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Impact of Competing Risk of Mortality on Association of Cognitive Impairment with Risk of Hip Fracture in Older Women

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Abstract

Previous studies examining the association of cognitive impairment and dementia with fracture outcomes in older adults have usually used standard approaches that did not take into account the competing risk of mortality. However, ignoring mortality may not provide accurate estimates of risk of fracture because dementia in older adults strongly predicts death, making mortality a competing risk. 1491 women (mean age 87.6 years) participating in the prospective Study of Osteoporotic Fractures (SOF) Year 20 exam were cognitively assessed and followed to ascertain vital status (deaths verified by death certificates) and hip fractures (confirmed by radiographic reports). Cognitive status was categorized as normal, MCI, or dementia, based on a standardized evaluation. Absolute probability of hip fracture by category of cognitive function was estimated using traditional Kaplan-Meier method and cumulative incidence function accounting for competing mortality risk. Risk of hip fracture by cognitive function category was determined using conventional Cox proportional hazards regression and sub-distribution hazards models with death as a competing risk. During an average follow-up of 5.6 years, 139 (9.3%) women experienced a hip fracture and 990 (66.4%) died before experiencing this outcome. Among women with dementia, the risk of hip fracture was 11.7% (95% CI, 7.3-17.2) at 5 years and 18.6% (95% CI, 9.1-30.9) at 10 years using traditional survival analysis versus 7.9% (95% CI, 5.1-11.6) at 5 years and 8.8% (95% CI, 5.8-12.8) at 9.8 years using a competing risk approach. Results were similar for women with MCI. Women with MCI and dementia have a higher risk of hip fractures than women with normal cognition. However, not taking into account the competing risk of mortality

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significantly overestimates the risk of hip fracture in women in the ninth and tenth decades of life with cognitive impairment.

Keywords

cognitive impairment; hip fracture; death; competing risk; elderly women

INTRODUCTION

Cognitive impairment and dementia have been associated with an increased risk of hip fracture in observational studies.(1–6) This association may be due in part to an increased risk of falls(7), although other mechanisms may play a role in the association, including effects of medications and limited mobility on bone mineral density (BMD). The observed increased risk of fractures observed in individuals with dementia has led to calls for consideration of initiation of pharmacologic treatment to improve BMD in patients with dementia to lower fracture risk.(8) However, an individual's life expectancy and the time to benefit of any intervention are important factors in the decision-making by clinicians and patients, particularly when contemplating a potential intervention in older adults.

Previous studies examining the association of cognitive impairment and dementia with fracture outcomes in older adults have usually used standard approaches that did not take into account the competing risk of mortality.(1,2,4–6,9,10) However, ignoring mortality may not provide accurate estimates of risk of fracture because dementia in older adults strongly predicts death(11–13), making mortality a competing risk.

To examine the associations of dementia and mild cognitive impairment with risk of hip fracture, we used data from 1491 women participating in the Year 20 (Y20) examination (2006-2008) of the Study of Osteoporotic Fractures who completed cognitive evaluation and were followed for hip fractures or mortality.

MATERIALS AND METHODS

Study population

From 1986-1988, SOF recruited 9,704 ambulatory women without bilateral hip replacement who were ≥65 years old from population-based listings in four areas of the US: Baltimore County, MD; Minneapolis, MN; Portland, OR; and the Monongahela Valley, PA.(14) At the Year 10 visit conducted between 1997 and 1998, an additional 662 African-American women were enrolled in the study.

From 2006-2008, all active surviving women at three clinical centers (Minneapolis, Portland, and Pittsburgh) were invited to participate in the Y20 visit. 2,368 of the original cohort (92.6% of survivors) had at least questionnaire data collected at this visit; of these, 1,495 completed an in-clinic examination which included a battery of neuropsychological tests and underwent adjudication of their cognitive status. Women were eligible for the present study if at Y20 they completed the cognitive assessment and had subsequent follow-up for the hip fracture outcome (N=1491) (Figure 1).

Hip Fracture and Mortality Assessment

Participants or their proxies were contacted every 4 months after Y20 to ascertain vital status and ask about hip fractures. Self-reported hip fracture events were confirmed by radiographic reports.(15) Deaths were verified with death certificates. Participants were followed for a maximum of 9.8 years, with mean (SD) follow-up time to event or censoring of 5.6 (2.9) years.

Measurement of Cognitive Function

Cognitive function was assessed at Y20 using a comprehensive neuropsychological test battery including Trails B(16), the Modified Mini-Mental State Examination (3MS)(17), the California Verbal Learning Test (second edition short form)(18), Digit Span (from the Wechsler Adult Intelligence Scale-Revised)(19), and category and verbal fluency tests.(20)

Cognitive impairment was determined in a 2-step process described elsewhere.(21) Women were screened for cognitive impairment at Year 20 using 1 or more of the following criteria: 1) score <88 on the 3MS; 2) score <4 on the California Verbal Learning Test delayed (10 minute) recall; 3) score ≥3.6 on the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE), a questionnaire designed to assess cognitive decline and dementia in elderly people completed by a relative or friend(22); 4) self-reported previous dementia diagnosis; or 5) nursing home or personal care home residence.

Women who screened negative were considered to have normal cognition. The women who screened positive had their cognitive status adjudicated by a panel of clinical experts, which included a neurologist, 2 neuropsychologists, and a geropsychologist, who were blinded to the actigraphy results. Information used for assessment included the Visit 9 neuropsychological battery scores, IQCODE, prior cognitive test scores, years of education, medical history, medications, Geriatric Depression Scale score (GDS), and functional status. A diagnosis of dementia was made based on the Diagnostic and Statistical Manual of Mental Disorders, 4^{th} edition criteria.(23) MCI was diagnosed using a modified Petersen Criteria.(24) Participants were classified as having cognitive impairment if they had a diagnosis of MCI or dementia.

Other Measures

At the Y20 visit, participants completed a questionnaire and were asked about self-reported health, smoking status, and whether they walked for exercise. A medical history was obtained, including a history of stroke, diabetes, Parkinson's disease, chronic obstructive pulmonary disease, prior fracture, arthritis, coronary heart disease (angina/myocardial infarction), congestive heart failure, and peripheral vascular disease. Using this self-reported medical history, a comorbidity score for each participant was calculated as the sum of these comorbid conditions (range 0-9). Women were classified as married or not married (a category that included widowed, divorced, separated, or never married). Body mass index (BMI) was calculated using measures of body weight and height. Participants were queried about race/ethnicity and education at the time of initial enrollment in SOF. Gait speed was calculated for each participant by measuring the time in seconds to walk six meters at a usual pace expressed as m/s.

Living situation was categorized as living independently if participants reported that they lived in a private home, retirement home or senior complex; they were categorized as not living independently if they lived in a nursing home or assisted living.

Statistical analysis

Characteristics of the 1491 participants in our analytic cohort were summarized using means and standard deviations for continuous data and counts and percentages for categorical data. We compared characteristics in the three cognitive status subgroups using analysis of variance for normally distributed continuous variables; chi-square or Fisher's exact test for categorical data; Kruskall-Wallis for skewed variables.

To estimate the absolute probability of hip fracture during follow-up by cognitive function category, we used two approaches: 1) calculating 1-KM, where KM is the traditional Kaplan-Meier (KM) survival function that that treats mortality as a censored observation; and 2) estimating the cumulative incidence function that considers mortality as a competing risk.(25) Kaplan-Meier estimates the cumulative incidence that would be observed if the competing risk could be removed, an approach appropriate for censoring by loss to follow-up, but less so for censoring by death. In contrast, the cumulative incidence function estimates cumulative incidence accounting for the fact that participants who experience the competing event first (death in this instance) can never go on to experience the event of interest (hip fracture in this instance).

To determine adjusted associations of cognitive function category with risk of hip fracture after the Y20 examination, we used conventional Cox proportional hazards regression models that treat mortality as uninformative censoring and sub-distribution hazards models proposed by Fine and Gray that consider death as a competing risk.(26) In Fine-Gray sub-distribution models, women who died prior to experiencing a hip fracture are not censored; rather those who die before hip fracture are 'immortalized" – that is, they are retained in the risk sets for all subsequent hip fracture events. The motivation behind the modification of the risk sets is to estimate the effect of covariates on cumulative risk as opposed to instantaneous risk. It is often the case that risk factors are similar for both the primary event and the competing event, in which case using the Fine-Gray model could result in the attenuation and perhaps even reversal of estimates for covariates from the standard Cox model. Using both approaches, associations were initially adjusted for age as a continuous variable, race, and site and then further adjusted for characteristics associated with cognitive function category (continuous variables education and gait speed, and categorical variables self-reported health and living independently). For standard Cox models, proportional hazards (PH) assumption was assessed using Schoenfeld's residuals and the Kolmogorov-type Supremum Test. For Fine-Gray sub-distribution models, proportional hazards (PH) assumption was assessed using Schoenfeld's residuals. Age was determined to be the only variable that violated the PH assumption in the models for both standard Cox and Fine-Gray approaches. Thus an interaction between age and log of follow-up time was included in the final base and multivariable models to account for the violation of PH assumption by age.

We used a complete case analysis for the multivariate models.

Statistical analysis was performed using SAS (version 9.4; SAS Institute, Cary, NC, USA).

RESULTS

Among the 1491 women in our analytical cohort, the mean (SD) age of the participants at the Y20 examination was 87.6 (3.4) years. 351 (23.5%) were categorized as having mild cognitive impairment, 268 (18.0%) were categorized as having dementia, and 872 (58.5%) were normal cognition. Characteristics of the cohort overall and by category of cognitive function category are shown in Table 1. Women not included in the analysis who had at least minimal information collected at Year 20 (N=873) were generally older, in poorer health and had slower walk speed and higher multimorbidity score, compared to those in our analytic cohort (Supplementary Table 4).

There were 139 women (9.3%) who had hip fracture and 990 (66.4%) who died without experiencing incident hip fracture in the follow-up period (up to 9.8 years) with mean (SD) time to event or censoring of 5.6 (2.9) years. The crude incidence rate of hip fracture was 16.7 (95% CI 13.9-19.5) per 1,000 person years and crude mortality rate was 113.5 (95% CI 106.4-120.6) per 1,000 person-years (Table 1). Women with dementia had the highest rate of hip fracture and mortality (20.8 [95% CI 12.3-29.2] and 199.2 [173.6-224.7] per 1,000 person-years, respectively). Compared to women with dementia, the rate of hip fracture was similar for women with MCI (20.3 [95% CI 13.7-26.9] per 1,000 person-years), but lower for women with normal cognition (14.7 [95% CI 11.5-18.0] per 1,000 person-years). Women with MCI had a lower mortality rate than women with dementia (130.9 [95% CI 114.6-147.2] per 1,000 person-years) and women with normal cognition had even lower mortality rate (89.8 [95% CI 82.0-97.6] per 1,000 person years).

Using traditional survival analysis (Figure 2A) or the competing risk approach (Figure 2B), the absolute probability of hip fracture was higher among women with dementia and those with MCI, compared to women with normal cognitive function. Among women with MCI and dementia, the competing risk approach compared with traditional survival analysis resulted in a lower estimate of absolute hip fracture probability and the difference in estimates was greater as duration of follow-up increased. For example, among women with dementia, the absolute probability of hip fracture was 11.7% (95% CI, 7.3-17.2) at 5 years and 18.6% (95% CI, 9.1-30.9) at 9.8 years using traditional KM survival analysis versus 7.9% (95% CI, 5.1-11.6) at 5 years and 8.8% (95% CI, 5.8-12.8) at 9.8 years using a competing risk approach (Table 2). Similarly, the absolute probability of hip fracture among women with MCI was 11.3% (95% CI, 7.8-15.5) at 5 years and 14.8% (95% CI, 10.3-19.9) using traditional KM approach versus 8.9% (95% CI, 5.9-11.9) at 5 years and 10.5% (95% CI, 7.5-13.9) at 9.8 years using a competing risk approach.

Women with dementia compared to those with normal cognition appeared to have a 1.45-fold higher risk of hip fracture (hazard ratio [HR] 1.45; 95% CI, 0.89, 2.34) as calculated by Cox regression (Table 3), adjusting for age, race, site, and interaction between age and log follow-up time, albeit not at the level of significance. Women with MCI had a 1.59-fold higher risk of hip fracture (HR 1.59; 95% CI, 1.07-2.38) compared to women with normal cognition. However, in sub-distribution models, this minimally adjusted risk of hip fracture

among women with dementia was substantially attenuated (HR 1.00; 95% CI, 0.63-1.60); it was also attenuated for women with MCI (HR 1.31; 95% CI, 0.88-1.96).

Further adjustment for potential confounders (education, self-reported health status, living independently) or consideration of potential mediators (gait speed) and interaction between age and log follow-up time, modestly reduced the association between dementia and MCI and risk of hip fracture in Cox regression models. The impact of consideration of these additional covariates was similar in sub-distribution models (Table 3).

In secondary analyses, we combined participants with MCI and dementia into one category of cognitive impairment. Those results appear in Supplemental Tables 1–3 and Supplemental Figures 1a and 1b. Findings were similar in this analysis, with an association between cognitive impairment and risk of hip fracture observed, although attenuated when accounting for the competing risk of mortality.

DISCUSSION

In this prospective study of primarily community-dwelling older women late in life, women with MCI and dementia, who comprised 41.5% of the overall cohort, were at higher risk of hip fracture compared to women with normal cognition. However, there was also a graded association between cognitive status and mortality with mortality among those with dementia nearly 10-fold the rate of hip fracture. Thus, not taking into account the competing risk of mortality among women with cognitive impairment overestimated their absolute fracture probability and adjusted fracture risk. Differences in the probability calculated by the two approaches increased with increasing duration of follow-up time.

Clinicians caring for older adults often face the conundrum of weighing the risks and benefits of interventions to prevent adverse outcomes or treat specific medical conditions against the competing risk of mortality.(27) However, many studies examining the association of potential risk factors with incidence of disease-related clinical outcomes in the geriatric population often do not take into account the competing risk of death, which can lead to overestimates of incidence of these disease events in this population, particularly if the competing risk of mortality is high. It has previously been suggested that older women with dementia may be at high risk of hip fracture and should be targeted for drug treatment to lower fracture risk.(8) However, our results highlight the importance of consideration of the competing risk of mortality when evaluating potential risk factors such as cognitive impairment as predictors of hip fracture in older adults.

Previous work has described an association of cognitive impairment and dementia with risk of hip fracture. This body of research has included cross-sectional analyses (5,6,10,28) which are limited by survival bias. Most prospective studies(1,2,4,9) which have evaluated the association of cognition with risk of incident hip fracture have not used rigorous adjudication of cognitive status as in the present study or have not assessed risk after accounting for competing mortality.

For clinicians caring for the oldest old, decisions about treatment options to prevent adverse outcomes, such as hip fracture, are complex. Hip fractures are associated with significant

morbidity and mortality and result in institutionalization for a significant proportion of those who survive.(29,30) However, the addition of an intervention in the oldest old, particularly those with dementia, is often associated with burden and risk of potential harm – oral bisphosphonates require regular dosing with significant restrictions on the timing of administration and measures to prevent gastrointestinal side effects. Intravenous zoledronic acid, administered once annually, or denosumab administered by subcutaneous injection every 6 months may be more convenient options for this population, but they too come with risk of adverse effects as well as logistical issues in the clinical setting, particularly for patients with limited mobility and supportive services.

Limited data is available in the very elderly (e.g. aged 80 years and older) regarding pharmacologic treatment to prevent hip fractures and those that have included women over 80 years of age (26–28) have excluded women with significant cognitive impairment. The HIP study (Hip Intervention Program Study)(31) enrolled women aged 80 years and older who were selected primarily based on non-skeletal risk factors (e.g. difficulty standing from a sitting position, a poor tandem gait, or a fall-related injury during the previous year), rather than based on a BMD T-score consistent with osteoporosis. In this trial, which also excluded women with cognitive impairment, there was no significant reduction in hip fractures (n=3886, relative risk 0.8, CI 0.6-1.20, p=0.35) amongst women aged ≥80 years randomized to risedronate vs. placebo.

The Zoledronic Acid for Osteoporotic Fracture Prevention (ZEST-II) trial is evaluating the safety and efficacy of intravenous zoledronic acid infusion for the prevention of fractures in women age 65 years and older residing in long-term care facilities; participants will include women with cognitive impairment and will include many women aged 80 and older.(32) The results of that trial will be informative, although the applicability to community dwelling women may be limited. Of note, the ZEST-II trial is testing whether drug treatment in institutionalized older women is efficacious in fracture prevention. Reducing hip fractures in older adults with underlying cognitive impairment will likely require interventions specifically targeted at reduction in fall risk, as an increased risk of falls has been observed in older adults with cognitive impairment(3) and is a significant contributor to hip fracture risk.

Although we report here the 10-year risk of fracture by category of cognitive impairment, given the age and risk of mortality in the cohort a shorter time horizon is likely more clinically relevant. At 5 years of follow-up, accounting for the competing risk of mortality also attenuated the association of cognitive impairment and hip fracture risk; at 3 years of follow-up, however, the effect of the competing risk of mortality was minimal. These results highlight the need for providers and patients to consider the time to benefit of any treatment, as well as an individual’s life expectancy in making clinical decisions about treatment. Thus, fracture risk assessment tools that provide individual patient-based estimates of fracture probability might be improved by incorporation of patient-based estimates of competing mortality risk because available tools either do not take into account competing risk of death or only account for country-specific death rates.(33–35)

Of note, estimates of the risk of hip fracture were similar for women with MCI and for women with dementia. This may be related to the small number of hip fractures in each category of cognitive impairment. Alternatively women with MCI, perhaps healthier and with fewer mobility limitations than women with dementia, may be more active than women with dementia and thus at increased risk of falls. Additional investigations into the comparative associations of MCI and dementia with incident hip fracture are warranted.

The study has several strengths, including a rigorous adjudication of cognitive status, as well as rigorous ascertainment of incident hip fractures and mortality. However, the study is limited by the small number of hip fractures in each category of cognitive function, as well as the homogenous cohort, which predominantly consists of Caucasian women, though this demographic accounts for approximately two-thirds of the hip fractures in the US.(36) In addition, our results cannot be generalized to women in long-term care facilities/nursing homes, as most of the women in the cohort were living in the community and likelier healthier than women with cognitive impairment who are institutionalized.

In summary, women with mild cognitive impairment and dementia who survive have a higher risk of hip fractures than women with normal cognition. However, not taking into account the competing risk of mortality significantly overestimates the risk of hip fracture in women in the ninth and tenth decades of life with cognitive impairment. Life expectancy, time to benefit from treatment, harms and burden of treatment, and magnitude of benefit of treatment are all important considerations when making decisions about approaches to hip fracture risk reduction.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Authors' Roles: Study design: SJD, KEE; Study conduct: KEE; Data collection: KEE; Data analysis: TNV and LL; Data interpretation: SJD, TNV, LL, JTS, KY, KEE; Drafting manuscript: SJD; Revising manuscript content: SJD; Approving final version of manuscript: TNV, LL, JTS, KY, KEE. TNV takes responsibility for the integrity of the data analysis.

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REFERENCES

(1). Buchner DM, Larson EB. Falls and fractures in patients with Alzheimer-type dementia. JAMA. 1987;257(11):1492–1495. [PubMed: 3820464]

(2). Guo Z, Wills P, Viitanen M, Fastbom J, Winblad B. Cognitive impairment, drug use, and the risk of hip fracture in persons over 75 years old: a community-based prospective study. Am J Epidemiol 1998;148(9):887–892. [PubMed: 9801019]

(3). Melton LJ, III, Beard CM, Kokmen E, Atkinson EJ, O'Fallon WM. Fracture risk in patients with Alzheimer's disease. J Am Geriatr Soc 1994;42(6):614–619. [PubMed: 8201146]

(4). Taylor BC, Schreiner PJ, Stone KL et al. Long-term prediction of incident hip fracture risk in elderly white women: study of osteoporotic fractures. J Am Geriatr Soc 2004;52(9):1479–1486. doi: 10.1111/j.1532-5415.2004.52410.x [PubMed: 15341549]

(5). Weller I I The relation between hip fracture and alzheimer's disease in the canadian national population health survey health institutions data, 1994-1995. A cross-sectional study. Ann Epidemiol 2000;10(7):461. doi: 10.1016/S1047-2797(00)00085-5

(6). Weller I, Schatzker J. Hip fractures and Alzheimer's disease in elderly institutionalized Canadians. Ann Epidemiol 2004;14(5):319–324. doi: 10.1016/j.annepidem.2003.08.005 [PubMed: 15177270]

(7). Muir SW, Gopaul K, Montero Odasso MM. The role of cognitive impairment in fall risk among older adults: a systematic review and meta-analysis. Age Ageing. 2012;41(3):299–308. doi: 10.1093/ageing/afs012 [PubMed: 22374645]

(8). Cummings SR, Eastell R. Risk and Prevention of Fracture in Patients With Major Medical Illnesses: A Mini-Review. J Bone Miner Res 2016;31(12):2069–2072. doi: 10.1002/jbmr.3030 [PubMed: 27813155]

(9). Baker NL, Cook MN, Arrighi HM, Bullock R. Hip fracture risk and subsequent mortality among Alzheimer's disease patients in the United Kingdom, 1988-2007. Age Ageing. 2011;40(1):49–54. doi: 10.1093/ageing/afq146 [PubMed: 21087990]

(10). Johansson C, Skoog I. A population-based study on the association between dementia and hip fractures in 85-year olds. Aging (Milano). 1996;8(3):189–196. [PubMed: 8862194]

(11). Dewey ME, Saz P. Dementia, cognitive impairment and mortality in persons aged 65 and over living in the community: a systematic review of the literature. Int J Geriatr Psychiatry. 2001;16(8):751–761. doi: 10.1002/gps.397 [PubMed: 11536341]

(12). Brodaty H, Seeher K, Gibson L. Dementia time to death: a systematic literature review on survival time and years of life lost in people with dementia. Int Psychogeriatr. 2012;24(7):1034–1045. doi: 10.1017/S1041610211002924 [PubMed: 22325331]

(13). Aevarsson O, Svanborg A, Skoog I. Seven-year survival rate after age 85 years: relation to Alzheimer disease and vascular dementia. Arch Neurol 1998;55(9):1226–1232. [PubMed: 9740117]

(14). Cummings SR, Black DM, Nevitt MC et al. Appendicular bone density and age predict hip fracture in women. The Study of Osteoporotic Fractures Research Group. JAMA. 1990;263(5):665–668. [PubMed: 2404146]

(15). Lewis CE, Ewing SK, Taylor BC et al. Predictors of non-spine fracture in elderly men: the MrOS study. J Bone Miner Res 2007;22(2):211–219. doi: 10.1359/jbmr.061017 [PubMed: 17059373]

(16). Reitan RM, Wolfson D. The Halstead-Reitan Neuropsychological Battery: Theory and Clinical Interpretation. 1st ed. Tuscon, AZ: Neuropsychology Press; 1985.

(17). Teng EL, Chui HC. The Modified Mini-Mental State (3MS) examination. J Clin Psychiatry. 1987;48(8):314–318. [PubMed: 3611032]

(18). Delis DC, Kramer JH, Kaplan E, Ober BA. California Verbal Learning Test - Second Edition (CVLT-II). 2nd ed. San Antonio, TX: Psychological Corporation; 2000.

(19). Wechsler D Wechsler Adult Intelligence Scale - Revised. New York, NY: Oxford University Press; 1991.

(20). Spreen O, Strauss E. A Compendium of Neuropsychological Test: Administration, Norms, and Commentary. New York, NY: Oxford University Press; 1991.

(21). Yaffe K, Middleton LE, Lui LY et al. Mild cognitive impairment, dementia, and their subtypes in oldest old women. Arch Neurol 2011;68(5):631–636. doi: 10.1001/archneurol.2011.82 [PubMed: 21555638]

(22). Jorm AF, Jacomb PA. The Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE): socio-demographic correlates, reliability, validity and some norms. Psychol Med 1989;19(4):1015–1022. [PubMed: 2594878]

(23). American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders. 4th ed. Washington, D.C.: American Psychiatric Association; 2000.

(24). Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: clinical characterization and outcome. Arch Neurol 1999;56(3):303–308. doi: 10.1001/archneur.56.3.303 [PubMed: 10190820]

(25). Coviello V, Boggess M. Cumulative incidence estimation in the presence of competing risks. Stata J 2004;4(2):103–112.

(26). Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc 1999;94(446):496–509. doi: 10.1080/01621459.1999.10474144

(27). Berry SD, Ngo L, Samelson EJ, Kiel DP. Competing risk of death: an important consideration in studies of older adults. J Am Geriatr Soc 2010;58(4):783–787. doi: J10.1111/j.1532-5415.2010.02767.x [PubMed: 20345862]

(28). Seitz DP, Adunuri N, Gill SS, Rochon PA. Prevalence of dementia and cognitive impairment among older adults with hip fractures. J Am Med Dir Assoc 2011;12(8):556–564. doi: 10.1016/j.jamda.2010.12.001 [PubMed: 21450227]

(29). Cummings SR, Kelsey JL, Nevitt MC, O'Dowd KJ. Epidemiology of osteoporosis and osteoporotic fractures. Epidemiol Rev 1985;7:178–208. [PubMed: 3902494]

(30). Haentjens P, Magaziner J, Colon-Emeric CS et al. Meta-analysis: excess mortality after hip fracture among older women and men. Ann Intern Med 2010;152(6):380–390. doi: 110.7326/0003-4819-152-6-201003160-00008 [PubMed: 20231569]

(31). McClung MR, Geusens P, Miller PD et al. Effect of risedronate on the risk of hip fracture in elderly women. Hip Intervention Program Study Group. N Engl J Med 2001;344(5):333–340. doi: 10.1056/NEJM200102013440503 [PubMed: 11172164]

(32). Greenspan SL Zoledronic Acid for Osteoporotic Fracture Prevention (ZEST II). www.clinicaltrials.gov. Updated 5-25-2017 Accessed 12-1-2017.

(33). Centre for Metabolic Bone Diseases, University of Sheffield UK. FRAX WHO Fracture Risk Assessment Tool. www.shef.ac.uk/FRAX . Updated 2011 Accessed 1-2-2018.

(34). ClinRisk Ltd. QFracture-2016 risk calculator. www.qfracture.org. Updated 2016 Accessed 1-2-2018.

(35). Garvan Institute of Medical Research. Bone fracture risk calculator. www.garvan.org.au/bone-fracture-risk. Updated 2017 Accessed 1-2-2018.

(36). Burge R, Dawson-Hughes B, Solomon DH, Wong JB, King A, Tosteson A. Incidence and economic burden of osteoporosis-related fractures in the United States, 2005-2025. J Bone Miner Res 2007;22(3):465–475. doi: 10.1359/jbmr.061113 [PubMed: 17144789]

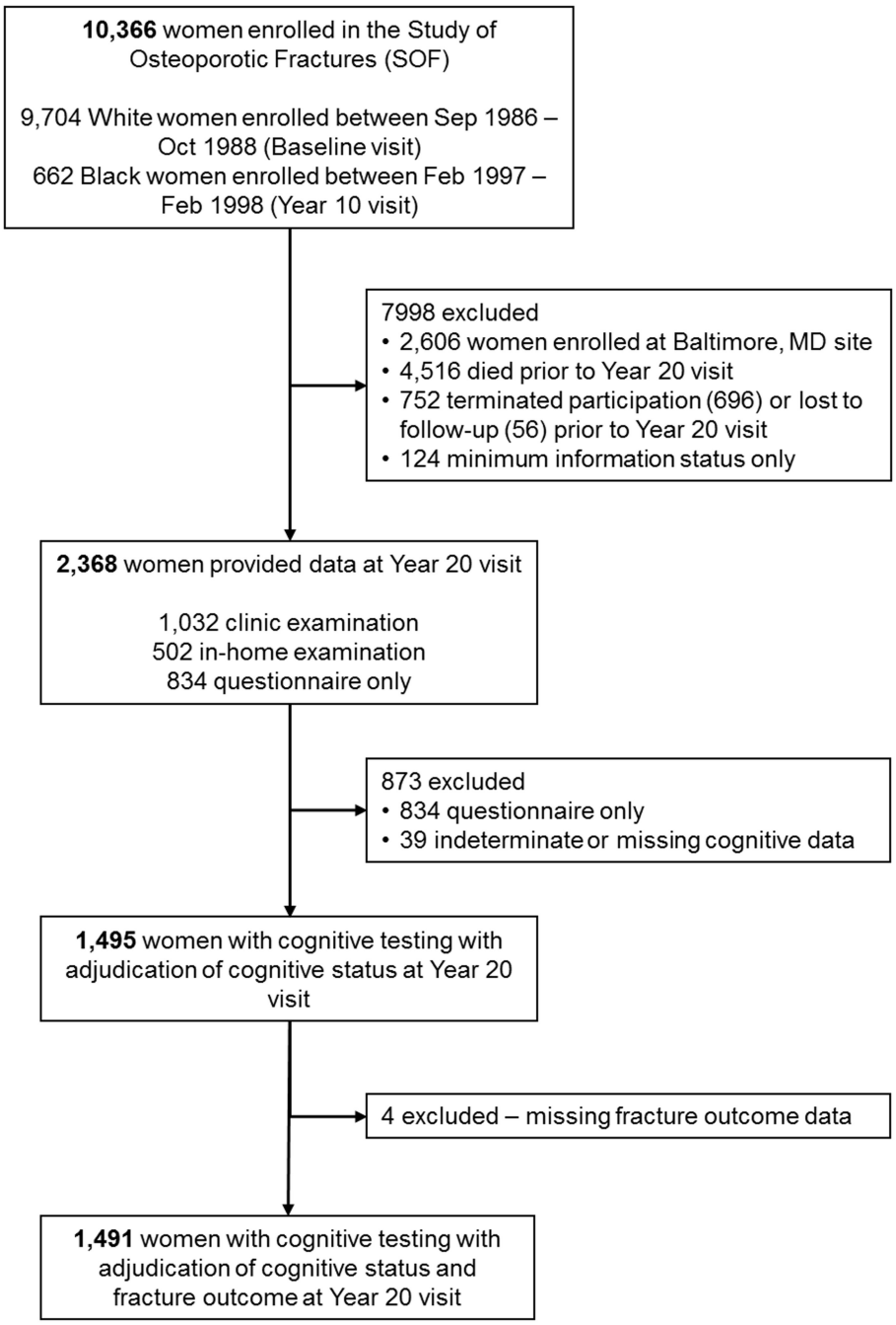
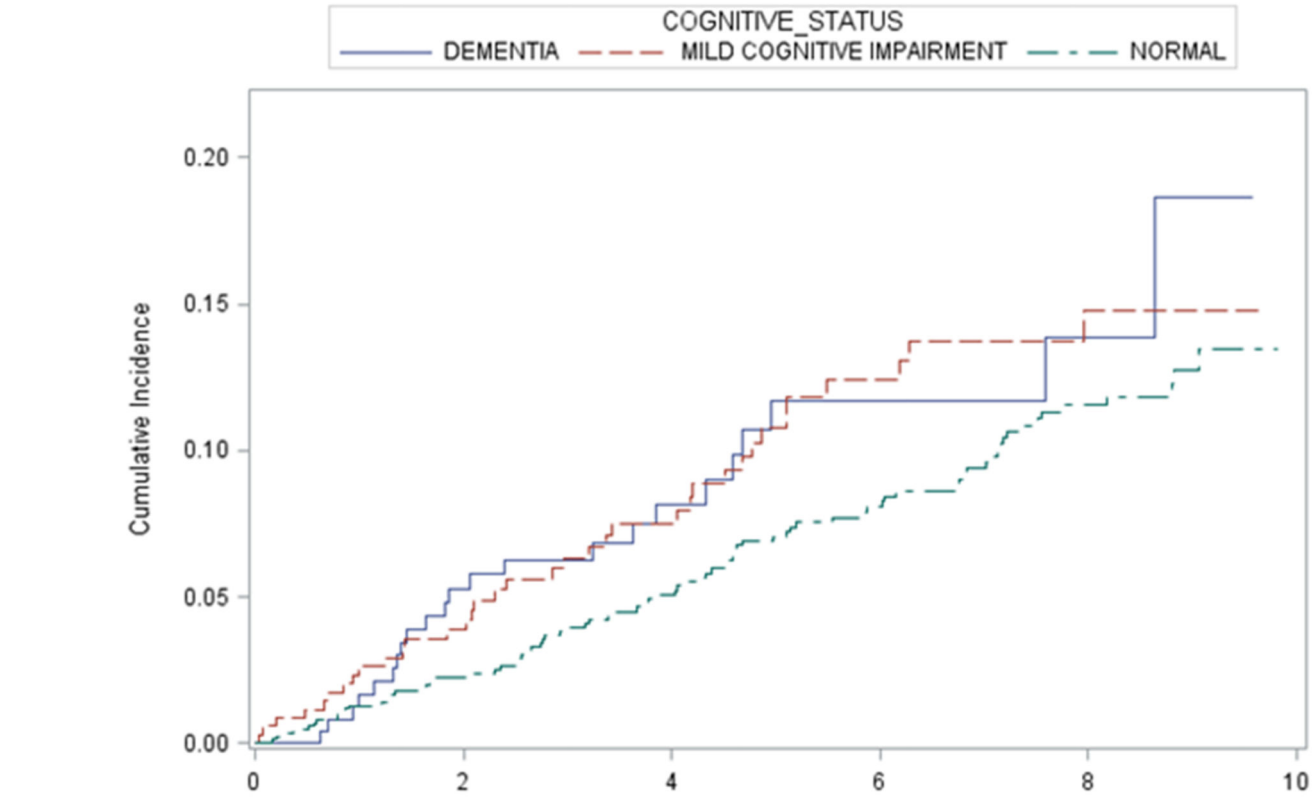
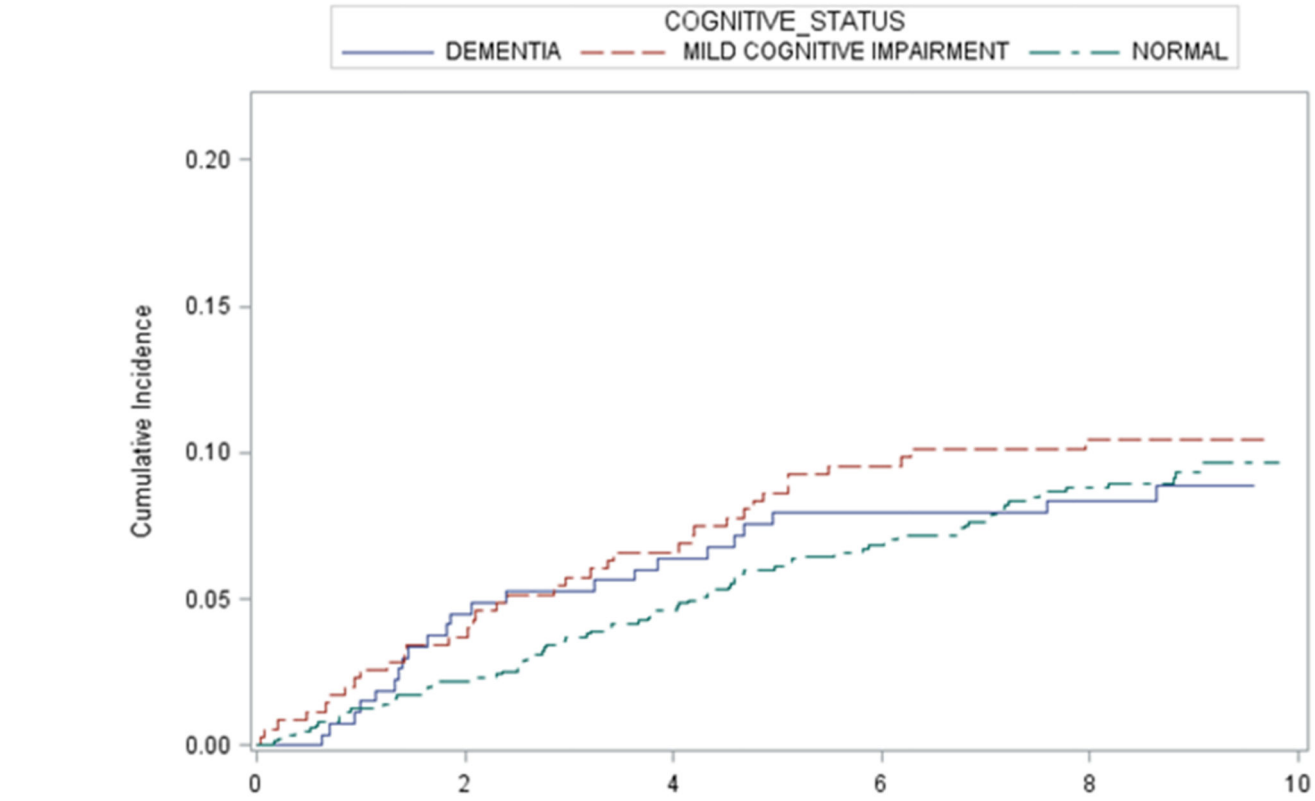


Figure 1:
Participant Flow



Number at risk	Year 0	Year 2	Year 4	Year 6	Year 8	Year 9
Normal	872	719	611	492	352	131
MCI	351	263	201	137	79	24
Dementia	268	185	119	66	28	13

Figure 2A:
Cumulative Absolute Probability of Hip Fracture by Cognitive Status Using Kaplan-Meier Method



Number at risk	Year 0	Year 2	Year 4	Year 6	Year 8	Year 9
Normal	872	850	825	801	761	583
MCI	351	335	322	307	295	251
Dementia	268	253	247	242	238	228

Figure 2B:
Cumulative Absolute Probability of hip fracture by cognitive status using Cumulative Incidence Function (Competing Risk Approach)

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Table 1.

Characteristics of 1491 Women by Category of Adjudicated Cognitive Status

Characteristic	Overall (N=1491)	Normal cognition (N=872)	MCI (N=351)	Dementia (N=268)	p-value[a]
Age, years, mean (SD)	87.6 (3.4)	87.2 (3.1)	87.8 (3.4)	88.8 (3.8)	<0.001
Caucasian race, n (%)	1318 (88.4)	786 (90.1)	300 (85.5)	232 (86.6)	0.04
Site, n (%)					0.19
Minneapolis	570 (38.2)	321 (36.8)	148 (42.2)	101 (37.7)	
Pittsburgh	490 (32.9)	280 (32.1)	116 (33.0)	94 (35.1)	
Portland	431 (28.9)	271 (31.1)	87 (24.8)	73 (27.2)	
Self-reported health, fair/poor/very poor, n (%)[b]	340 (22.9)	185 (21.2)	78 (22.4)	77 (29.1)	0.03
Smoking status, n (%)[c]					0.25
No	1456 (98.0)	857 (98.3)	338 (96.8)	261 (98.5)	
Yes	30 (2.0)	15 (1.7)	11 (3.2)	4 (1.5)	
Education, years, mean (SD)[d]	12.8 (2.6)	13.1 (2.5)	12.3 (2.6)	12.5 (2.6)	<0.001
Living independently, n (%)[c]	1373 (92.4)	836 (95.9)	324 (92.8)	213 (80.4)	<0.001
Married, n (%)	262 (17.6)	168 (19.3)	52 (14.8)	42 (15.7)	0.12
Taking walks for exercise, n (%)[e]	606 (41.7)	375 (43.9)	149 (43.8)	82 (31.7)	0.001
Gait speed, m/s, mean (SD)[f]	0.72 (0.24)	0.77 (0.23)	0.68 (0.23)	0.58 (0.22)	<0.001
Body mass index, kg/m^2, mean (SD)[g]	26.5 (4.9)	26.6 (4.8)	26.3 (4.6)	26.1 (5.3)	0.25
Multimorbidity score (0–9), mean (SD)[c,h]	1.26 (1.25)	1.25 (1.24)	1.25 (1.20)	1.32 (1.34)	0.70
Femoral neck BMD, g/cm^2, mean (SD)[i]	0.639 (0.119)	0.642 (0.116)	0.637 (0.129)	0.624 (0.114)	0.49
Total Hip BMD (g/cm^2), mean (SD)[i]	0.744 (0.129)	0.753 (0.126)	0.725 (0.127)	0.727 (0.150)	0.04
Dead, n (%)	990 (66.4)	507 (58.1)	249 (70.9)	234 (87.3)	<0.001
Hip fracture incidence rate per 1,000 person-years (95% CI)	16.7 (13.9–19.5)	14.7 (11.5–18.0)	20.3 (13.7–26.9)	20.8 (12.3–29.2)	0.78[j]
Mortality incidence rate per 1,000 person-years (95% CI)	113.5 (106.4–120.6)	89.8 (82.0–97.6)	130.9 (114.6–147.2)	199.2 (173.6–224.7)	<0.001[j]

Abbreviations: MCI, mild cognitive impairment; BMD, bone mineral density

[a]ANOVA or non-parametric equivalent i.e. Kruskal–Wallis test for continuous variables, chi-square or Fisher's exact test for categorical variables

[b] N=1485

[c] N=1486

[d] N=1490

[e] N=1453

[f] N=1364

[g] N=1449

[h] including stroke, diabetes, Parkinsonism, chronic obstructive pulmonary disease, congestive heart failure, osteoarthritis, peripheral vascular disease, heart attack, and coronary artery blockage; 9 conditions but the maximum number of conditions was 7

[i] N=664

[j] p-value was obtained by running Poisson model with offset parameter as log (1000 person years)

Table 2.

Absolute Probability of Hip Fracture at 3, 5 Years and at End of Follow-up, with and without Accounting for Competing Risk of Mortality

	Probability of Hip Fracture, % (95% CI)		
	Normal Cognition	**MCI**	**Dementia**
3-year Follow-up			
Traditional survival analysis	4.1 (2.9-5.6)	6.7 (4.3-9.9)	6.8 (4.0-10.7)
Competing risk approach	3.8 (2.7-5.2)	6.0 (3.8-8.9)	5.6 (3.3-8.8)
5-year Follow-up			
Traditional survival analysis	7.2 (5.5-9.2)	11.3 (7.8-15.5)	11.7 (7.3-17.2)
Competing risk approach	6.2 (4.8-7.9)	8.9 (5.9-11.9)	7.9 (5.1-11.6)
End of Follow-up (9.8 years)			
Traditional survival analysis	13.5 (10.5-16.8)	14.8 (10.3-19.9)	18.6 (9.1-30.9)
Competing risk approach	9.7 (7.7-11.8)	10.5 (7.5-13.9)	8.8 (5.8-12.8)

Abbreviations: MCI, mild cognitive impairment

Table 3.

Traditional Cox Proportional Hazards Models and Sub-distribution Models for Association of Cognitive Status with Hip Fracture

		Hazard Ratio (95% CI)		
Hip fracture (n=139)	**N**	**Normal**	**MCI**	**Dementia**
Base model[a]	1491	*n-event=80*	*n-event=36*	*n-event=23*
Cox proportional model		1.00 (referent)	1.59 (1.07-2.38)	1.45 (0.89-2.34)
Sub-distribution model		1.00 (referent)	1.31 (0.88-1.96)	1.00 (0.63-1.60)
Multivariable model[b]	1360	*n-event=78*	*n-event=33*	*n-event=20*
Cox proportional model		1.00 (referent)	1.48 (0.98-2.28)	1.39 (0.82-2.36)
Sub-distribution model		1.00 (referent)	1.29 (0.84-1.98)	1.08 (0.65-1.79)

Abbreviations: MCI, mild cognitive impairment

[a] adjusted for site, age, and race

[b] adjusted for site, age, race, education, gait speed, self-reported health status, living independently and interaction between age and log follow-up time