Fractures, a longitudinal epidemiologic study of older women with over 20 years of follow-up. Study 1 evaluated the association between physical performance and incident disability,

using time-dependent exposures and confounders, and age-based risk sets to control for age. Women with poorer performance based on individual measures of physical function had an increased risk of incident disability over follow-up. Similarly, a whole body summary physical performance score was linearly associated with increased risk of death. Study 2 evaluates the association between low bone mineral density and mortality. Women with low bone mineral density were more likely to experience a fracture and to die compared to women with normal bone mineral density. Mediation analyses suggested that incident fracture had a measureable impact on this association, though this varied by fracture site. Study 3 evaluates the association between slow gait speed and risk of long-term nursing home placement while controlling for death as a competing risk. Women with slow gait speed had an increased risk of long-term nursing home residence, which was slightly attenuated when considering death as a competing risk.

These results extend previous studies of the health effects of physical function among older women. The findings underscore the clinical importance of physical function and bone mineral density (BMD) for identifying older adults for whom interventions to improve their physical function may prolong their independence and optimize health.

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LIST OF ABBREVIATIONS

aHR ……. Adjusted Hazards Ratio

BMD……...Bone Mineral Density

BMI …….....……Body Mass Index

BU ..... Boston University

CI ……...……Confidence Interval

DXA…….Dual-Energy X-Ray Absorptiometry

GEE ……Generalized Estimating Equations

HR ……...……Hazards Ratio

IADL……....Instrumental Activities of Daily Living

IR ……...……Incidence Rate

Kg ……...……Kilogram

M/S……...Meters Per Second

MMSE……...Mini Mental Status Exam

NHANES……...……National Health and Nutrition Examination Survey

PY……..…Person Years

QDR ……. Quantitative Digital Radiography

SAS…….Statistical Analysis System

SD……Standard Deviation

Sec……Seconds

SOF …….……Study of Osteoporotic Fractures

SPPB…….Short Physical Performance Battery

WHO……...World Health Organization

INTRODUCTION

Poor performance-based physical function has been associated with many adverse health and functional outcomes in older adults, including disability,[23,46,48,49,103,124] mortality,[12,22,23,47,75,106,109] hospitalization,[23] and placement in long-term care facilities.[23,47] These relationships are highly confounded by time-varying health and sociodemographic characteristics, particularly age.[3] They are also affected by competing risks and confounders that are on the causal pathway. Studies to date do not adequately account for these biases; previous studies have evaluated only cross-sectional associations,[68,88] followed participants for less than ten years,[3,23,124] or inadequately controlled for confounders by using only baseline values of characteristics that vary over time.[5,75,106] In addition, few studies have evaluated the role of competing risks (e.g., mortality) of the association between physical function and health outcomes.[20]

This dissertation evaluated prospectively the associations between physical function, as well as skeletal health, with incident disability, mortality, and long-term nursing home placement in a large sample of community-dwelling older women. To reduce potential confounding and bias in the measured associations between physical function and health outcomes, several methods were employed. These included the use of age instead of follow-up time as the time scale, evaluating direct and indirect effects through mediation models, and controlling for the potential competing risk of mortality. These methods yielded a more valid and precise estimate, as well as more complete description, of the association between physical function and skeletal health, respectively, with incident disability, mortality, and long-term nursing home placement.

The knowledge gained from the following studies contributes to a better understanding of the role of physical function in aging among older women and extends findings from previous studies of the health effects of physical function and skeletal health in this population. These results underscore the clinical importance of physical function and skeletal health, as both indicators may identify older women for whom interventions to improve their physical function may prolong their independence and optimize health.

Study Population

All three studies used data from the Study of Osteoporotic Fractures (SOF), a prospective cohort study. SOF is ideal for evaluating the longitudinal health impact of physical function in older adult women due to the wide age range of the participants, large sample size, biennial assessments, and follow-up period of 20 years.

The SOF sample includes 9,704 White women aged 65 or older who were recruited between 1986 and 1988 from population-based listings in four areas of the United States: Baltimore County, MD; Minneapolis, MN; Portland, OR; and the Monongahela Valley, PA.[32] Women were excluded if they could not walk without assistance or had a history of bilateral hip replacement. Although Black women were initially excluded because of their low incidence of hip fracture, 662 Black women who met the same inclusion criteria were enrolled during 1996–97. Approximately every two years, SOF participants completed a comprehensive clinical evaluation. All participants provided written informed consent and the Institutional Review Boards of each study site approved the study protocol.

Approximately every two to six years, SOF participants had a comprehensive clinical evaluation to assess physical and cognitive health. Over the study period, White women contributed a maximum of nine examinations (spanning 1986–2010) and Black women contributed a maximum of four examinations (spanning 1996–2010). Studies 1 and 2 were conducted on these longitudinal data.

Study 3 made use of the linked SOF-Medicare dataset. Of the 10,366 participants in SOF, 9,228 were linked to Medicare Claims Files by their social security and/or Medicare numbers. Medicare claims data were available starting from 1/1/1991, which corresponded most closely to the fourth SOF interview.

Common Measures

The three studies reported in this dissertation describe similar sociodemographic and health characteristics of the SOF participants. Sociodemographic variables included the respondent's age, marital status (married versus other), self-reported race (White versus Black), highest level of education (> 12 years versus ≤ 12 years), and SOF study site. Health status variables included body mass index (BMI, weight in kilograms/height in meters^2, categorized according to standard cut points as <18.5, 18.5–24.9, 25–30, ≥30 km/m^2) based on measured weight and height; smoking status (never, past, current); cognitive function based on the modified Mini Mental State Exam (MMSE, possible scores 0–26, higher scores mean better cognitive performance),[42] and whether or not a physician told the participant that she ever, or since the previous visit, had osteoarthritis (yes/no), hypertension (yes/no), diabetes (yes/no), or chronic obstructive pulmonary disease (COPD, yes/no).

A multimorbidity score was calculated by summing five domains of medical conditions, a common measure of multimorbidity.[52] Participants reported whether they had ever been diagnosed, or had been diagnosed since their last examination, with any of 11 medical conditions (osteoarthritis, osteoporosis, rheumatoid arthritis, cancer, stroke, myocardial infarction, congestive heart failure, other heart disease, hypertension, type 2 diabetes, and chronic obstructive pulmonary disease). If participants reported having been diagnosed at any point over follow-up, they were considered to have that medical condition for the rest of their time in the study.

These 11 medical conditions were further classified into five physical health domains (cardiovascular and respiratory, metabolic, cancer, immune, and musculoskeletal). No linear association with nursing home residence was found across a summary score of the five domains and few participants reported conditions in more than three domains, so the five health domains were summed and operationalized as a three-level categorical variable (no conditions in any domain, conditions in a single domain, and conditions in two or more domains).

Demographic and clinical characteristics were evaluated at baseline only for cross-sectional analyses and as time-varying covariates in time-dependent longitudinal analyses.

STUDY 1: PERFORMANCE-BASED PHYSICAL FUNCTIONING AND INCIDENT DISABILITY

Introduction

Disability, the inability to perform socially-defined activities and roles,[47] affects the psychological and social health of older adults. Self-reported limitations in any of the Instrumental Activities of Daily Living (IADLs) incorporates aspects of an older adult's ability to function in everyday life, and also encompasses perceived physical competence, mastery, and even depressive symptoms.[66] However, the relationship between performance-based physical function and self-reported disability is inconsistent. Several studies have found moderate to strong associations between performance-based physical function and subsequent disability,[47,124] but results vary by study sample and the particular performance measures used. These inconsistent associations may result from inadequate control for age as a confounder of this association. Age is the strongest predictor of function and disability: physical function declines with age[36,39] and the rate of this decline is faster at older ages.[97] As such, physical function that is not updated over time is vulnerable to misclassification over long follow-up periods, particularly among older adults. To date, previous studies have evaluated performance-based functioning as a baseline exposure,[47,63] and others had short follow-up time (e.g., three years)[51] or excluded women.[51,72] Further, to my knowledge, no study of this association has included time-varying exposures and confounders, nor utilized risk-set sampling and the Andersen-Gill data structure to more finely control for age. The current study utilizes time-dependent analysis and age-based risk sets to minimize confounding by age and

misclassification of physical function over time.

Performance-based physical function is frequently used to evaluate the health and functional status of older adults in both clinical and research settings. Physical performance measures range from individual tests such as usual or fast gait speed [23,48,49,102,124] to summaries such as the Short Physical Performance Battery (SPPB), which assesses lower-extremity function by combining scores on tests of gait speed, balance, and chair stand speed.[47] Associations observed with summary measures of lower body strength and function may be due to the inclusion of gait speed, which may be as strong a predictor of disability as the summary score itself.[49] Associations between other summary measures and health outcomes are inconsistent,[27] and have been restricted to measures of either lower-extremity or upper-extremity function.[47,91,111] To our knowledge, no studies have combined measures of lower- and upper-extremity function to reflect whole-body function. Such measures may more accurately estimate risk of disability in individual IADLs that incorporate upper body function.

In this study, we examined the association of three individual measures of lower- and upper-extremity physical functioning independently, and together in a summary score, with the first occurrence of an IADL disability. The performance measures were updated at every clinical interview to allow for time-dependent analyses. We hypothesized that older community-dwelling women with poorer physical function of each individual summary measure (e.g., slower gait speed, lower grip strength, slower chair stand speed) over time would have a greater incidence of IADL disability and greater risk of an increase in IADL limitations compared to those with the best physical

function, and these associations would be strongest for gait speed. We also hypothesized that older women with poorer performance overall (e.g., low summary performance score) over time would have a greater incidence of IADL disability and greater risk of an increase in IADL limitations compared to those with the best physical function. Furthermore, these time-varying associations would be stronger than those using only baseline measures of physical function.

Methods

Data Collection and Analytic Sample

Approximately every two to six years, SOF participants had a comprehensive clinical evaluation to assess physical and cognitive health. At Visit 1 (1986–1987), 6,296 White women (65% of the sample) reported no limitations in any IADLs. At their baseline clinical evaluation (Visit 6, 1997–1998), 320 Black women (48% of the sample) reported no limitations in any IADLs. Participants contributed person-time from the date of their first clinical visit to either the date of incident disability, withdrawal from SOF, death, or end of the follow-up period on December 31, 2010, whichever came first. White women contributed a maximum of nine visits and Black women contributed a maximum of four visits through December 31, 2010, for a maximum of 24 years and 14 years of follow-up, respectively. The analytic sample consisted of 6,282 White women and 310 Black women who reported no IADL difficulties and completed all three measures of physical performance at baseline, and excluded 14 White women and 10 Black women who lacked these measures at baseline. Women who reported difficulty with a single IADL were added to the original sample in sensitivity analyses of increasing disability

(n=1,775 White women and n=131 Black women were added to the original sample), while women who reported difficulty in two or more IADLs were excluded from both the main and sensitivity analyses.

Measures

All measures of physical performance and covariates were initially evaluated at baseline only and then updated at each study visit in a time-varying analysis. Race-specific sample-based quartiles were calculated for each individual summary performance score, and participants who attempted but were unable to complete the measure were excluded from the quartiles and scored as 0 (range: 0 – 4).[47] Missing values for covariates due to participant non-response were populated with the response from the previous study visit. Participants who did not attempt any of the three physical performance measures at baseline were excluded from the sample, and therefore there is no missing exposure data at the first study visit. Variables evaluated as potential confounders are described in the section Common Measures.

Usual gait speed (meters/second, m/s) was measured by trained interviewers over a straight six-meter course and averaged over two timed trials.[38] Interviews conducted in the participant's home where a straight six meter-long area was not available were measured over either a two- or three-meter course, and speed was calculated as course length divided by time in seconds. Faster speeds indicated better performance (i.e., higher values for m/s). Gait speed was found to have good test-retest reliability.[38,113]

Maximum isometric grip strength (kilograms, kg) was measured in both hands with a dynamometer (Preston Grip dynamometer, Takei Kikikogyo, Tokyo, Japan). Grip

strength was tested twice in each hand and averaged over the four trials. If participants could not complete the test in one hand, the two trials from the other hand were averaged. Stronger grip strength indicated better performance (i.e., higher values for kilograms, kg). Earlier studies in SOF found that weaker grip strength was associated with impaired function.[38]

Chair stand speed (seconds, sec) was measured as the time it took participants to stand up from a seated position in a straight-back chair five times, with their arms folded across their chest.[30,89] Faster chair stand speed indicated better performance (i.e., fewer seconds to complete). The chair stand speed test has good test-retest reliability in older, community-dwelling adults.[13]

A summary performance score was calculated based on the three component measures: usual gait speed, maximum isometric grip strength, and chair stand speed. Scores for each component measure were divided into race-based quartiles (1–4, 0 if the participant attempted but was not able to complete the test) and then summed to create a composite summary score (0–12). Higher scores indicated better performance. The summary performance score was evaluated as both a categorical variable, based on previous research,[47] and a continuous variable, which had greater power to detect a significant association between physical function and disability as the sample was divided into fewer categories which increased the sample for comparison.

The summary performance score is based on the SPPB,[47] a measure of lower body function and strength which sums the quartiles of usual walking speed, three measures of tandem stands, and chair stand speed. The SPPB range is 0–12 and was found to be

highly associated with disability in cross-sectional analyses.[47] While similar measures of tandem stand were collected in the baseline cohort of White women in SOF, these measures were not collected at every clinical evaluation, nor were they collected at baseline in the Black sample. As such, the SPPB could not be replicated in the current analysis of time-varying physical performance. Instead, maximum isometric grip strength, which was collected at every clinical evaluation, was used in place of the tandem stand. As such, the resulting summary performance score was a measure of both lower- and upper-extremity function and strength.

Instrumental Activities of Daily Living (IADL) tasks[61,73] were self-reported at every interview. Participants reported whether they could complete each of five tasks with or without difficulty: walking 2–3 blocks outside on level ground, climbing 10 steps without stopping/resting, preparing own meals, doing heavy housework, and shopping. The resulting dichotomous response variables (no difficulty versus any difficulty) were then summed to create a summary IADL score (range: 0–5), with higher values indicating greater disability. Incident disability among participants with an IADL summary score of 0 was defined as the first SOF follow-up interview at which a woman reported difficulty in any one of the five IADL tasks. In sensitivity analyses, increasing disability among participants with at most one IADL limitation was defined as the first SOF follow-up visit at which an increase in the number of IADL tasks was reported.

Statistical Analyses

SOF participants contributed person-time from the age of their baseline clinical evaluation (Visit 1 for White and Visit 6 for Black women) until incident disability,

withdrawal from SOF, or the end of follow-up, whichever came first. Black women were enrolled several years after White women, and therefore contributed less follow-up time (maximum possible follow-up time was 14 years versus 24 years, respectively). To accommodate the race-dependent differences in the enrollment period, regression analyses were stratified by race. The relationship between physical function and disability was evaluated in two sets of models: baseline only and time-dependent performance measures and covariates.

Descriptive analyses compared distributions of baseline sociodemographic and health characteristics in the total analytic sample and also stratified by race. Means and standard deviations were compared for continuous variables, while frequencies and proportions were calculated for dichotomous and categorical variables. Crude incidence rates of the association between each physical performance measure and first IADL limitation.

In regression analyses, Cox proportional hazards models using age as the time scale were performed to calculate age-adjusted and adjusted hazard ratios (HR and aHR) and 95% confidence intervals (CI) between physical performance (individual measures and summary score) and incident IADL disability. The Andersen-Gill data structure[6] was used to accommodate time-dependent covariates and delayed entry, a consequence of using age as the time scale. Covariates were included in the model if they were established risk factors for poor physical performance or disability, if they were associated with any physical performance measure or disability in the current sample, or if their inclusion in the proportional hazards model meaningfully changed the HR of the

association between poor physical performance and disability by 10% or more. The final adjusted models included education, marital status, smoking status, BMI, multimorbidity score categories, and SOF clinical center. Departures from proportional hazards were assessed by comparing models with and without interaction terms between physical performance quartiles and age (median cut point of <75 versus ≥75 years of age) using the likelihood ratio test, as well as by examining the log-negative-log survival curves of these models.

In time-dependent sensitivity analyses, the sample was expanded to included women with one prevalent IADL disability at baseline and increasing disability, instead of incident disability, was modeled. Descriptive statistics and regression analyses were repeated as described above.

Analyses were conducted using SAS software (Statistical Analysis System, version 9.4, Cary, North Carolina). All statistical tests were two-sided and used 95% confidence intervals.

Results

Sample Characteristics

At the baseline clinical examination, the mean age of the 6,282 White women was 71.05 years (SD=4.91), 51% were married, and 80% had graduated high school. More than a third of the cohort reported medical conditions in at least one domain (37.71%). Two-thirds of the sample (66.59%) experienced incident disability over the follow-up period. Over the entire follow-up period, 3,593 (57.20%) women died and 678 (10.79%) terminated from SOF. Women included in the analytic sample were younger, had lower

BMI, and performed better on each individual performance measure than those who were excluded because of prevalent IADL limitations (Table 1-1a).

Black women were older and had more medical conditions than White women. At the baseline clinical examination, the mean age of the 310 Black women was 74.76 years (SD=4.45), 28% were married, and 75% had graduated high school. Almost half of the cohort reported medical conditions in at least one domain (47.42%). About a third of the sample experienced incident disability over follow-up (36.77%), which likely was a much lower proportion than the White cohort due to a shorter follow-up time. Over the entire follow-up period, 60 (19.35%) women died and 34 (10.9%) terminated from SOF. Like the White cohort, Black women included in the analytic sample were younger, had lower BMI, and performed better on each of the individual performance measures than those who were excluded because of prevalent IADL limitations (Table 1-1a).

Physical Performance

Sample-based cut points for the performance measures were calculated across all study visits separately for each race cohort (Table 1-A1). At the baseline clinical examination, no participant attempted but did not complete any of the physical performance measures, as complete physical performance data was an eligibility requirement.

Distributions of gait speed and chair stand speed were different between the two cohorts, with Black women performing more poorly than White women (Table 1-A1). For example, only the fastest Black women (quartile four) walked faster than the clinically relevant gait speed cut point of 1.0 m/s.[113] However, in both cohorts, the

lowest grip strength quartile cut point was the same (16.50 kg) and closely corresponded to cut points that predict IADL disability in women over 65 years of age.[74]

At baseline, mean gait speed was 1.07 m/s (SD=0.20) and 35.28% of White women walked slower than 1.0 m/s. Mean grip strength was 21.55 kgs (SD=4.89) and mean chair stand speed was 11.29 seconds (SD=3.30, Table 1-1b). At the baseline visit, the largest proportion of White women were in the highest quartile of gait speed (37.23%) and grip strength (42.93%), and the second highest quartile of chair stand speed (26.23%) compared to the lower quartiles (Table 1-2). Mean summary performance score was 7.20 (SD=1.48, Table 1-1b).

Black women had poorer performance across all measures at baseline than White women. At baseline, mean gait speed was 0.92 m/s (SD=0.17) and 68.71% of Black women walked slower than 1.0 m/s. At the baseline visit, mean grip strength was 20.32 (SD=4.89) and mean chair stand speed was 13.53 seconds (SD=4.08, Table 1-1b). The largest proportion of Black women were in the highest quartile of gait speed (31.29%), grip strength (30.00%), and the second lowest quartiles of chair stand speed (26.77%), noting that quartile cut points for all physical performance measures were lower in this cohort than for the White cohort (Table 1-2). Mean summary performance score was 7.35 (SD=1.58, Table 1-1b).

Physical Performance and Incident Disability

Over 92,901 years of person-time, 4,193 White women developed an IADL disability (IR = 451.34 per 10,000 person-years). In both age-adjusted and fully adjusted analyses of baseline gait speed, there was a monotonic increase in rate of incident

disability across gait speed quartiles (Q1 vs. Q4 adjusted HR: 1.65, 95% CI: 1.48 – 1.84, Table 1-3a). This association was stronger in time-dependent analyses (Q1 vs. Q4 aHR: 3.83, 95% CI: 3.41 – 4.31, Table 1-4a). A similar pattern was found with grip strength and chair stand speed. Women in the lowest quartile of each measure had a greater rate of incident disability than those in the highest quartile, and these associations were stronger in time-dependent analyses (grip strength Q1 vs. Q4 aHR: 2.15, 95% CI 1.91 – 2.41; chair stand Q1 vs. Q4 aHR: 2.69, 95% CI: 2.42 – 2.99, Table 4a) compared to baseline analyses (grip strength Q1 vs. Q4 aHR: 1.49, 95% CI 1.33 –1.68; chair stand Q1 vs. Q4 aHR: 1.65, 95% CI: 1.50 – 1.80, Table 1-4a). While patterns of increased rate of disability across performance quartiles remained similar between the baseline and time-dependent analyses, the estimated rate of incident disability was attenuated in the baseline analyses.

Across highest to lowest summary performance scores there was a clear pattern of greater rate of incident disability, although as with the individual performance measures these rates were lower in the baseline analysis compared to the time-dependent analysis (baseline score 3 vs. score 12 aHR: 2.77, 95% CI: 2.06 – 3.72; time-dependent score 3 vs. score 12 aHR: 8.26, 95% CI 5.95 – 11.47, Tables 1-3b and 1-4b). For every one point increase in summary performance score, rate of disability was 10% lower in baseline analyses (HR: 0.90, 95% CI: 0.89 – 0.92, Table 1-3b) and 21% lower in time-dependent analyses (HR: 0.79, 95% CI: 0.78–0.80, Table 1-4b).

Over 3,264 years of person-time, 118 Black women developed an IADL disability (IR = 361.52 per 10,000 person-years). Similar to the White cohort, there was a

monotonic relation between women with slower gait speed quartile and increased rate of IADL disability, although the small number of cases and short follow-up time led to imprecise estimates that often included the null value. These associations were less precise using baseline measurements only (baseline Q1 vs. Q4 aHR: 0.61, 95% CI: 0.29 – 1.24; time-dependent Q1 vs. Q4 aHR: 2.59, 95% CI: 1.42 – 4.73, Tables 1-3a and 1-4a).

Results were less clear across grip strength quartiles for both the baseline and time-dependent analyses (baseline Q1 vs. Q4 aHR: 0.94, 95% CI: 0.53 – 1.64; time-dependent Q1 vs. Q4 aHR: 1.50, 95% CI: 0.86 – 2.62, Tables 1-3a and 1-4a). Results across chair stand speed quartiles were inconclusive: there were no events in the lowest quartile and slight, but imprecise, increased rates of IADL disability in women with the slowest chair stand speed in the time-dependent analysis but not the baseline analysis (baseline Q1 vs. Q4 aHR: 0.76, 95% CI: 0.45 – 1.30; time-dependent Q1 vs. Q4 aHR: 1.28, 95% CI 0.72 – 2.30, Tables 1-3a and 1-4a). Results among all performance measure quartiles were imprecise in the Black cohort due to small number of events and short follow-up time. This pattern was similar to that observed in the White cohort, even though follow-up time was shorter for Black women.

Across the 12 summary performance categories, there was no clear pattern of greater rate of disability with lower summary scores in either the baseline analyses or the time-dependent analysis. This is likely due to small numbers in all categories: there was 1 participant in the highest category (score = 12) and 2 in the second lowest category (score = 1), which is the lowest category that included a successfully completed performance measure. However, continuous summary performance score showed a

similar pattern of decreased rate of disability with increasing score as was seen in the White women, but only for time-dependent analyses. In baseline analyses, Black women had a 6% increased rate of disability for every one point increase in score, but this association was imprecise (HR: 1.06, 95% CI: 0.98 – 1.16, Table 1-3b). In time-dependent analyses, rate of disability was 13% less for every one point increase in score (HR: 0.87, 95% CI: 0.81 – 0.94, Table 1-4b).

Physical Performance and Increasing Disability among Women with 0 or 1 IADL Limitation

Over 111,654 years of person-time, 5,655 White women experienced an increase in IADL disability (IR = 506.47 per 10,000 person-years). Among all three individual performance measures, women in lower quartiles had a higher rate of an increase in IADL disability than those in the highest quartile. However, due to small numbers, the rate of increasing IADL was inconsistent in the lowest category of those who attempted but were unable to complete a physical performance measure. As with the main analyses of incident IADL disability, there was a monotonic increase in the association between gait speed quartiles (Q1 vs. Q4 aHR: 3.67, 95% CI: 3.31 – 4.06), grip strength quartiles Q1 vs. Q4 aHR: 2.19, 95% CI: 1.98 – 2.42), and chair stand speed quartiles (Q1 vs. Q4 aHR: 2.65, 95% CI: 2.41 – 2.91, Table 1-5a). Slower gait speed was a stronger predictor of increasing disability than either poor grip strength or slow chair stand performance. There was also a trend towards lower summary performance being associated with a higher rate of disability (score 3 vs. score 12 aHR: 7.61, 95% CI: 5.64 – 10.28, Table 1-5b). For every one point increase in summary performance score, rate of increasing

disability was 11% lower (HR: 0.79, 95% CI: 0.78 – 0.80)

Over 4,510 years of person-time, 172 Black women experienced an increase in IADL disability (IR = 381.37 per 10,000 person-years). Despite the larger sample size that included participants with prevalent IADL disability at baseline, there were still few events in this cohort. As with White women, slower gait speed was the strongest predictor of increasing disability (Q1 vs. Q4 aHR: 2.92, 95: CI: 1.71 – 4.99, Table 1-5a), while weaker grip strength (Q1 vs. Q4 aHR: 1.73, 95% CI: 1.09 – 2.73) and slower chair stand speed (Q1 vs. Q4 aHR: 1.38, 95% CI: 0.87 – 2.21) were associated with more modest increases in rate across quartiles. Women with poorer performance had an increased rate of IADL disability (score 3 vs. score 12 aHR: 2.18, 95% CI: 0.74 0 6.41, Table 1-5b), but this trend was not monotonic, likely due to small sample sizes in each category. However, for every one point increase in summary score, rate of increasing disability was 14% lower (HR: 0.86, 95% CI: 0.81 – 0.91).

Discussion

In this longitudinal study of community-dwelling older women, women with poorer performance in individual measures of gait speed, grip strength, and chair stand speed, as well as poorer performance in a summary measure, had an increased rate of incident IADL disability over the follow-up period compared to women with the best performance. These associations remained after adjusting for confounders and were stronger among White women compared with Black women. Sensitivity analyses among women with up to one reported IADL limitation who were followed until they reported an increase in the number of IADL disabilities showed similar associations. These

findings support the initial hypotheses that women with poorer performance would have an increased rate of disability, and confirm previous research using cross-sectional data[47,63] and shorter follow-up periods.[51] However, while results in the Black cohort suggest a similar relation, the small number of events limited the conclusions that could be made from these associations.

The observed relations between the individual measures of physical performance and the summary score were stronger in the time-dependent analyses than those limited to baseline measurements only. Previous research has suggested that the predictive ability of these types of summary performance scores deteriorates after six years.[49] This is likely due to exposure misclassification that biased the baseline-only results toward the null. Physical function is known to decrease with age and is expected to change over time in a longitudinal epidemiologic study with such a long follow-up period. As such, it is unlikely that baseline analyses accurately captured a participant's true exposure status when they experienced incident IADL disability. Thus, time-dependent analyses more precisely measure a participant's true functional status and are more appropriate to use for analyses with long follow-up.

The summary performance score evaluated in the current study included measures of both lower and upper body strength and function, and therefore was a measure of whole body physical function. Previous studies of physical function have concluded that the association between gait speed alone and disability was similar to that of summary performance scores of lower extremity function,[49,91] while grip strength was nearly as strongly associated with disability as a summary performance score of upper extremity

function.[111] However, these studies utilized baseline measurements of physical performance only, and none evaluated lower- and upper-extremity function together in a single summary scale. In the current study we found that the summary performance score, when measured longitudinally, was a stronger predictor of incident disability than any of the individual components and was also able to distinguish gradations of physical function better than any individual component. Given these findings, there is added benefit of including several measures of physical performance in a summary score, particularly when taking measurements longitudinally.

In both race cohorts, gait speed was the strongest predictor of incident and increasing disability, and likely contributed more than grip strength or chair stand speed to the strong association between the summary performance score and disability. This finding confirms previous research that suggests gait speed is a strong predictor of disability and other adverse health outcomes in older adults.[9,22,47,106,113] Gait speed incorporates a variety of factors relating to physical function, including motor control,[45] muscle strength,[18,93] and musculoskeletal condition;[17] it also is associated with health characteristics that are not related to physical capabilities, such as cognitive function[99,122] and comorbidities.[98] Gait speed is likely a mediator on the causal pathway from poor health to disability, and can be considered a proxy measure of general health[44,86] that affects risk of future disability. Updating gait speed measurements over time allow to better capture current physical function, which resulted in even strong associations between gait speed and disability.

There are several potential limitations to the current study. Notably, there was a

concern about outcome misclassification, as disability is not a simple or straightforward diagnosis. Over a lengthy follow-up period, as is the case in SOF, participants may report IADL limitations at one interview but not report that same limitation at subsequent interviews. This improvement may be real (i.e., recovery after a hip replacement or illness) or an incorrect perception of their abilities after acclimating to their disability. However, research suggests that a very small proportion of those who report increased disability actually improve,[127] and fewer than 20% of SOF participants who reported a limitation over follow-up never reported a limitation again. The sensitivity analysis which included women with prevalent IADL limitations addressed this issue; results from these sensitivity analyses demonstrated that potential outcome misclassification was minimal. Further, any misclassification that did occur was unlikely to be dependent given that the exposure was based on self-report and the performance-based measures were administered at the clinic by a trained interviewer.

White women contributed a larger amount of person-years than Black women, which allowed for the observation of fewer events in this group. As such, rates were imprecise for the Black cohort, though there was still suggestion of the general pattern that women in lower quartiles of all three physical performance measures had higher rates of disability than those in the highest quartile. We expected that the larger sample size in the sensitivity analyses would allow for more events to be observed in the Black cohort, which would improve the precision of the results. However, this was not the case. It is not clear whether the lack of association between the individual performance measures or the summary performance score was due to small numbers of events,

insufficient follow-up time, or a true relationship. However, results for gait speed were an exception to this observation. These results suggested that there was an association between slower gait speed and greater rates of disability in the Black cohort.

Another concern was possible dependent misclassification of gait speed, which may have strong effects on the association between both the individual measure of function as well as the summary measure, which included gait speed quartiles. While participants who completed the SOF questionnaires at the clinic all complete a six-meter walking course, participants who opted to complete an interview at their home (often because poor health made it difficult for them to travel to the clinic) may not have had that length of unobstructed walking space available, and may have had data only on shorter course lengths (i.e., 2-meter or 3-meter). Shorter course lengths likely over-estimate the amount of disability in a population[81] and in this sample, those who completed the shorter course lengths were more likely to be in poor health, and were more likely to develop a disability, than those who completed the longer course length. This relationship between poorer health and shorter course length may bias the association between gait speed and disability toward the null. However, less than 3% of all the gait speed measurements over follow-up were completed on course less than 6 meters long, and all baseline gait speeds were measured on a 6 meter course, so this bias should be minimal.

In addition, the poorest performers, those who attempted but were unable to complete at least one physical performance measure, contributed the least amount of follow-up time. It is possible that these women were poor performers because of their

overall health, which would not only increase their likelihood of developing IADL disability, but would also be related to their censoring (discontinuation from SOF or death). If censoring prevented the observation of incident disability, this might have resulted in underestimating the association between performance and disability. In several instances, for example the regression results for the summary performance score in both race cohorts, the lowest performers (score = 0) had a lower adjusted risk of incident disability compared to the highest performers (score = 12). These results may be attenuated, though further investigation via quantitative bias analysis is needed to determine the extent.

Nonetheless, this study had many strengths. The sample was relatively large with a long follow-up period (18 years for Whites and 13 years for Blacks) allowing enough time to accrue to capture a large number of events, particularly in the White cohort. The exposure utilized sample-based cut points to categorize physical performance, which replicated previous studies[47] and accommodated the distributions in function in this cohort that are not accurately captured with clinical cut points[11,108,113] used for other populations. Unlike previous studies of the association between physical performance and disability, which used only baseline measurements and cross-sectional analyses,[47,63] the current study used time-varying measures of physical performance to predict incident disability longitudinally. In addition, physical performance deficits increase with age,[36,39,97] and allowing these performance measures to vary over time reduced the likelihood of exposure misclassification. Accounting for variability over time also captured improvements in function which, while not common in this population of older

women, would bias the results toward the null if not accounted for.

Similarly, as physical performance and disability are so closely linked to age, using age as the time scale instead of time in study allows for more precise control for age-related confounding. In the current study using the Andersen-Gill data structure, participants were included in the analysis in age-based risk sets; if an event occurred at an age at which a participant was under observation, that participant would contribute person-time for that age. As such, risk of IADL disability was only compared among women of the same age. This reduced, and may have even eliminated, confounding by age-related factors that were not collected or controlled for in the analysis. Further study is needed to evaluate potential time-dependent confounding and potential effect measure modification by age that is not addressed with the current analysis.

In summary, in this longitudinal study of community-dwelling older women, physical performance measured at baseline and over time was associated with incident and increasing IADL disability. Utilizing time-dependent physical performance measures yielded higher, and less misclassified, risks across performance categories. Objective measures of physical performance, particularly gait speed, are associated with a variety of health and functional outcomes. Taken together, these results suggest that poorer physical performance is likely on the causal pathway of poor health to disability.

Figure 1-1: Selection of analytic sample for Study 1

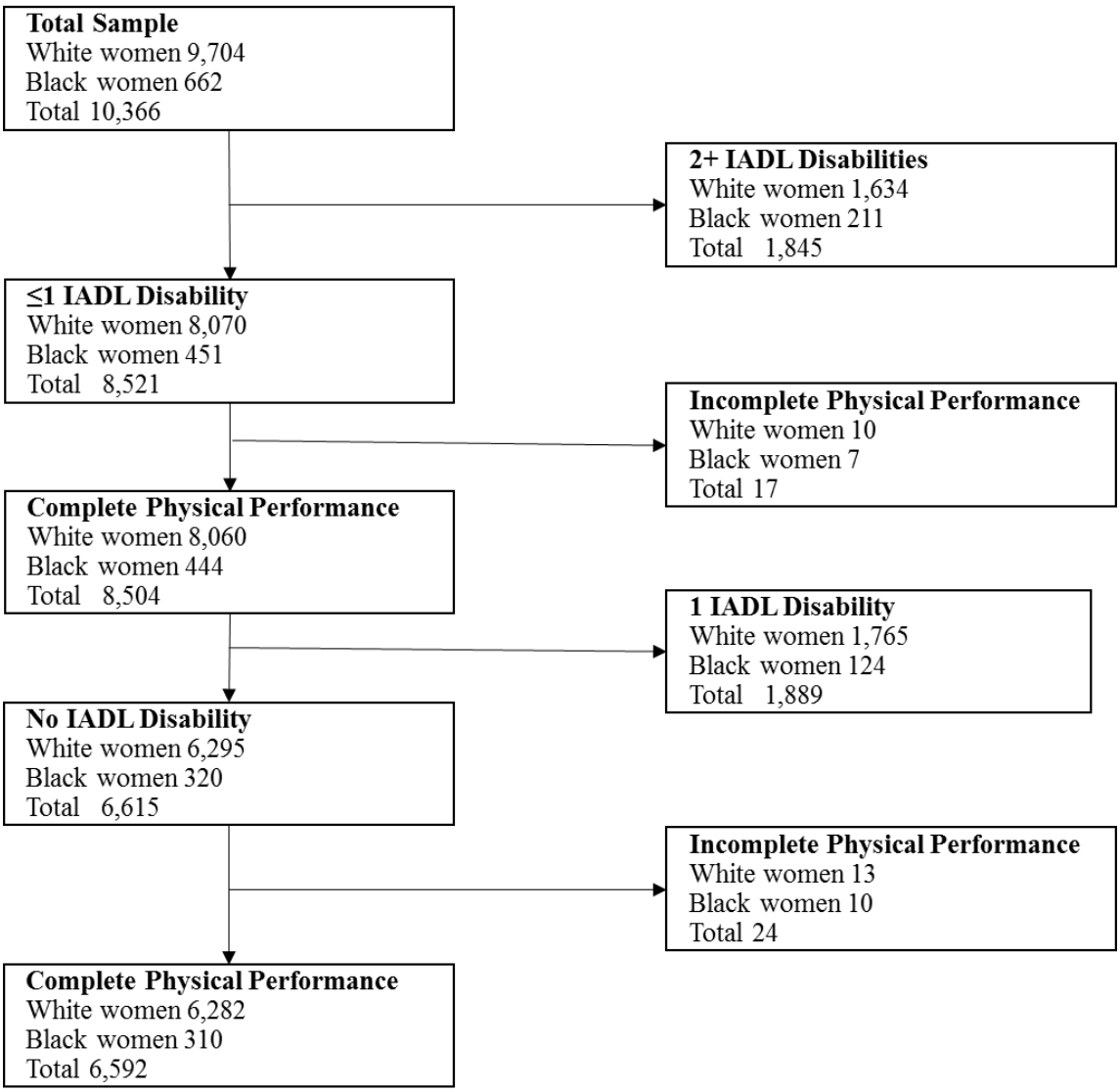

Table 1-1a: Baseline demographic and health characteristics of 6,592 SOF participants with no IADL disability at baseline

	Total sample		White women		Black women	
Total	6,592		6,282	(95.30)	310	(4.70)
Demographics						
Age, mean (sd)	71.22	(4.95)	71.05	(4.91)	74.76	(4.45)
65–69, n (%)	2,930	(44.45)	2,926	(46.58)	4	(1.29)
70–74, n (%)	2,169	(32.90)	1,995	(31.79)	174	(56.13)
75–79, n (%)	963	(14.61)	878	(13.98)	85	(24.42)
80–84, n (%)	435	(6.60)	397	(6.32)	38	(12.26)
≥85, n (%)	95	(1.44)	86	(1.37)	9	(2.90)
High school education, n (%)	5,274	(80.01)	5,040	(80.23)	234	(75.48)
Married, n (%)	3,294	(49.97)	3,207	(51.05)	87	(28.06)
Smoking status, n (%)						
Never smoker	4,062	(61.62)	3,868	(61.57)	194	(62.58)
Ever smoker	1,891	(28.69)	1,796	(28.59)	95	(30.65)
Current smoker	615	(9.33)	594	(9.46)	21	(6.77)
Health Characteristics						
Short Mini Mental Status Exam, mean (sd)	24.71	(1.66)	24.78	(1.60)	23.37	(2.27)
BMI, mean (sd)	26.01	(4.18)	25.85	(4.09)	29.34	(4.71)
<18.5, n (%)	109	(1.65)	86	(1.37)	23	(7.42)
18.5–24.9, n (%)	2,927	(44.40)	2,872	(45.72)	55	(17.74)
25–29.9, n (%)	2,495	(37.85)	2,374	(37.79)	121	(39.03)
≥30, n (%)	1,061	(16.10)	950	(15.12)	111	(35.81)
Osteoarthritis, n (%)	1,790	(27.15)	1,769	(28.16)	21	(6.77)
Myocardial infarction, n (%)	8	(0.12)	0	(0.00)	8	(2.58)
Hypertension, n (%)	1,219	(18.49)	1,109	(17.65)	110	(35.48)
Diabetes, n (%)	214	(3.24)	185	(2.94)	155	(50.00)
COPD, n (%)	16	(0.24)	0	(0.00)	16	(5.15)
Multimorbidity score, n (%)						
No domains	4,076	(61.83)	3,913	(62.29)	163	(52.58)
1 domain	1,586	(24.06)	1,490	(23.72)	96	(30.97)
≥ 2 domains	930	(14.11)	879	(13.99)	51	(16.45)

Table 1-1b: Baseline physical performance characteristics of 6,592 SOF participants with no IADL disability at baseline

	Total Sample		Black Women		White Women	
Total	6,592		6,282	(95.30)	310	(4.70)
Physical Performance Characteristics						
Gait speed, (m/second) mean (sd)	1.06	(0.20)	1.07	(0.20)	0.92	(0.17)
Grip strength (kg), mean (sd)	21.50	(4.13)	21.55	(4.08)	20.32	(4.89)
Chair stand speed (s), mean (sd)	11.39	(3.37)	11.29	(3.30)	13.53	(4.08)
Summary performance score, mean (sd)	8.43	(2.20)	8.46	(2.20)	7.92	(2.25)

Table 1-2: Baseline performance measure characteristics among 6,592 SOF participants with no IADL disabilities at baseline

	Total		White women		Black women	
Performance Measure Quartiles	n	(%)	n	(%)	n	(%)
Gait Speed, m/s						
Q1 (lowest performers)	903	(13.70)	861	(13.71)	42	(13.55)
Q2	1,350	(20.48)	1,268	(20.18)	82	(26.45)
Q3	1,903	(28.87)	1,814	(28.88)	89	(28.71)
Q4 (highest performers)	2,436	(36.95)	2,339	(37.23)	97	(31.29)
Grip strength, kg						
Q1 (lowest performers)	672	(10.19)	606	(9.65)	66	(21.29)
Q2	1,166	(17.69)	1,092	(17.38)	74	(23.87)
Q3	1,964	(29.79)	1,887	(30.04)	77	(24.84)
Q4 (highest performers)	2,790	(42.32)	2,697	(42.93)	93	(30.00)
Chair stand speed, sec						
Q1 (lowest performers)	1,564	(23.73)	1,490	(23.72)	74	(23.87)
Q2	1,722	(26.12)	1,639	(26.09)	83	(26.77)
Q3	1,721	(26.11)	1,648	(26.23)	73	(23.55)
Q4 (highest performers)	1,585	(24.04)	1,505	(23.96)	80	(25.81)
Summary Score						
3	104	(1.58)	99	(1.58)	5	(1.61)
4	225	(3.41)	205	(3.26)	20	(6.45)
5	399	(6.05)	376	(5.99)	23	(7.42)
6	600	(9.10)	561	(8.93)	39	(12.58)
7	821	(12.45)	774	(12.32)	47	(15.16)
8	1,015	(15.40)	969	(15.43)	46	(14.84)
9	1,098	(16.66)	1,055	(16.79)	43	(13.87)
10	1,039	(15.76)	995	(15.84)	44	(14.19)
11	815	(12.36)	788	(12.54)	27	(8.71)
12	476	(7.22)	460	(7.32)	16	(5.16)
Continuous, mean (sd)	8.18	(2.26)	8.20	(2.26)	7.71	(2.26)

** A score of 12 means the participant scored in the highest quartile for all three performance measures.

Table 1-3a: Associations between baseline physical performance quartiles with incident IADL disability, by race, among 6,592 SOF participants

	White women				Black women			
	Cases	Person-years	Adjusted		Cases	Person-years	Adjusted	
			HR	95% CI			HR	95% CI
Gait Speed, m/s								
Q1	655	9,737	1.65	(1.48 – 1.84)	13	348	0.61	(0.29 – 1.24)
Q2	916	17,318	1.33	(1.21 – 1.46)	36	817	1.15	(0.68 – 1.96)
Q3	1,242	27,523	1.20	(1.10 – 1.31)	40	1,008	1.33	(0.80 – 2.20)
Q4	1,380	38,323	1.00		29	1,091	1.00	
Grip strength, kg								
Q1	461	6,963	1.49	(1.33 – 1.68)	26	703	0.94	(0.53 – 1.64)
Q2	774	14862	1.19	(1.08 – 1.31)	28	829	1.03	(0.59 – 1.78)
Q3	1,265	27,771	1.13	(1.04 – 1.22)	33	788	1.43	(0.84 – 2.43)
Q4	1,693	43,305	1.00		31	944	1.00	
Chair stand speed, s								
Q1	1,117	18,095	1.65	(1.50 – 1.82)	26	686	0.76	(0.45 – 1.30)
Q2	1,103	23,162	1.30	(1.18 – 1.44)	25	820	0.85	(0.49 – 1.46)
Q3	1,076	25,682	1.18	(1.07 – 1.30)	33	835	1.23	(0.75 – 2.03)
Q4	897	25,962	1.00		34	923	1.00	

*adjusted for education, marital status, smoking status, BMI, multimorbidity score categories, and SOF clinical center
** A score of 12 means the participant scored in the highest quartile for all three performance measures

Table 1-3b: Associations between baseline physical performance summary score with incident IADL disability, by race, among 6,592 SOF participants

	White women				Black women			
	Cases	Person-years	Adjusted		Cases	Person-years	Adjusted	
			HR	95% CI			HR	95% CI
Summary Score								
3	81	764	2.77	(2.06 – 3.72)	2	56	0.73	(0.12 – 4.47)
4	164	2,102	2.26	(1.80 – 2.84)	6	161	0.52	(0.12 – 2.30)
5	291	4,042	2.17	(1.79 – 2.63)	10	224	0.89	(0.23 – 3.52)
6	433	6,831	1.98	(1.66 – 2.36)	14	391	1.14	(0.32 – 4.07)
7	553	10,538	1.73	(1.46 – 2.04)	9	476	0.63	(0.16 – 2.43)
8	672	13,767	1.67	(1.42 – 1.97)	28	507	2.15	(0.63 – 7.30)
9	675	16,319	1.46	(1.24 – 1.72)	22	443	1.69	(0.49 – 5.88)
10	622	16,325	1.33	(1.13 – 1.57)	12	524	0.75	(0.21 – 2.75)
11	470	13,708	1.19	(1.00 – 1.41)	12	283	1.23	(0.33 – 4.57)
12	232	8,505	1.00		3	199	1.00	
Continuous			0.90	(0.89 – 0.92)			1.06	(0.98 – 1.16)

*adjusted for education, marital status, smoking status, BMI, multimorbidity score categories, and SOF clinical center

** A score of 12 means the participant scored in the highest quartile for all three performance measures.

Table 1-4a: Associations between time-dependent physical performance quartiles with incident IADL disability, by race, among 6,592 SOF participants

	White women				Black women			
	Cases	Person-years	Adjusted		Cases	Person-years	Adjusted	
			HR	95% CI			HR	95% CI
Gait Speed, m/s								
Unable	14	64	6.55	(3.81 – 11.24)	2	8	3.72	(0.79 – 17.49)
Q1	1,759	19,890	3.83	(3.41 – 4.31)	50	546	2.59	(1.42 – 4.73)
Q2	1,021	22,323	2.03	(1.79 – 2.30)	33	833	1.36	(0.73 – 2.54)
Q3	836	25,236	1.53	(1.35 – 1.74)	17	886	1.25	(0.62 – 2.50)
Q4	563	25,388	1.00		16	991	1.00	
Grip strength, kg								
Unable	49	586	2.19	(1.61 – 2.99)	6	66	1.81	(0.70 – 4.67)
Q1	1,563	21,613	2.15	(1.91 – 2.41)	38	697	1.50	(0.86 – 2.62)
Q2	1,050	22,194	1.54	(1.37 – 1.73)	27	905	1.01	(0.55 – 1.84)
Q3	894	24,586	1.23	(1.09 – 1.39)	25	772	1.18	(0.65 – 2.16)
Q4	637	23,922	1.00		22	824	1.00	
Chair stand speed, s								
Unable	13	125	2.14	(1.20 – 3.81)	0	10	0.00	(0.00 – 0.00)
Q1	1,597	20,453	2.69	(2.42 – 2.99)	32	728	1.28	(0.72 – 2.30)
Q2	1,118	23,292	1.82	(1.63 – 2.03)	33	821	1.27	(0.72 – 2.26)
Q3	867	24,289	1.35	(1.20 – 1.52)	32	857	1.42	(0.80 – 2.52)
Q4	628	24,742	1.00		21	848	1.00	

*adjusted for education, marital status, smoking status, BMI, multimorbidity score categories, and SOF clinical center
**A score of 0 means the participant attempted, but was unable to complete, all three performance measures. A score of 12 means the participant scored in the highest quartile for all three performance measures.

Table 1-4b: Associations between time-dependent physical performance summary score with incident IADL disability, by race, among 6,592 SOF participants

	White women				Black women			
	Cases	Person-years	Adjusted		Cases	Person-years	Adjusted	
			HR	95% CI			HR	95% CI
Summary Score								
0	17	168	5.66	(3.15 – 10.16)	1	19	0.64	(0.06 – 6.65)
1	52	263	9.21	(5.83 – 14.53)	2	6	2.84	(0.43 – 18.76)
2	162	826	11.15	(7.77 – 16.00)	5	50	0.78	(0.16 – 3.87)
3	515	4,056	8.26	(5.95 – 11.47)	21	137	2.34	(0.66 – 8.26)
4	576	6,193	6.11	(4.41 – 8.46)	12	217	0.79	(0.21 – 3.01)
5	599	8,608	4.74	(3.43 – 6.56)	15	257	1.03	(0.27 – 3.87)
6	533	10,448	3.53	(2.55 – 4.88)	15	335	1.68	(0.47 – 5.98)
7	533	12,600	2.85	(2.06 – 3.95)	12	448	0.63	(0.17 – 2.33)
8	424	12,843	2.25	(1.62 – 3.13)	14	548	0.55	(0.15 – 2.01)
9	339	13,390	1.68	(1.20 – 2.35)	11	455	0.66	(0.18 – 2.43)
10	261	11,228	1.49	(1.06 – 2.10)	3	385	0.28	(0.06 – 1.45)
11	120	8,011	1.05	(0.72 – 1.53)	4	241	0.63	(0.14 – 2.91)
12	62	4,267	1.00		3	166	1.00	
Continuous			0.79	(0.78 –0.80)			0.87	(0.81 –0.94)

*adjusted for education, marital status, smoking status, BMI, multimorbidity score categories, and SOF clinical center
**A score of 0 means the participant attempted, but was unable to complete, all three performance measures. A score of 12 means the participant scored in the highest quartile for all three performance measures.

Table 1-5a: Associations between physical performance quartiles and increasing IADL disability, by race, among 8,481 SOF participants

	White women				Black women			
	Cases	Person-years	Adjusted		Cases	Person-years	Adjusted	
			HR	95% CI			HR	95% CI
Gait Speed, m/s								
Unable	15	68	6.08	(3.62 – 10.22)	5	14	7.97	(2.78 – 22.89)
Q1	2,504	26,319	3.67	(3.31 – 4.06)	79	953	2.92	(1.71 – 4.99)
Q2	1,374	27,265	1.97	(1.77 – 2.20)	43	1,198	1.47	(0.83 – 2.60)
Q3	1,034	29,302	1.43	(1.28 – 1.60)	27	1,145	1.42	(0.77 – 2.60)
Q4	728	28,700	1.00		18	1,200	1.00	
Grip strength, kg								
Unable	65	701	2.29	(1.74 – 3.00)	8	79	2.24	(0.99 – 5.06)
Q1	2,146	27,121	2.19	(1.98 – 2.42)	60	1055	1.73	(1.09 – 2.73)
Q2	1,450	27,251	1.60	(1.44 – 1.77)	41	1,202	1.17	(0.71 – 1.93)
Q3	1,148	28,765	1.22	(1.10 – 1.36)	34	1,013	1.33	(0.80 – 2.23)
Q4	846	27,816	1.00		29	1,161	1.00	
Chair stand speed, s								
Unable	15	137	2.06	(1.21 – 3.51)	1	12	2.68	(0.34 – 20.90)
Q1	2,288	27,805	2.65	(2.41 – 2.91)	57	1,152	1.38	(0.87 – 2.21)
Q2	1,462	28,249	1.78	(1.61 – 1.96)	46	1,191	1.26	(0.78 – 2.04)
Q3	1,117	28,224	1.35	(1.21 – 1.50)	39	1,051	1.32	(0.80 – 2.17)
Q4	773	27,239	1.00		29	1,104	1.00	

*adjusted for education, marital status, smoking status, BMI, multimorbidity score categories, and SOF clinical center
**A score of 0 means the participant attempted, but was unable to complete, all three performance measures. A score of 12 means the participant scored in the highest quartile for all three performance measures.

Table 1-5b: Associations between physical performance summary scores and increasing IADL disability, by race, among 8,481 SOF participants

	White women				Black women			
	Cases	Person-years	Adjusted		Cases	Person-years	Adjusted	
			HR	95% CI			HR	95% CI
Summary Score								
0	21	183	5.47	(3.16 – 9.45)	1	19	0.75	(0.08 – 6.99)
1	67	315	9.77	(6.50 – 14.68)	5	21	3.07	(0.77 – 12.22)
2	210	1,029	10.94	(7.87 – 15.22)	13	88	1.65	(0.50 – 5.43)
3	753	5,773	7.61	(5.64 – 10.28)	29	237	2.18	(0.74 – 6.41)
4	835	8,390	6.00	(4.45 – 8.08)	24	366	1.22	(0.41 – 3.63)
5	795	11,038	4.37	(3.29 – 5.98)	23	392	1.30	(0.43 – 3.92)
6	747	13,204	3.51	(2.60 – 4.73)	18	494	1.35	(0.45 – 4.07)
7	704	15,314	2.79	(2.07 – 3.76)	13	613	0.60	(0.19 – 1.88)
8	550	15230	2.20	(1.63 – 2.98)	16	731	0.53	(0.17 – 1.64)
9	426	15,346	1.62	(1.19 – 2.20)	14	560	0.78	(0.25 – 2.40)
10	325	12,542	1.48	(1.08 – 2.03)	6	494	0.50	(0.14 – 1.80)
11	149	8,754	1.03	(0.73 – 1.46)	6	294	0.65	(0.18 – 2.39)
12	73	4,536	1.00		4	201	1.00	
Continuous			0.79	(0.78 – 0.80)			0.86	(0.81 – 0.91)

*adjusted for education, marital status, smoking status, BMI, multimorbidity score categories, and SOF clinical center
**A score of 0 means the participant attempted, but was unable to complete, all three performance measures. A score of 12 means the participant scored in the highest quartile for all three performance measures

STUDY 2: LOW BONE MINERAL DENSITY AND MORTALITY

Introduction

Low bone mineral density has been associated with disease-specific [19,79,94] and all-cause mortality among older adults.[101] It is also a risk factor for incident osteoporotic fractures,[55] which in turn are independently associated with increased risk of death.[126] However, the extent to which the association between low bone mineral density and mortality is mediated by incident fractures remains unknown. Identification of the direct and indirect effects of bone mineral density on mortality is important to inform clinical interventions to reduce medical costs and patient burden, as well as disability and mortality in older adults.

Almost half of adults aged 50 or older have some bone loss, the degree to which differs by gender and age. Women are at higher risk of low bone mineral density than men, and non-Hispanic White women are at an increased risk of low bone mineral density compared to non-Hispanic Black women, at the same ages.[78] Lower bone mineral density is independently associated with higher all-cause mortality risk.[101] Among White women aged 65 and older participating in the Study of Osteoporotic Fractures (SOF), those with low bone mineral density of the proximal radius had greater mortality rates than those with normal bone mineral density.[15] Moreover, older women with a faster rate of bone loss at the hip had a higher risk of death, independent of baseline bone mineral density.[59] Another study of women aged 50 and older found that 10-year mortality risk was greater for those with osteopenia and osteoporosis compared to those with higher bone mineral density.[95] Previous studies of the association between

bone mineral density and mortality have accounted for prevalent fractures[15,100] or included incident fractures as a covariate in the analysis,[59] but none has addressed the potential mediating effects of fractures. As such, the etiologic role of osteoporotic fractures as a mediator of this association is still unknown.

Low bone mineral density also increases fracture risk in older adults.[55] Fractures are an important public health concern for older women, as almost half of women older than age 60 will experience a fracture over the rest of their lifetime.[90] Depending on the fracture site, risk of fracture can double for each standard deviation decrease in bone mineral density.[85] Bone fractures generally occur after an event, which may range from non-traumatic like normal lifting and bending to a traumatic fall.[1] Bone fractures are associated with increased risk of disability and death,[41,126] even when adjusting for age.[10] However, morbidity and mortality outcomes differ by fracture site. For example, vertebral and hip fractures are a strong predictor of subsequent fractures, reduced physical function and mortality,[58,84] but wrist fractures are associated with less physical decline,[37] in part because wrist fractures tend to occur after a fall while walking in individuals who are currently healthy and active.[64] As a result, the mediating effects of hip fracture may be larger than those of wrist fracture, because hip fracture is more strongly associated with death.

While the association between bone mineral density and mortality is well-established, the mechanism for this association is not well understood, and the role that fractures play in this relationship is less clear. To our knowledge, no study to date has investigated the association between bone mineral density and mortality while evaluating

the potential mediating effects of incident fractures. We hypothesized that older women with low bone mineral density (comprising both low BMD and preclinical osteoporosis) would have an increased risk of mortality compared to those with normal bone mineral density. Further, we hypothesized that this association would be partially mediated by incident fractures at any site, with stronger mediation for fractures of the hip than the wrist.

Methods

Data Collection and Analytic Sample

Approximately every two to six years, SOF participants had a comprehensive clinical evaluation to assess physical and cognitive health. At Visit 2 (1989–1990), 8,074 White women received bone mineral density scans. At their baseline clinical evaluation (Visit 6, 1997–1998), 647 Black women received bone mineral density scans. Women who reported having a fracture before their DXA scans were excluded from the analysis. Therefore, the analytic sample consisted of 8,026 White women and 647 Black women who completed a clinical evaluation at the time of their bone mineral density scan (Figure 2-1). White women contributed a maximum of 21 years and Black women 14 years of follow-up.

Measures

Variables evaluated as potential confounders are described in Common Measures. Femoral neck bone mineral density (grams/centimeter^2, g/cm^2) was measured using dual-energy x-ray absorptiometry (DXA) (Hologic QDR 1000 and QDR 2000, Hologic Inc., Bedford, MA, USA). Different QDR machines were used in the 1989–1990 and 1997–

1998 clinical evaluations and are not comparable; therefore, the White and Black cohorts were analyzed separately.

Femoral neck BMD was operationalized as a dichotomous variable of normal BMD versus low BMD and preclinical osteoporosis combined, based on the recommendations of the International Osteoporosis Foundation [60] and the World Health Organization (WHO).[92] These recommendations use the National Health and Nutrition Examination Survey III (NHANES III) reference database for femoral neck measurements,[76,77] which sets census-defined race-based measurements from women aged 20–29 years as bone mineral density comparison groups. The NHANES III data are taken from a representative sample of the United States population. Because bone mineral density changes little until age 50[77] and is normally distributed, bone mineral density values of older adults can be compared to this distribution of bone mineral density of younger adults in standard deviation units (T-scores).

Normal bone mineral density was defined by a bone mineral density value of less than one standard deviation below the race-specific mean for young adult women; low bone mineral density was defined by a bone mineral density value equal to or more than one standard deviation below this mean, and preclinical osteoporosis was defined by a bone mineral density value equal to or below 2.5 standard deviations of the mean. Low bone mineral density and preclinical osteoporosis were combined as the exposure for the main analyses. The race-specific bone mineral density cut-offs were ($\geq$0.738 g/cm^2, $\geq$0.558 g/cm^2, and <0.558 g/cm^2 respectively) for White women and ($\geq$0.817 g/cm^2, $\geq$0.6175 g/cm^2, and <0.6175 g/cm^2 respectively) for Black women.[77] For mediation

analyses, bone mineral density was dichotomized as normal versus low BMD or preclinical osteoporosis combined. In sensitivity analyses, bone mineral density was dichotomized as low or normal BMD versus preclinical osteoporosis.

Incident fracture was first determined by self-reported fractures at any site (i.e., ankle, clavicle, elbow, face, finger, foot, hand, heel, hip, humerus, knee, lower leg, pelvis, rib, toe, upper leg, wrist, and vertebra) and/or specific sites (i.e., hip and wrist), which was then adjudicated by a panel of SOF clinical investigators. At the in-person interviews, respondents reported whether their doctor or health care provider ever (for Black women at Visit 6) or since the last questionnaire about 12 months ago (for White women at Visit 2) said that they had a broken or fractured bone, or specifically had a fracture of the spine or vertebrae. Participants were also asked to complete post-cards every four months to indicate whether they had experienced a fall or fracture during the previous four-month interval. If post-cards were not returned, participants were contacted by telephone. Data on incident fracture were collected longitudinally over follow-up.

For the main analyses limited to ten-year mortality, only data on incident fractures up to ten years after DXA scan were used. For secondary analyses of all follow-up time through December 31, 2010, all available data on incident fractures was used.

All-Cause Mortality through December 31, 2010 was documented through death certificates obtained at each SOF site. SOF participants contributed person-time from their first SOF DXA scan until death, withdrawal from SOF, or the end of follow-up, whichever came first.

SOF participants contributed up to twenty years of follow-up, and a large proportion died over follow-up (57% of White women and 30% of Black women died by December 31, 2010). Thus, the assumptions for causal mediation analysis for survival data were violated because the outcome was not rare. To accommodate this assumption, ten year mortality since the participant's DXA scan was evaluated (16% of White participants and 25% of Black participants died up to ten years after their DXA scan). Secondary analyses using all available follow-up data are presented in tables in the Appendix.

Statistical Analyses

Descriptive analyses compared distributions of sociodemographic and health status characteristics by bone mineral density category in the total analytic sample and also stratified by race. Means and standard deviations were compared for continuous variables, while frequencies and proportions were calculated for dichotomous and categorical variables.

The total number of deaths, total follow-up time (in years), mortality rates and 95% confidence intervals were computed comparing women with low bone mineral density and osteoporosis to women with normal bone mineral density. All rates were reported per 1,000 person-years (PY).

Cox proportional hazards regression[28] was used to produce unadjusted and adjusted hazards ratios and 95% confidence intervals of the association between low bone mineral density and all-cause mortality through ten years and December 31, 2010 in the main analyses and with all available follow-up for secondary analyses presented in the

appendix. All models were stratified by race to account for the different QDR machines that were used to measure BMD in each race-specific cohort. The proportional hazards assumption was examined using log-negative-log survival curves. Covariates were added to the models to estimate adjusted hazard ratios (aHR) and 95% confidence intervals (CI) for the association between bone mineral density group and all-cause mortality.

Potential confounders were identified from existing theory and previous studies of bone mineral density, death, and/or fractures.[31,33,67,79] Associations between each potential confounder and low bone mineral density and death were evaluated using Cox proportional hazards regression. Covariates were included in the model if they were established risk factors for fracture or mortality, were associated with bone mineral density or mortality in the current sample, or their inclusion in the proportional hazards model meaningfully changed the HR of the association between bone mineral density category and mortality by 10% or more. The final adjusted models included both the established risk factors and statistical confounders: baseline age, education, marital status, BMI category, smoking status, and multimorbidity score.

Causal mediation analysis using survival data was used to assess the extent to which incident fracture mediated the association between bone mineral density and mortality.[116,117] Separate sets of models were performed for each specific potential mediator (i.e., any fracture, hip fracture, wrist fracture). Unadjusted, mediator-adjusted, and fully adjusted (confounders identified above) proportional hazards regression was used to evaluate the crude and adjusted associations between low bone mineral density and all-cause mortality over ten years and the entire follow-up period, respectively.

Sensitivity analyses modeled the association between preclinical osteoporosis and all-cause mortality over ten years and the entire follow-up period.

The direct and indirect effects of bone mineral density on mortality, adjusting for covariates, were computed using Cox proportional hazards models.[7,116,117] The proportion of the total effect of bone mineral density on mortality that was explained by the presence of any fracture, hip fracture, or wrist fracture respectively (percent mediated) was computed as the beta coefficient for the indirect effect operating through the specific fracture mediator divided by the beta coefficient for the total effect.[54,105] The natural direct and indirect effects add up to the total effect of the specific fracture mediator on the association between BMD and mortality.[104] They are defined as the expected contrast $E(Y(a, M(a^*)) - Y(a^*, M(a^*)))$,[96,104] such that the total causal effect minus the natural direct effect measures the natural indirect effect.[118] When evaluating causal effects, natural direct and indirect effects on the exposed give the effect of low bone mineral density and preclinical osteoporosis on those with these characteristics, rather than the average effect of bone mineral density on the population.[119]

Analyses were conducted using SAS software (Statistical Analysis System, version 9.4, Cary, North Carolina). All statistical tests were two-sided and used 95% confidence intervals.

Results

Sample Characteristics

At the Year 2 clinical evaluation, the mean age of White women was 71.67 (sd=4.07) years, 78% had a high school education, and 55% were married.

Approximately 18% had normal BMD, 60% had low BMD, and 22% had preclinical osteoporosis. White women with low BMD or preclinical osteoporosis were older, less likely to be married, had lower mean BMI, were less likely to have a diagnosis of diabetes and more likely to have a diagnosis of COPD than women with normal BMD. They were also more likely to report having any fracture over ten years (67% versus 18%, Table 2-1) or the entire follow-up period (46% versus 29%, Table 2-A1) compared to women with normal BMD.

At baseline (Year 6), the mean age of Black women was 75.23 (sd=4.31) years, about a third had graduated high school and 25% were married. Approximately 29% had normal BMD, 52% had low BMD, and 18% had preclinical osteoporosis. Black women with low BMD or preclinical osteoporosis were older, had lower mean BMI, were less likely to be diagnosed with hypertension, and were more likely to have a diagnosis of osteoporosis than those with normal BMD. Incident fractures were rare in this group, and few fractures at any site were observed over ten years (Table 2-1). Similar to the White women, Black women with low BMD or preclinical osteoporosis were more likely to report having any fracture over the entire follow-up period (17% versus 8%) compared to women with normal BMD (Table 2-A1).

Bone Mineral Density and Mortality

In the White cohort, 1,974 (24.6%) participants died within ten years of their DXA scan. Women with low BMD or preclinical osteoporosis were more likely to die over ten years than women with normal BMD (age-adjusted HR: 1.31, 95% CI: 1.21–1.41). In the fully adjusted model, women with low BMD or preclinical osteoporosis had

12% increased risk of death (aHR: 1.12, 95% CI: 1.04, 1.21) compared to women with normal BMD (Table 2-2).

Over the entire follow-up period through December 31, 2010, 4,889 (60.9%) White women died. Though mortality was higher in women with low BMD and preclinical osteoporosis than those with normal BMD, these rates were lower than those in the shorter follow-up period. In age-adjusted models, women with low BMD or preclinical osteoporosis had a higher risk of death than those with normal BMD (HR: 1.47, 95% CI: 1.30, 1.68). When adjusting for covariates, this association was attenuated (aHR: 1.14, 95% CI: 1.00–1.31) (Table 2-A2).

In the Black cohort, 163 participants (25.2%) died within ten years of their DXA scan. Ten-year mortality rates were lower for Black women than for White women. In unadjusted analyses, Black women with low BMD or preclinical osteoporosis had 1.31 times increased risk of death compared to those with normal BMD (95% CI: 0.91 – 1.88), though this association disappeared after adjusting for confounders (aHR: 1.01, 95% CI: 0.69 – 1.49, Table 2-2).

Over the full follow-up period through December 31, 2010, 196 Black participants (30.3%) died. While age-adjusted associations between low BMD or preclinical osteoporosis and mortality were similar to those found among White women (HR: 1.32, 95% CI: 0.95 – 1.84), after adjustment this association was eliminated (aHR: 1.01, 95% CI: 0.71 – 1.43, Table 2-A2).

Mediation by Incident Fractures

In the White sample, incident fractures mediated a small, but measurable proportion of the association between low bone mineral density and mortality. Over 10 years, 7.2% of the association between low bone mineral density and mortality was mediated by incident fractures at any site 5.4% was mediated by hip fractures and 0.4% was mediated by wrist fractures (Table 2-3). These proportions remained similar when including all available follow-up. Over the entire follow-up period, 7.1% of the association between low bone mineral density and mortality was mediated by incident fractures, 7.0% was mediated by incident hip fractures and 0.6% was wrist fractures mediated (Table 2-A3).

In sensitivity analyses modeling preclinical osteoporosis with a lower cut point for low bone mineral density, the mediating effects of all fracture types varied. Over 10 years, incident fractures at any site mediated 7.7%, hip fractures mediated 9.1%, and wrist fractures mediated 0.3% of the associations between preclinical osteoporosis and mortality. Over the entire follow-up period, incident fractures at any site mediated 7.2%, hip fractures mediated 9.7%, and wrist fractures mediated 0.4% of the association between preclinical osteoporosis and mortality.

Black women experienced few fractures over follow-up, leading to imprecise estimates of the mediating effect of fractures on the association between bone mineral density and mortality. Over 10 years, incident fractures mediated 1.6%, hip fractures mediated 0.5%, and wrist fractures mediated 0.0% of the association between low bone mineral density and mortality (Table 2-3). Over the entire follow-up period, any incident

fractures mediated 1.8%, incident hip fractures mediated 0.5%, and wrist fractures mediated 0.9% of the association between low bone mineral density and mortality (Table 2-A3).

In sensitivity analyses, incident fractures played less of a mediating role in the association between preclinical osteoporosis and death among Black women. Over 10 years, fractures at any site mediated 3.1%, hip fractures mediated 2.7%, and wrist fractures mediated 0.0% of this association. Over the entire follow-up period, incident fractures at any site mediated 3.7%, hip fractures mediated 4.0%, and wrist fractures mediated 0.4% of the association between preclinical osteoporosis and mortality.

Discussion

In this longitudinal study of community-dwelling older women participating in SOF, women with low bone mineral density and preclinical osteoporosis identified by DXA had an increased risk of death over ten years and over the entire follow-up period compared to women with normal bone mineral density. While these associations attenuated in the White cohort when adjusting for confounders, this association went away completely in the Black cohort.

This association was mediated through incident fracture, and the proportion mediated varied by fracture site and race. Among White women, any fracture and hip fracture explained a larger proportion of the association between low bone mineral density and mortality than wrist fracture over 10 years. In sensitivity analysis comparing White women with preclinical osteoporosis to those with normal or low bone mineral density, incident fractures at any site was the strongest mediator of this association. In

both the main analyses and sensitivity analyses, the mediating effects of fractures were variable and unreliable among the Black cohort due to the small number of mediating events and endpoints; only 28 (14.3%) Black women who died over the entire follow-up period experienced any type of fracture. This small number of fractures was particularly problematic for the analyses including wrist fracture as a mediator, since no Black women with normal bone mineral density experienced a wrist fracture over 10 years or over the entire follow-up period and thus there were no individuals available for a comparison. Similarly, the mediation results for the entire follow-up period may be unreliable in the White cohort because of the high number of deaths in this group. Mediation analyses with survival data require a low proportion of deaths, but because of the long follow-up in this study, more than half (61%) of the White women died by the end of December 31, 2010. Therefore, results in this group utilizing the entire follow-up period should be interpreted cautiously.

These findings are consistent with previously reported results in SOF and other studies of fracture and mortality in older women.[10,15,59,95] However, none of these studies evaluated different fracture sites as potential mediators of the association between bone mineral density and mortality, and therefore could not comment on the etiologic role that fractures play in this association. In addition, this study confirmed the race-specific differences in the association between bone mineral density, fractures, and mortality, though further research is needed to determine if this is an artifact of the low incidence of fractures among Black women.

The mediating effects of incident fractures on the association between low BMD and mortality differ by fracture site, and are stronger for any incident fractures when using a lower bone mineral density cut point (i.e., using preclinical osteoporosis instead of low bone mineral density as the exposure). This suggests that there is a relationship between low bone mineral density and mortality independent of fracture risk. However, results for the specific fracture sites (hip and wrist) remained largely unchanged in the analyses using the lower bone mineral density cut point, suggesting that fractures at other sites may be driving this increase in mediation. Hip fracture is associated with greater health decline before and after the fracture,[29] and among these women, low bone mineral density may be a marker for poor health and frailty.[26] In contrast, wrist fracture most often occurs in healthy, active individuals, and as a result, fracture at this site mediates less of the association between bone mineral density and mortality than hip fracture, though this association is reliable only for the White cohort. The mediating effects of fractures at other less-studied sites, such as the femur or radius, should be evaluated to confirm their role in the relationship between bone mineral density and mortality.

In the general population, most older adults over age 50 have low BMD.[128] In the current sample, 82% of White women and 70% of Black women had low bone mineral density or preclinical osteoporosis at baseline. As such, there is a large exposed population at risk for death because of low BMD, which may artificially increase the measured association simply because the sample at-risk is larger. Whether or not the increased risk of mortality is found in younger populations with a smaller proportion of low bone mineral density should be the focus of future studies.

Interventions for osteoporosis have been effective at reducing risk of death,[14,80] suggesting that the influence of bone mineral density on death can be mitigated not just by preventing fractures, but by improving overall health as well. For example, low bone mineral density may be a marker for factors related to poor health, which increases the risk of all-cause and cardiovascular mortality.[101] One proposed biological mechanisms is through cardiovascular calcification, due to the similarity between the processes of vascular calcification and bone formation.[34,56,121] The varying risk factors and consequences of fracture at different sites[65] supports this hypothesis. Unlike fractures at sites such as the wrist, vertebral and hip fractures are related to bone fragility, which is closely related to calcification. A recent study in SOF found that abdominal aortic calcification was associated with vertebral and hip fracture, but not fractures at other sites.[114] In other studies, vertebral fracture was associated with stroke[115] and hip fracture was associated with myocardial infarction.[24,25] Further research is needed to confirm these associations at other fracture sites.

The current study had several limitations which should be taken into account when evaluating the results. The SOF sample included only older women, which may limit the generalizability to populations of men and younger individuals. Dichotomizing BMD based on standard deviation units may diminish or even eliminate the statistical differences between bone mineral density groups, however, this was unavoidable due to existing methods for mediation analysis of survival data and was addressed through sensitivity analyses with a stricter cut point for low bone mineral density. One of the assumptions of mediation analysis is that there is no unmeasured confounding. While

unmeasured confounding may occur in any study, the longitudinal and long-term nature of SOF yielded a rich dataset which minimized this possibility.

In addition, the sample included a much smaller proportion of Black women than White women, limiting the precision of the estimates and the ability to comment on the public health impacts for this cohort. The low incidence of fracture among the Black cohort made measuring the mediating effect of fracture difficult and resulted in estimates that likely overstate the true relationship between low bone mineral density, fractures, and mortality. Further research with a larger sample size is needed to precisely measure the impact of incident fractures in this understudied population.

Nevertheless, this study had several strengths. The sample was relatively large and followed for over ten years, allowing for the accumulation of many mediating events and endpoints. Longitudinal measurement of the mediator was thorough, through self-report by questionnaire, postcards or phone call every four months over follow-up, followed by adjudication to reduce misclassification. In addition, the exposure, mediator and outcome were all measured using different methods, minimizing the likelihood of dependent misclassification.

In this longitudinal study of community-dwelling older women, we found that low BMD and preclinical osteoporosis was a predictor of mortality over ten years or longer, and this association varied by race. In addition, we found that incident fractures mediated a proportion of this association, the strength of which varied by fracture site and race cohort. Low incidence of fracture at any site reduced our ability to comment on the proportion of this association in the Black cohort, and further research is needed to better

understand the mediating effects of fracture on this relationship in this understudied population.

Figure 2-1: Selection of analytic sample for Study 2

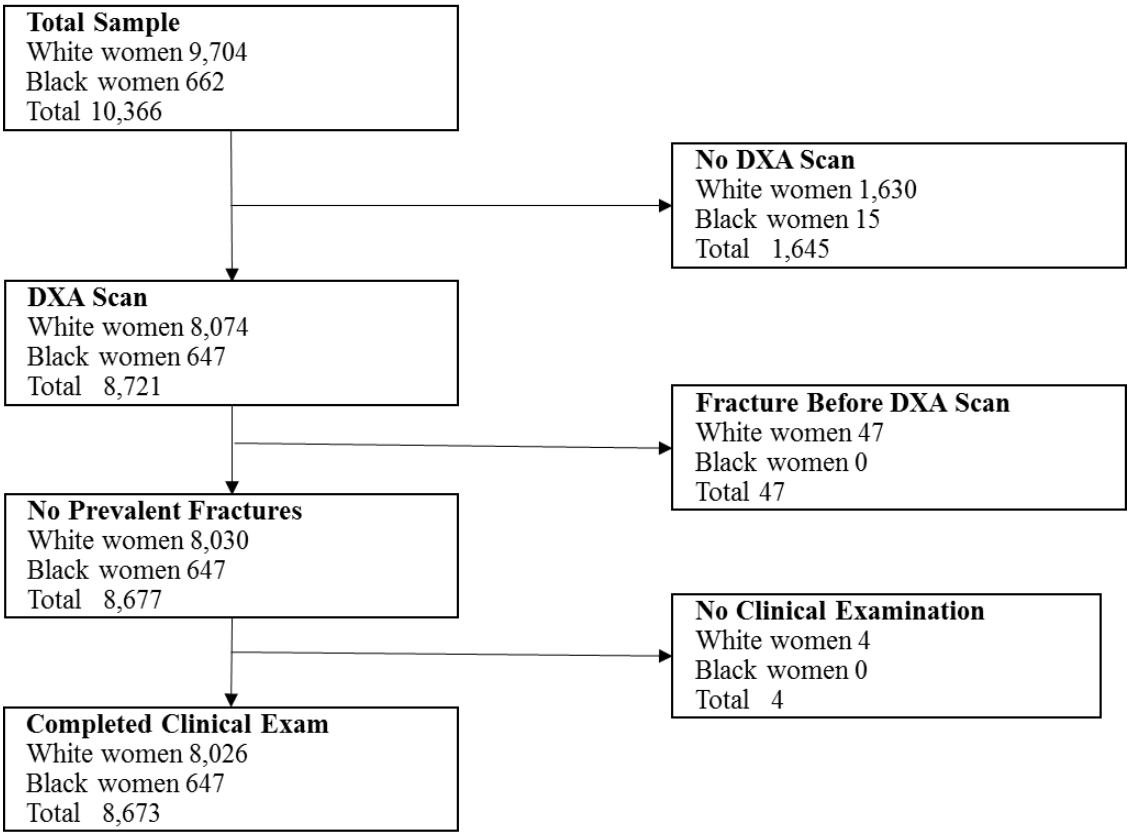

Table 2-1: Baseline health and demographic information among n=8,026 White women with DXA data and a completed clinical evaluation at V2 and among n=647 Black women with DXA data and a completed clinical evaluation at V6.

	White Women				Black Women			
	Normal BMD (n=1,479)		Low BMD (n=6,547)		Normal BMD (n=189)		Low BMD (n=458)	
Baseline age, years, mean (sd)	71.67	(4.07)	73.76	(5.14)	74.05	(4.05)	75.73	(4.32)
High school education, n (%)	1149	(77.69)	5,144	(78.57)	58	(30.69)	158	(34.50)
Married, n (%)	816	(55.17)	3,207	(48.98)	54	(28.57)	111	(24.24)
BMI, mean (sd)	28.68	(4.65)	25.58	(4.18)	31.60	(4.98)	28.66	(5.07)
<18.5	42	(2.84)	292	(4.46)	4	(2.12)	24	(5.24)
18.5–24.9	325	(21.97)	3006	(45.91)	16	(8.47)	85	(18.56)
25–29.9	585	(39.55)	2303	(35.18)	41	(21.69)	170	(37.12)
≥30	527	(35.63)	946	(14.45)	126	(66.67)	174	(37.99)
Smoking status								
Never	910	(61.53)	3,941	(60.20)	121	(64.02)	270	(58.95)
Past	450	(30.43)	1,969	(30.07)	57	(30.16)	144	(31.44)
Current	119	(8.05)	637	(9.73)	11	(5.82)	41	(8.95)
Osteoarthritis, n (%)	974	(65.86)	3,980	(60.79)	53	(28.04)	90	(19.65)
Myocardial infarction, n (%)	83	(5.61)	390	(5.96)	23	(12.17)	47	(10.26)
Hypertension, n (%)	630	(42.60)	2,416	(36.90)	134	(70.90)	277	(60.48)
Diabetes, n (%)	148	(10.01)	246	(3.76)	36	(19.05)	76	(16.59)
COPD, n (%)	111	(7.51)	613	(9.36)	23	(12.17)	68	(14.85)
Multimorbidity Score, n (%)								
No domains	823	(55.65)	3,629	(55.43)	98	(51.85)	232	(50.66)
1 domain	311	(21.03)	1,584	(24.19)	46	(24.34)	124	(27.07)
≥2 domains	345	(23.33)	1,334	(20.38)	45	(23.81)	102	(22.27)

Table 2-2: Ten-year mortality rate, unadjusted and adjusted* hazards ratios of death by BMD category among 8,026 White women and 647 Black women in SOF

	Deaths	PY	Rate per 1,000 PY	HR	95% CI	aHR	95% CI
White women							
Normal BMD	273	13,557	20.14	1.00		1.00	
Low BMD	1,701	57,935	29.36	1.31	(1.21–1.41)	1.12	(1.04–1.21)
Black women							
Normal BMD	40	1,570	25.48	1.00		1.00	
Low BMD	123	3,869	31.79	1.31	(0.91–1.88)	1.01	(0.69–1.49)

PY = person-years; aHR = adjusted hazards ratio; BMD = bone mineral density

*Models adjusted for age, education, marital status, BMI, smoking status, and previously diagnosed conditions (osteoarthritis, hypertension, diabetes, COPD)

**Low BMD includes low BMD and preclinical osteoporosis

Table 2-3: Unadjusted and Adjusted Cox proportional hazards regression models of the association between BMD category and death over ten years mediated by fractures among 8,026 White women and 647 Black women in SOF

	Over 10 years									
	White Women					Black Women				
	HR	95% CL	aHR	95% CL	% mediated	HR	95% CL	aHR	95% CL	% mediated
Fracture at any site										
Normal BMD	1.00		1.00			1.00		1.00		
Low BMD	1.19	(1.19–1.54)	1.08	(0.94–1.23)		1.23	(0.86–1.74)	0.97	(0.66–1.42)	
Any fracture	1.97	(1.79–2.17)	1.12	(1.01–1.32)	7.23	1.38	(0.86–2.23)	1.35	(0.83–2.21)	1.59
Hip fracture										
Normal BMD	1.00		1.00			1.00		1.00		
Low BMD	1.34	(1.18–1.53)	1.10	(0.96–1.26)		1.22	(0.86–1.75)	0.98	(0.66–1.44)	
Hip fracture	3.62	(3.15–4.16)	2.32	(2.01–2.67)	5.35	2.70	(1.10–6.61)	1.95	(0.77–4.91)	0.50
Wrist fracture										
Normal BMD	1.00		1.00			1.00		1.00		
Low BMD	1.47	(1.29–1.67)	1.15	(1.01–1.31)		1.25	(0.87–1.79)	0.98	(0.67–1.44)	
Wrist fracture	1.21	(0.99–1.49)	1.11	(0.91–1.36)	0.40	0.89	(0.22–3.61)	1.04	(0.25–4.27)	0.00

BMD = bone mineral density

*Models adjusted for age, education, marital status, BMI, smoking status, and previously diagnosed conditions (osteoarthritis, hypertension, diabetes, COPD)

% mediated = proportion of the total effect that was explained by the mediator was computed as the beta coefficient for the indirect effect divided by the beta coefficient for the total effect

**Low BMD includes low BMD and preclinical osteoporosis

STUDY 3: RISK OF LONG-TERM NURSING HOME RESIDENCE BY USUAL GAIT SPEED AND ACCOUNTING FOR MORTALITY AS A COMPETING RISK

Introduction

Long-term residence of 12 months or more in a nursing facility is an enormous financial burden for both the individual and public programs. National expenditures for nursing home residence of one year or more range from $25 to $29 billion largely paid out-of-pocket or by programs such as Medicare, and are estimated to be three times as high compared to costs experienced by community-dwelling older adults.[62] Thirty percent of nursing home residents stay for 13 months or more and 25% go on to stay for over three years.[57] Identifying and intervening on factors that could prevent or delay nursing home residence would significantly reduce the financial burden on both individuals and federal programs, and is therefore an important issue for health policy and management.

Slow gait speed is an objective measure of poor physical function that is associated with increased risk of disability and morbidity in older adults.[9,22,47,106,113] Poor physical function is a predictor of nursing home residence even among healthy individuals[47] and when controlling for cognitive status, a common indication for nursing home admission.[120] Slow gait speed is also strongly predictive of mortality,[22,23,47,75,106] which shares many of the same risk factors as nursing home placement, making death a competing risk of these associations.

Insofar as older adults with poor physical function are at a greater risk of both

nursing home placement [47] and mortality,[22,47,75,106,113] use of traditional Cox proportional hazards survival models does not account for those who die before they have the opportunity to have a long-term care stay. In this situation, mortality should not be treated as an uninformative censoring event because subjects censored due to death may not have the same distribution of time-to-event as subjects who experience long-term nursing home residence.[35] Recent longitudinal studies that accounted for death as a competing risk found that poor physical function[20] and slow gait speed[83] measured at one point in time predicted nursing home placement[20] and long-term nursing home residence,[83] yet the magnitude of the associations was attenuated compared with traditional survival models. However, gait speed generally decreases over time in older adults,[43,50,107,125] thus measuring it at a single time point may underestimate associations with nursing home residence.

To extend these previous studies, we evaluated the associations between time-dependent gait speed and risk of long-term nursing home placement in a cohort of 5,584 community-dwelling women aged 65 and older. We hypothesized that slow usual gait speed over time would be associated with a higher risk of long-term nursing home residence relative to faster usual gait speed. In addition, we hypothesized that this association would become attenuated when accounting for mortality as a competing risk.

Methods

Data Collection and Analytic Sample

The SOF cohort was linked to Medicare Claims files by submitting participant social security or Medicare numbers to the Centers for Medicare and Medicaid

Services.[110] Medicare records were available for SOF participants starting January 1, 1991. Participants were followed from the date of their first Medicare record through long-term nursing home residence, death, withdrawal from SOF, Medicare disenrollment, or the end of the follow-up period on December 31, 2010. Of the 9,986 White and African-American SOF women who were alive as of January 1, 1991, 9,228 were enrolled in Medicare (including fee-for-service and/or managed care plans) for at least one month over the eligible follow-up period. Of these women, 5,584 were enrolled in a Medicare fee-for-service plan (parts A and B alone), and had completed information on gait speed for at least one SOF examination (Figure 1). Baseline data were selected from the first SOF examination that occurred prior to when Medicare claims files became available for each individual.

Approximately every two to six years, SOF participants had a comprehensive clinical evaluation to assess physical and cognitive health. White women contributed a maximum of nine examinations (median=6) and Black women contributed a maximum of four examinations (median=3) over the follow-up period. For all analyses, the exposure and covariate values were updated at each in-person examination. In the case of missing data, values were carried forward from previous examinations for participants who were present at a later examination. Less than 5% of covariate data were missing due to non-response at each examination and gait speed missingness increased from 0% at Visit 1 to 30% at Visit 8.

Measures

Usual gait speed (meters/second, m/s) was ascertained at every SOF examination by trained interviewers over a straight six-meter course and averaged over two timed trials.[38] Usual gait speed was dichotomized as slower (< 1.0 m/s) and faster (≥ 1.0 m/s), a clinically-useful cut point strongly predictive of mortality.[113] Alternative measures of gait speed using other cut-points (i.e., 0.6–0.8 m/s) have been associated with adverse health outcomes in older adults,[2,113] therefore we conducted sensitivity analyses dichotomizing usual gait speed at 0.8 m/s.

Incident long-term nursing home residence was defined by a modified version of a previously published algorithm that used Medicare claims data to distinguish between short-term (usually intended for purposes of post-hospital rehabilitation, Medicare Part A) and long-term (usually for custodial residence, Medicare Part B) nursing home stays.[123,129] This algorithm used billing information for services that were delivered to nursing home residents because Medicare does not cover long-term nursing home stays. We first identified a month with a carrier or outpatient bill that did not occur during Part A-covered nursing home stay and examined the following 12 months for subsequent Part B outpatient services delivered in the nursing home. We then calculated long-term nursing home residence (long-term: yes vs. no) based on the proportion of months that had Part B claims submitted during this 13-month period. We defined long-term nursing home residents as women who had a Part B nursing home claim submitted for 40% or more of their eligible follow-up months as long as no Part A nursing home claims were submitted during this period; this definition had high predictive validity (sensitivity 87%,

specificity 96%) of custodial residence in a nursing home.[129]

All-Cause Mortality was defined as date of death from any cause by Medicare records

Statistical Analyses

SOF participants contributed person-time from the earliest date of Medicare data availability until long-term nursing home residence, death, withdrawal from SOF, termination from Medicare, or the end of follow-up, whichever came first. Black women were enrolled several years after White women, and therefore contributed less follow-up time (maximum possible follow-up time was 14 years vs. 24 years, respectively). To accommodate the race-dependent differences in the enrollment period, regression analyses were stratified by race.

In the first set of multivariable regression analyses, Cox proportional hazards regression models using age as the time scale were conducted to calculate age-adjusted and adjusted hazard ratios (HR) and 95% confidence intervals (CI) for the association between time-dependent gait speed and long-term nursing home residence, with death as an uninformative censoring event. The Andersen-Gill data structure[6] was used to manage time-dependent covariates and delayed entry, a result of using age as the time scale. Covariates were included in the model if they were established risk factors for slow gait speed, long-term nursing home residence, or death; if they were associated with slow gait speed and long-term nursing home residence in the current sample, or if their inclusion in the proportional hazards model meaningfully changed the hazards ratio of the association between slow gait speed and nursing home residence by 10% or more. The final adjusted

models included baseline age, race, marital status, high school education, smoking status, BMI, MMSE, multimorbidity score, and SOF clinical center.

The Fine and Gray subdistribution approach for competing risk analysis[40] was used to account for death as a competing risk. These subdistribution models were stratified by race and included the same covariates as the Cox models. This subdistribution model estimates the HR in the presence of the rate of death that was observed in these data, while the traditional Cox model estimates the HR as it would have been had death not occurred.

In sensitivity analyses, the cut point for slow gait speed was reduced from 1.0 m/s to 0.8 m/s, and both the Cox proportional hazards and Fine-Gray subdistribution models were repeated as described above.[70]

Analyses were conducted using SAS software (Statistical Analysis System, version 9.4, Cary, North Carolina).

Results

Sample Characteristics

At the baseline examination (determined by the date of Medicare data availability for each participant, not by date of SOF enrollment), the mean age of the 5,584 participants was 76.0 (SD=5.6) years and 6.7% were Black (Table 3-1). Mean gait speed was 0.88 (SD=0.26) m/s and 67.1% of participants were classified as slow walkers (i.e., mean gait speed < 1.0 m/s). Slow walkers were more likely than faster walkers to be Black and of older age. Slow walkers also were less likely to be married or to have graduated high school. Over the follow-up period, 1,438 participants (25.8%) became

long-term nursing home residents, while 1,513 (27.1%) died before experiencing this outcome. Participants with long-term nursing home residence had slower gait speed compared with those who were censored for reasons other than death, but not compared with those who died (Table 3-A1a, Table 3-A1b). Those who experienced long-term nursing home residence were also more likely to be White, unmarried, older at baseline, and have higher multimorbidity than those who were censored (Table 3-A1).

Baseline Gait Speed and Incident Long-Term Nursing Home Residence

Among White women, slow walkers at baseline were more likely than faster walkers to reside in a nursing home long-term, even when adjusting for covariates (age-adjusted hazard ratio (HR) = 1.53, 95% CI: 1.37–1.70, and adjusted hazard ratio (aHR) = 1.50, 95% CI: 1.33–1.68) (Table 3-2). In subdistribution models adjusted for covariates and accounting for death as an informative censoring event, rate of long-term nursing home residence was similar to the Cox results, though attenuated: aHR= 1.29, 95% CI: 1.15–1.45 (Table 3-2).

Among Black women, slow walkers at baseline were more likely than faster walkers to reside in a nursing home long-term, although this association was imprecise (HR= 1.49, 95% CI: 0.57–3.88, and aHR= 1.64, 95% CI: 0.60–4.52) (Table 3-2). In subdistribution models adjusted for covariates and accounting for death as an informative censoring event, slower walkers had a similar rate of long-term nursing home residence, but this association remained imprecise (aHR= 1.61, 95% CI: 0.58–4.49) (Table 3-2).

Time-Dependent Gait Speed and Incident Long-Term Nursing Home Residence

Among White women, slow walkers were more likely than faster walkers to reside in a nursing home long-term, even when adjusting for covariates (age-adjusted HR = 2.08, 95% CI: 1.81–2.40, and aHR = 1.94, 95% CI: 1.68–2.25) (Table 3-3). In subdistribution models adjusted for covariates and accounting for death as an informative censoring event, rate of long-term nursing home residence was similar to the Cox results: aHR= 1.88, 95% CI: 1.62–2.17 (Table 3-3).

Among Black women, slow walkers were more likely than faster walkers to reside in a nursing home long-term, although this association was imprecise (HR= 1.88, 95% CI: 0.56–6.27, and aHR= 1.92, 95% CI: 0.52–7.07) (Table 3-3). In subdistribution models adjusted for covariates and accounting for death as an informative censoring event, slower walkers had a slightly higher risk of long-term nursing home residence, but this association remained imprecise (aHR= 2.04, 95% CI: 0.50–8.29) (Table 3-3).

Sensitivity Analyses

Similar associations were found for White women when 0.8 m/s was used as the cut-point for slow gait speed, (proportional aHR= 2.02, 95% CI: 1.80–2.26, subdistribution aHR=1.85, 95% CI: 1.64–2.08). Among Black women, the more conservative gait speed cut point produced stronger associations with risk of long-term nursing home residence, with more precise confidence intervals (proportional aHR= 2.20, 95% CI: 0.96–5.01, subdistribution aHR=1.99, 95% CI: 0.99–4.42) than in models using the 1 m/s cutpoint (Table 3-4).

Discussion

In this large prospective study of community-dwelling older women with up to 24 years of follow-up, slow gait speed was associated with an increased risk of long-term nursing home residence while accounting for the competing risk of death. This was the first study of this association to model gait speed as a time-dependent variable. Adjusting for the competing risk did not substantially alter the association between gait speed and long-term nursing home residence, despite the fact that almost a third of the sample died before having the opportunity for a long-term nursing home stay. Although the associations between slow gait speed and long-term nursing home residence were slightly stronger among Black women, these results were imprecise because fewer events were observed in this group, possibly due to the shorter follow up time. These results confirmed our hypothesis that slow gait speed would be associated with long-term nursing home residence over time. Our findings agreed with those from previous studies of physical function and nursing home placement[20] as well as gait speed and long-term residence.[83] Furthermore, they indicate that gait speed measurements taken over time have a stronger association than those taken at a single point that occurred much earlier in time than either nursing home placement or the competing risk of death.[82]

Sensitivity analyses demonstrated that using more conservative gait speed cut points resulted in similar associations with long-term nursing home placement as a cut point of 1.0 m/s for White women and slightly stronger associations for Black women. Given that slow gait speed cut points as low as 0.65 m/s have been recommended for older adults,[113] these results further support the conclusion that lower gait speed cut

points are clinically relevant among adults later in life.

Results from all models, regardless of the gait speed cut point used, indicated that slow gait speed was a strong predictor of long-term nursing home residence even when accounting for cognitive functioning (as measured by the Short MMSE) and multimorbidity status (as measured by a sample-specific health domain score), which are both major risk factors for nursing home placement. This finding underscores previous studies that gait speed is an independent indicator of health and functional status, and may be valuable in the clinical setting to identify and recommend interventions for patients at risk of long-term nursing home residence.[21,112,113] This is an important finding because studies have shown that interventions can increase gait speed in older adults with disability,[53] stroke,[71] and Parkinson's Disease,[16] suggesting that despite the presence of multimorbidity, improving gait speed may result in delaying or preventing long-term nursing home residence. Future studies with adequate samples should evaluate this hypothesis.

We found a smaller difference between the results of subdistribution models and Cox proportional hazards models compared with previous analyses of the SOF sample that measured gait speed at a single time point.[82] The smaller difference can be attributed to the temporal relationship between walking speed and death (i.e., a competing risk), as time-dependent measures can reduce the amount of follow-up time between an exposure measurement and an outcome. The end result is that the competing risk has a smaller impact in time-dependent analyses than in analyses using only baseline data. While accounting for death as a competing risk is recommended for many investigations of

older adults,[8,69] the benefit may be lessened when using time-dependent exposure and covariate measures.

Measuring gait speed only at baseline, while informative, may underestimate associations between gait speed and nursing home residence. Evidence suggests that changes in gait speed over time predict declines in functional status even among the fastest walkers.[4] By contrast, baseline measurements in older community-dwelling populations usually reflect the time point when participants are at their healthiest and most functional, but ignore subsequent change in gait speed that may be more relevant to risk of nursing home placement and may lead to misclassification of exposure at the time of the outcome or censoring. A time-varying measurement of gait speed uses all the available exposure data, thereby providing a more accurate estimate of the association with nursing home residence.

This study had several potential limitations. The SOF sample is comprised of only older women, which may limit generalizability to other populations that include older men. Due to later years of enrollment, there were fewer outcomes observed for Black women than White women, leading to imprecise estimates for this group. The algorithm to predict long-term nursing home residence included only participants enrolled in Medicare fee-for-service plans, which also may limit generalizability to older adults with other types of Medicare plans (Part C or Medicare Advantage), particularly because nursing home admission and coverage rules vary across plans and may have an impact on when, and for how long, a resident stays in a nursing home. In addition, gait speed was operationalized as a dichotomous exposure variable, which does not capture

absolute decline or rate of decline if the change does not cross the 1.0 m/s threshold. This could have minimized the differences between very fast walkers and very slow walkers whose gait speed may have decreased over the follow-up period but not have been reflected because it remained within the same gait speed category. Gait speed measurements were more likely to be missing from later examinations when women were older and at greater risk of death or nursing home residence, which could lead to an underestimate of the association between gait speed and nursing home residence.

Strengths of the study included a large sample with a long follow-up period allowing for the observation of many deaths and long-term residences. The study combined Medicare data for outcomes and longitudinal epidemiologic study data for the exposure and covariates which allowed us to control for more covariates than would be possible if we relied solely on Medicare data. This method also eliminated the possibility of dependent misclassification because exposure and outcome data were collected from different sources. Gait speed itself is a valid and reliable measure of function, and can be performed at the clinic or in the participant's home.[87,112] In addition, nursing home outcomes as well as competing risk events were confirmed using Medicare fee-for-service data. This information can be difficult to reliably capture in cohort studies because participants may be lost to follow-up when they are institutionalized.

In summary, this study applied a method to account for death in a longitudinal analysis of gait speed and nursing home residence, and extended the evidence from previous studies that slow gait speed is an important predictor of long-term nursing home residence even when controlling for cognitive status and multimorbidity. These results

further support the potential for use of gait speed measurement to identify older adults at risk of long-term nursing home stays and for whom interventions to improve physical function may help to delay nursing home placement.

Figure 3-1. Selection of analytic sample for Study 3

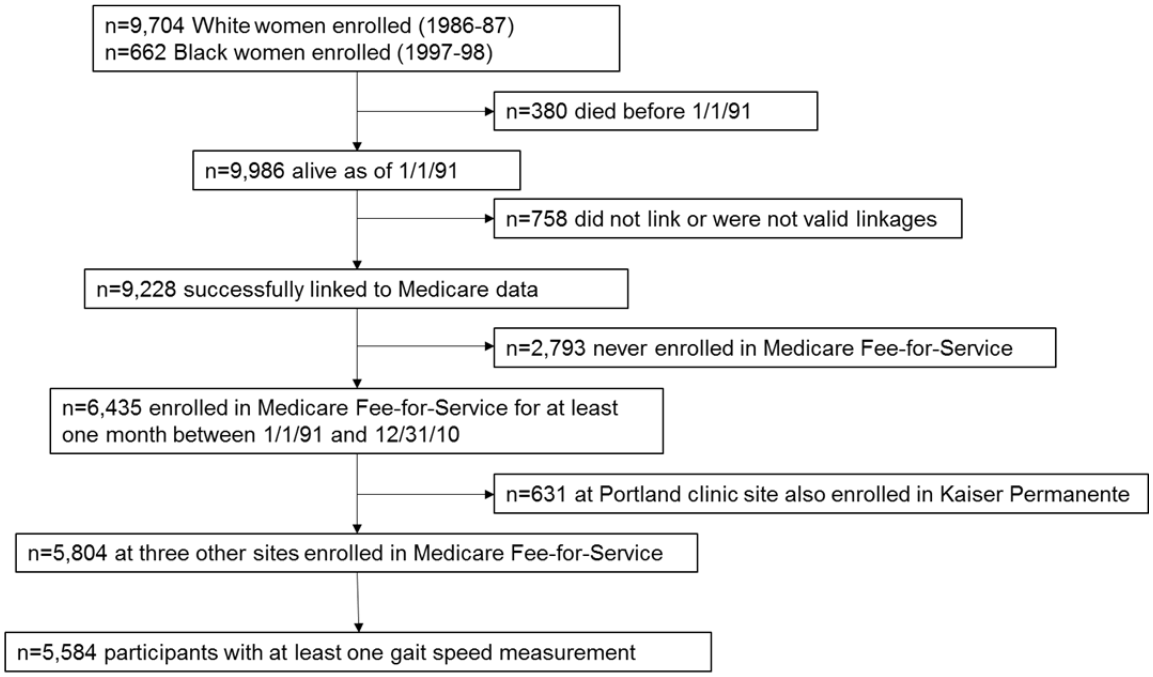

Table 3-1. Baseline characteristics of 5,584 SOF participants by gait speed

	Total		Slow gait speed < 1 m/s		Faster gait speed ≥ 1 m/s	
	n=5,584		n=3,747		n=1,837	
Outcomes						
Long-term nursing home residence, n (%)	1,438	(25.75)	1,192	(31.81)	246	(13.39)
Death before residence, n (%)	1,513	(27.10)	1,171	(31.25)	342	(18.62)
Demographics						
Baseline age, years, mean (sd)	76.02	(5.58)	77.04	(5.77)	73.96	(4.53)
Black race, n (%)	372	(6.66)	293	(7.82)	79	(4.30)
High school education, n (%)	4212	(75.43)	2679	(71.50)	1533	(83.45)
Married, n (%)	2315	(41.46)	1397	(37.28)	918	(49.97)
BMI (kg/m^2), mean (sd)	26.63	(4.68)	27.03	(4.87)	25.81	(4.16)
Short MMSE, mean (sd)	24.5	(1.94)	24.30	(2.09)	24.91	(1.51)
Smoking status, n (%)						
Never smoker	3277	(58.69)	2209	(58.95)	1068	(58.14)
Ever smoker	1714	(30.69)	1114	(29.73)	600	(32.66)
Current smoker	574	(10.28)	414	(11.05)	160	(8.71)
Multimorbidity score, n (%)						
No domains	873	(15.63)	470	(12.54)	403	(21.94)
1 domain	2168	(38.83)	1397	(37.28)	771	(41.97)
≥ 2 domains	2543	(45.54)	1880	(50.17)	663	(36.09)

*All models are adjusted for SOF clinic site
BMI: Body Mass Index
MMSE: Mini Mental Status Exam

Table 3-2: Adjusted race-specific hazard ratios and 95% confidence intervals of long-term nursing home residence from baseline slow gait speed accounting for death as a competing risk

	White Women				Black Women			
	Traditional Cox Model		Subdistribution Model		Traditional Cox Model		Subdistribution Model	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Gait speed < 1 m/s	1.50	(1.33, 1.68)	1.29	(1.15, 1.45)	1.64	(0.60, 4.52)	1.61	(0.58, 4.49)
Gait speed ≥ 1 m/s	1.00		1.00		1.00		1.00	
Married	0.78	(0.69, 0.87)	0.81	(0.73, 0.91)	0.55	(0.21, 1.48)	0.57	(0.22, 1.53)
Baseline age (years)	1.00	(0.98, 1.01)	1.06	(1.05, 1.07)	0.90	(0.79, 1.02)	0.98	(0.90, 1.06)
BMI (kg/m^2)	0.98	(0.97, 1.00)	0.99	(0.98, 1.00)	1.00	(0.92, 1.07)	1.00	(0.92, 1.08)
Short MMSE	0.94	(0.91, 0.97)	0.95	(0.93, 0.98)	0.84	(0.71, 0.99)	0.84	(0.70, 1.00)
Multimorbidity score								
≥ 2 domains	0.88	(0.76, 1.02)	1.19	(1.03, 1.39)	1.16	(0.36, 3.77)	1.03	(0.33, 3.24)
1 domain	1.08	(0.96, 1.22)	1.05	(0.91, 1.21)	1.23	(0.39, 3.87)	1.15	(0.38, 3.45)
0 domains	1.00		1.00		1.00		1.00	
Smoking status								
Never smoker	1.00		1.00		1.00		1.00	
Ever smoker	1.04	(0.93, 1.18)	0.96	(0.85, 1.08)	1.229	(0.57, 2.63)	1.24	(0.57, 2.67)
Current smoker	1.32	(1.09, 1.59)	0.98	(0.81,. 1.19)	2.92	(0.92, 9.24)	2.04	(0.68, 6.14)
High school education	1.06	(0.93, 1.21)	1.05	(0.92, 1.19)	2.574	(1.00, 6.63)	2.67	(0.86, 8.32)

*All models are adjusted for SOF clinic site
BMI: Body Mass Index
MMSE: Mini Mental Status Exam

Table 3-3. Adjusted race-specific hazard ratios and 95% confidence intervals of long-term nursing home residence from time-dependent slow gait speed accounting for death as a competing risk

	White Women				Black Women			
	Traditional Cox Model		Subdistribution Model		Traditional Cox Model		Subdistribution Model	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Gait speed < 1 m/s	1.94	(1.68, 2.25)	1.88	(1.62, 2.17)	1.92	(0.52, 7.07)	2.04	(0.50, 8.29)
Gait speed ≥ 1 m/s	1.00		1.00		1.00		1.00	
Married	0.82	(0.73, 0.93)	0.78	(0.69, 0.88)	0.25	(0.06, 1.09)	0.30	(0.05, 1.67)
Baseline age (years)	1.00	(0.99, 1.01)	1.06	(1.04, 1.07)	0.71	(0.60, 0.84)	0.93	(0.85, 1.01)
BMI (kg/m^2)	0.97	(0.96, 0.98)	0.98	(0.97, 1.00)	0.98	(0.91, 1.06)	0.98	(0.90, 1.07)
Short MMSE	0.89	(0.87, 0.91)	0.88	(0.87, 0.90)	0.79	(0.69, 0.91)	0.79	(0.71, 0.87)
Multimorbidity score								
≥ 2 domains	1.31	(1.11, 1.55)	1.10	(0.93, 1.30)	1.36	(0.38, 4.87)	1.09	(0.39, 3.05)
1 domain	1.06	(0.90, 1.26)	1.04	(0.88, 1.23)	1.68	(0.50, 5.67)	1.38	(0.50, 3.79)
0 domains	1.00		1.00		1.00		1.00	
Smoking status								
Never smoker	1.00		1.00		1.00		1.00	
Ever smoker	1.04	(0.92, 1.17)	0.97	(0.86, 1.10)	1.81	(0.80, 4.07)	1.67	(0.78, 3.60)
Current smoker	1.28	(1.06, 1.54)	0.96	(0.79, 1.17)	2.87	(0.82, 10.13)	1.78	(0.57, 5.58)
High school education	1.10	(0.97, 1.25)	1.13	(1.00, 1.28)	2.08	(0.84, 5.15)	2.51	(0.90, 7.00)

*All models are adjusted for SOF clinic site

BMI: Body Mass Index

MMSE: Mini Mental Status Exam

Table 3-4. Associations between gait speed and long-term nursing home residence among SOF women (n=5,584), using a more stringent definition of slow gait speed (<0.8 m/s vs. ≥0.8 m/s)

	White Women				Black Women			
	Traditional Cox Model		Subdistribution Model		Traditional Cox Model		Subdistribution Model	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Gait speed < 0.8 m/s	2.02	(1.80, 2.26)	1.85	(1.64, 2.08)	2.17	(0.97, 4.88)	1.93	(0.87, 4.25)
Gait speed ≥ 0.8 m/s	1.00		1.00		1.00		1.00	
Married	0.84	(0.73, 0.94)	0.78	(0.70, 0.90)	0.27	(0.06, 1.16)	0.30	(0.05, 1.68)
Baseline age	1.00	(0.98, 1.01)	1.05	(1.04, 1.06)	0.70	(0.59, 0.83)	0.93	(0.85, 1.01)
BMI	0.97	(0.96, 0.98)	0.98	(0.97, 0.99)	0.98	(0.90, 1.06)	0.98	(0.90, 1.07)
Short MMSE	0.89	(0.88, 0.91)	0.88	(0.87, 0.90)	0.79	(0.69, 0.91)	0.79	(0.72, 0.88)
Multimorbidity score								
≥ 2 domains	1.27	(1.07, 1.10)	1.07	(0.89, 1.25)	1.48	(0.42, 5.30)	1.13	(0.40, 3.14)
1 domain	1.06	(0.89, 1.25)	1.03	(0.87, 1.22)	1.77	(0.52, 6.05)	1.35	(0.48, 3.83)
0 domains	1.00		1.00		1.00		1.00	
Smoking status								
Never smoker	1.00		1.00		1.00		1.00	
Ever smoker	1.06	(0.94, 1.19)	0.97	(0.86, 1.10)	1.781	(0.70, 4.03)	1.66	(0.77, 3.59)
Current smoker	1.32	(1.10, 1.60)	0.96	(0.79, 1.17)	3.11	(0.88, 10.99)	1.81	(0.55, 5.92)
High school education	1.12	(0.98, 1.27)	1.13	(1.00, 1.28)	2.11	(0.86, 5.21)	2.51	(0.90, 7.03)

*All models adjusted for SOF clinic site
BMI: Body Mass Index
MMSE: Mini Mental Status Exam

CONCLUSION

This dissertation evaluated the associations between physical function and skeletal health, respectively, with disability, mortality and long-term nursing home residence in a large cohort of White and Black women participating in the Study of Osteoporotic Fractures. Physical function and skeletal health are important contributors to the health and well-being of older adults, and directly impact quality of life and independence. However, physical function changes over time and has complicated relationships with other time-dependent covariates such as bone health and comorbidities. As such, this may result in biased associations with adverse health outcomes such as mortality and long-term nursing home residence. This dissertation utilized novel methods to reduce the bias that can affect longitudinal associations between physical function and health outcomes by utilizing age-based risk set sampling, evaluating mediation by osteoporotic fractures, and controlling for death as a competing risk.

The first study examined the relation between poor physical function and incident disability, and whether this association was strengthened when physical function was assessed as a time-dependent exposure in comparison to using a baseline assessment only. Among White women, the lowest performers in each individual and summary performance measure had a greater risk of developing a disability over the follow-up period than the highest performers, even when adjusting for confounders. However, this association was stronger when using time-dependent measures that were updated at every interview compared to the baseline measurements. Due to low numbers of outcome events in the Black cohort, these associations were imprecise and few conclusions could

be drawn about the association between physical function and disability in these women.

In both baseline and time-dependent analyses, lower scores in the summary measure of physical function were associated with increased risk of disability. Unlike other measures of lower body function,[47] the summary measure used in this dissertation included grip strength, a measure of upper body function, and did not include tandem stand. As such, this summary performance measure reflected whole body function, which may be a better indicator of disability in IADLs involving the upper body, such as heavy housework and shopping. As found in previous studies,[47] including more than one physical performance measure in the summary score allowed for greater precision in defining the lowest and highest performers, as there was more variability within the summary measure than within the individual performance measures divided into quartiles. There was a monotonic increase in the association between poorer summary performance and risk of incident disability among White women, though this was less evident in the Black women due to the small number of events. Nonetheless, this linear relationship suggests that there are gains to using the summary score of total body physical function over any of the individual measures alone.

While baseline measures of physical function showed a pattern of increased risk of incident disability across lower quartiles of each measure, these hazards ratios were greater when using time-dependent measures. This finding confirms that measuring physical function at a single time point may lead to misclassified estimates compared to using time-varying measures. Physical function decreases with increasing age and the rate of change increases at older ages. As such, baseline measurements within long-term

longitudinal studies appear to be more likely to be biased because they are taken when a participant is at her youngest and most functional. Therefore, updating physical performance measures at every interview more accurately represents a participant's current physical function status and minimizes exposure misclassification.

The second study examined the mediating effects of incident fracture at two different sites and overall on the association between low bone mineral density and death over ten years. White women with low bone mineral density had an increased risk of fracture at any site, the hip, or the wrist, and an increased risk of death compared to women with normal bone mineral density. In this cohort, hip fracture was associated with increased risk of death, but wrist fracture was protective against death, likely due to the fact that women with wrist fractures tended to be healthier and experience a fracture while being active.[65] These findings were consistent with other studies of fracture and mortality in older women.[10,95] Due to the low fracture rate over follow-up among Black women, estimates of these same associations were imprecise.

The proportion of the association between low bone mineral density and mortality that was mediated by incident fracture varied by site. Among both White and Black women, the proportion of these associations mediated by fracture was highest for any fracture and lowest for wrist fracture, although the proportion mediated was higher for White women than for Black women at all three fracture sites. These results suggest that fracture plays a small but measurable role in the association between bone mineral density and mortality.

The third study examined the relationship between gait speed measured at

baseline and as a time-dependent exposure, respectively, with risk of long-term nursing home residence while controlling for death as a competing risk. Death is often a competing risk for other events in longitudinal analyses of older adults, which means that without controlling for the competing effects of death, estimates may be biased toward the null.

Slow gait speed was associated with increased risk of long-term nursing home residence regardless of the timing used (i.e., baseline only or time-dependent), however the association using baseline gait speed only may have been underestimated due to exposure misclassification. We found that controlling for death as a competing risk of the association between slow gait speed and long-term nursing home residence had a greater impact on the estimates of association in baseline analyses compared to time-dependent analyses, which updated gait speed and covariates at every clinical visit. The smaller impact may be attributed to the temporal relationship between gait speed and death, as time-dependent assessments can reduce the amount of follow-up time between an exposure measurement and an outcome.

In this study, sensitivity analyses using a lower cut point to define slow gait speed demonstrated that among older women, lower cut points for defining slow gait speed were meaningful and clinically relevant, and may be more appropriate for this population. Slow gait speed using lower cut points were more strongly associated with risk of long-term nursing home residence than slow gait speed using higher cut points. This supports previous research that suggested lower cut points of gait speed are better able to define low function in older populations[113] and may be more useful than higher cut points at

identifying older adults at risk of long-term nursing home residence.

The studies comprising this dissertation used novel methods to address potential misclassification and bias that are inherent with longitudinal research of the health effects of physical functioning in older women. As appropriate, analyses with time-dependent exposures and covariates were evaluated by repeating analyses of baseline-only variables with those using time-dependent variables. In this way, potential misclassification of time-varying exposures could be evaluated. In this population, age is an important confounder and predictor of all of the outcomes evaluated. As such, all three studies utilized age as the time scale instead of time-in-study to construct risk-sets and more precisely control for age over time. Lastly, mediation analyses using time-dependent mediators and a competing risk analysis were conducted to better understand the complex associations between bone mineral density and death, and gait speed and long-term nursing home residence over time.

These studies suggested several important findings about the etiologic associations between physical function, as well as skeletal health, with disability, mortality, and nursing home residence. In the two studies of physical function, time-dependent analyses found stronger relationships between physical performance and incident disability and long-term nursing home placement than baseline analyses. Further, the competing risk of death had a greater effect in baseline-only analyses compared to time-dependent analyses because there was more time between the exposure measurement and the timing of the competing risk. In the study of physical health, incident fracture at the hip, but not the wrist, was found to be a mediator of the

association between bone mineral density and death.

These findings confirm previous research of the etiologic relationships between poor physical function, along with poor skeletal health, and health outcomes among older women. The methods used within this dissertation have improved the validity of the measured associations by more accurately recording physical function over time, controlling for indirect effects, and accounting for death as a competing risk. Interventions for improving physical function may be an important step in delaying health decline and maintaining independence in older adults. Furthermore, these findings underscore the clinical importance and potential of using these measures to identify older adults for whom interventions to improve their physical function may improve health and quality of life in older adults.

APPENDIX

Table 1-A1: Quartile cut points for each individual performance measure, by race cohort

	White Women	Black Women
Gait Speed (m/s)		
Quartile 1	<0.86	<0.75
Quartile 2	0.86 – 0.98	0.75 – 0.87
Quartile 3	0.99 – 1.12	0.88 – 0.99
Quartile 4	≥1.13	≥1.00
Grip Strength (kg)		
Quartile 1	<16.50	<16.50
Quartile 2	16.50 – 19.49	16.50 – 19.99
Quartile 3	19.50 – 22.49	20.00 – 22.99
Quartile 4	≥22.50	≥23.00
Chair Stand Speed (sec)		
Quartile 1	≥13.10	≥16.00
Quartile 2	10.80 – 13.09	13.10 – 15.99
Quartile 3	9.10 – 10.79	10.70 – 13.09
Quartile 4	<9.10	<10.70

Table 2-A1: Mortality and fractures over the entire follow-up period among n=8,026 White women with DXA data and a completed clinical evaluation at V2 and among n=647 Black women with DXA data and a completed clinical evaluation at V6.

	White Women				Black Women			
	Normal BMD (n=1,479)		Low BMD (n=6,547)		Normal BMD (n=189)		Low BMD (n=458)	
Incident fracture over entire follow-up								
Incident fracture, any site, n (%)	265	(17.92)	4,402	(67.24)	15	(7.94)	80	(17.47)
Hip, n (%)	24	(1.62)	594	(9.07)	1	(0.53)	15	(3.28)
Wrist, n (%)	41	(2.77)	450	(6.87)	0	(0.00)	14	(3.06)
Outcome over entire follow-up								
Death, n (%)	813	(54.97)	4,076	(62.26)	48	(25.40)	148	(32.31)

*Low BMD includes low BMD and preclinical osteoporosis

Table 2-A2: Entire follow-up period mortality rate, unadjusted and adjusted* hazards ratios of death by BMD category among 8,026 White women and 647 Black women in SOF

	Deaths	PY	Rate per 1,000 PY	HR	95% CI	aHR	95% CI
White women							
Normal BMD	813	21,478	37.85	1.00		1.00	
Low BMD	4,076	86,868	46.92	1.47	(1.30–1.68)	1.14	(1.00–1.31)
Black women							
Normal BMID	48	1,744	27.52	1.00		1.00	
Low BMD	148	4,262	34.73	1.32	(0.95–1.84)	1.01	(0.71–1.43)

PY = person-years; aHR = adjusted hazards ratio; BMD = bone mineral density

*Models adjusted for age, education, marital status, BMI, smoking status, and previously diagnosed conditions (osteoarthritis, hypertension, diabetes, COPD)

**Low BMD includes low BMD and preclinical osteoporosis

Table 2-A3: Entire follow-up period adjusted Cox proportional hazards regression models of the association between BMD category and death mediated by fractures among 8,026 White women and 647 Black women in SOF

	Over the entire follow-up					
	White Women			Black Women		
	HR	95% CL	% mediated	HR	95% CL	% mediated
Fracture at any site						
Normal BMD	1.00			1.00		
≤Low BMD	1.05	(0.97–1.13)		0.96	(0.68–1.36)	
Any fracture	1.53	(1.44–1.63)	7.13	1.37	(0.90–2.09)	1.78
Hip fracture						
Normal BMD	1.00			1.00		
Low BMD	1.05	(0.97–1.13)		0.97	(0.69–1.38)	
Hip fracture	1.97	(1.82–2.14)	7.04	1.87	(0.86–4.08)	0.50
Wrist fracture						
Normal BMD	1.00			1.00		
Low BMD	1.11	(1.03–1.21)		0.97	(0.68–1.37)	
Wrist fracture	1.11	(1.00–1.23)	0.60	1.55	(0.56–4.26)	0.90

BMD = bone mineral density

*Models adjusted for age, education, marital status, BMI, smoking status, and previously diagnosed conditions (osteoarthritis, hypertension, diabetes, COPD)

% mediated = proportion of the total effect that was explained by the mediator was computed as the beta coefficient for the indirect effect divided by the beta coefficient for the total effect

**Low BMD includes low BMD and clinical osteoporosis

Table 3-A1a. Baseline characteristics of 5,584 SOF participants by competing risk group

	Censored*		Died		Long-term Residence	
	n=2,633		n=1,513		n=1,438	
Exposure						
Gait speed, mean (sd)	0.98	(0.22)	0.80	(0.25)	0.77	(0.26)
Demographics						
Baseline age, years, mean (sd)	74.36	(4.98)	76.95	(5.33)	78.10	(5.95)
Black race, n (%)	285	(10.82)	53	(3.50)	34	(2.36)
High school education, n (%)	2016	(76.57)	1136	(75.08)	1060	(73.71)
Married, n (%)	1274	(48.39)	580	(38.33)	474	(32.96)
BMI, mean (sd)	26.95	(4.64)	26.48	(4.95)	26.20	(4.44)
Short MMSE, mean (sd)	24.63	(1.83)	24.53	(1.82)	24.25	(2.22)
Multimorbidity score, n (%)						
No domains	496	(18.84)	186	(12.29)	191	(13.28)
1 domain	1089	(41.36)	532	(35.16)	547	(38.04)
≥ 2 domains	1048	(39.80)	795	(52.54)	700	(48.68)

*Censored do to loss to follow-up, withdrawal, or end of study
BMI: Body Mass Index
MMSE: Mini Mental Status Exam

Table 3-A1b: Outcome and competing risk status of n=5,584 SOF participants by gait speed category

	Total		Slow gait speed < 1 m/s		Faster gait speed ≥ 1 m/s	
	n=5,584		n=3,747		n=1,837	
Outcomes						
Long-term nursing home residence, n (%)	1,438	(25.75)	1,192	(31.81)	246	(13.39)
Death before residence, n (%)	1,513	(27.10)	1,171	(31.25)	342	(18.62)

Table 3-A2. Baseline characteristics of 5,584 SOF participants by race

	White women		Black women	
	n=5,212		n=372	
Study Characteristics				
Baseline examination				
Visit 1, n (%)	24	(0.46)		
Visit 2, n (%)	52	(1.00)		
Visit 3, n (%)	4,577	(87.82)		
Visit 4, n (%)	228	(4.37)		
Visit 5, n (%)	79	(1.52)		
Visit 6, n (%)	117	(2.24)	364	(97.85)
Visit 7, n (%)	12	(0.23)	2	(0.54)
Visit 8, n (%)	83	(1.59)	5	(1.34)
Visit 9, n (%)	40	(0.77)	1	(0.27)
Exposure				
Gait speed, mean (sd)	0.88	(0.26)	0.82	(0.23)
Outcomes				
Long-term nursing home residence, n (%)	1,404	(26.94)	34	(9.14)
Death before residence, n (%)	1,460	(28.01)	53	(14.25)
Demographics				
Baseline age, years, mean (sd)	76.04	(5.62)	75.85	(5.02)
High school education, n (%)	3,967	(76.11)	245	(65.86)
Married, n (%)	2,238	(42.94)	90	(24.19)
BMI, mean (sd)	26.40	(4.59)	29.83	(4.86)
Short MMSE, mean (sd)	24.59	(1.87)	23.25	(2.44)
Multimorbidity score, n (%)				
No domains	821	(15.75)	52	(13.98)
1 domain	1,998	(38.33)	170	(45.70)
$\geq$ 2 domains	2,393	(45.91)	150	(40.32)

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