Memory complaints and risk of cognitive impairment after nearly 2 decades among older women

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ABSTRACT

Objectives: To investigate the association between subjective memory complaints (SMCs) and long-term risk of cognitive impairment in aging because most previous studies have followed individuals for only a few years.

Methods: Participants were 1,107 cognitively normal, community-dwelling older women (aged 65 years and older at baseline) in a prospective study of aging. SMCs were assessed shortly after baseline and repeatedly over time with the yes/no question, "Do you feel you have more problems with memory than most?" Cognitive status 18 years later (normal or impaired with mild cognitive impairment or dementia) was determined by an expert panel. Using logistic regression, we investigated the association between SMCs over time and risk of cognitive impairment, adjusting for demographics, baseline cognition, and characteristics that differed between those with and without SMCs.

Results: At baseline, 8.0% of participants (n = 89) endorsed SMCs. Baseline SMCs were associated with increased risk of cognitive impairment 18 years later (adjusted odds ratio [OR] = 1.7, 95% confidence interval 1.1–2.8). Results were unchanged after excluding participants with depression. The association between SMCs and cognitive impairment was greatest at the last SMC assessment time point (18 years before diagnosis: adjusted OR = 1.7 [1.1–2.9]; 14 years before diagnosis: adjusted OR = 1.6 [0.9–2.7]; 10 years before diagnosis: adjusted OR = 1.9 [1.1–3.1]; 4 years before diagnosis: adjusted OR = 3.0 [1.8–5.0]).

Conclusions: SMCs are associated with cognitive impairment nearly 2 decades later among older women. SMCs may be a very early symptom of an insidious neurodegenerative disease process, such as Alzheimer disease. ***Neurology*® 2015;85:1852–1858**

GLOSSARY

AD = Alzheimer disease; **CI** = confidence interval; ***DSM-IV*** = *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition); **GDS** = Geriatric Depression Scale; **MCI** = mild cognitive impairment; **mMMSE** = modified Mini-Mental State Examination; **OR** = odds ratio; **SMC** = subjective memory complaint; **SOF** = Study of Osteoporotic Fractures.

Alzheimer disease (AD) and other neurodegenerative disorders manifest with an insidious course, making it challenging to detect their subtle beginnings in an individual patient. Indeed, the neuropathologic changes of AD may occur many years before an individual begins to exhibit cognitive impairment.[1] Subjective cognitive complaints among cognitively normal older adults may be an early symptom of AD or other neurodegenerative processes.[2] Some studies of cognitively normal older adults have found that individuals with subjective memory complaints (SMCs) have greater amyloid burden,[3,4] while others have found no such associations[5,6] or have argued that SMCs merely reflect symptoms of depression or anxiety.[5] A recent meta-analysis[7] of longitudinal studies supports an overall association between SMCs and the development of mild cognitive impairment (MCI) and dementia, but also revealed that previous studies have followed individuals for an average of only 4 to 5 years.[7] This is a key limitation in the field given that neurodegenerative processes such as AD can take several years to decades to unfold.[8]

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Additional research is needed to clarify the long-term predictive utility of an older adult's subjective report of memory problems and the extent to which SMCs may reflect an early symptom of a neurodegenerative disorder. Our objective was to examine whether SMCs are associated with long-term risk of cognitive impairment (MCI or dementia) 18 years later among older women. We also explored the association between SMCs assessed across time and risk of cognitive impairment, in order to evaluate whether the sensitivity of SMCs as a potential early indicator of future cognitive impairment may change over time.

METHODS

Population. Participants were community-dwelling older women (aged 65 years and older) in the prospective cohort Study of Osteoporotic Fractures (SOF), recruited by study centers in Baltimore, MD, Minneapolis, MN, Portland, OR, and the Monongahela Valley near Pittsburgh, PA. A total of 9,704 Caucasian women were enrolled between 1986 and 1988, and 662 African American women were enrolled later, between 1997 and 1998. Women with a history of hip fracture or bilateral hip replacement or who were unable to walk without assistance were excluded. Further details regarding SOF recruitment methods and study design have been published previously.[9]

As part of the SOF–Women, Cognitive Impairment Study of Exceptional Aging ancillary study, year-20 (2006–2008) clinical cognitive diagnosis of normal cognition, MCI, or dementia was evaluated by an expert panel among 1,338 women from the Caucasian cohort. For our primary analyses, we included 1,107 women who were cognitively normal at baseline (as defined by a baseline modified Mini-Mental State Examination [mMMSE] score no more than 1.5 SD below the mean compared with age- and education-matched peers in the entire Caucasian cohort), who completed SMC assessment shortly after baseline (year 2), and whose year-20 cognitive diagnosis was determined. Compared with the remaining women in the SOF Caucasian cohort, these 1,107 women were younger and more highly educated, had fewer comorbidities and endorsed fewer depressive symptoms (all $p < 0.001$), and had higher body mass index ($p = 0.03$). Included women were less likely to endorse SMCs at baseline and at all subsequent SMC assessments (all $p < 0.001$).

Standard protocol approvals, registrations, and patient consents. All participants gave written informed consent to participate in SOF. The study was approved by institutional review boards at each study site and at the University of California, San Francisco (coordinating center).

Measures. ***Subjective memory complaints.*** SMCs were assessed shortly after baseline at year 2 (henceforth referred to as baseline SMCs) and again in years 6, 10, and 16 using the following yes/no question from the 15-item Geriatric Depression Scale (GDS)[10]: "Do you feel you have more problems with memory than most?"

Cognition and cognitive diagnosis. Global cognitive functioning was assessed using a 26-item mMMSE[11] at baseline and repeatedly over time. At year 20, a larger cognitive battery was given that included the following: (1) the mMMSE,[9] which is an expanded measure of global cognition; (2) the California Verbal Learning Test–II Short Form,[12] a measure of learning and memory; (3) Digit Span–Forward and Backward,[13] a measure of auditory attention/working memory; (4) Trail Making Test, Part B,[14] a measure of executive functioning; and (5) Verbal Associative Fluency (letter and category),[15] a measure of language. Year-20 clinical cognitive diagnosis of normal cognition, MCI, or dementia was determined using a previously described process.[16] First, the following screening criteria were applied as indicators of possible cognitive impairment: (1) mMMSE score <88[17]; (2) California Verbal Learning Test delayed recall score <4[12]; (3) Informant Questionnaire on Cognitive Decline in the Elderly score ≥ 3.6[18]; (4) self-reported dementia diagnosis; or (5) living in a nursing home. Women who did not meet any of these screening criteria were considered cognitively normal. Data from women who met any of the screening criteria were then further examined by a team of clinicians, who reviewed individuals' cognitive test results from year 20 and all prior cognitive assessment data, functional status, medical history, medications, and depressive symptoms and then diagnosed individuals as having MCI (based on modified Peterson criteria),[19] dementia (based on *DSM-IV* criteria), or as being cognitively normal.

Other variables. Participants completed self-report questionnaires assessing basic demographics and educational history at baseline. Information about comorbidities was collected repeatedly over time, based on participants' self-report of physician diagnoses of hypertension, diabetes, stroke, and myocardial infarction. Body mass index was calculated based on participants' height and weight (kg/m^2). Depressive symptoms were assessed with the 15-item GDS.[10] Because our primary variable of interest (SMCs) was taken from this inventory, we utilized a GDS score out of 14 that excluded the memory item, and we applied a prorated cutoff (6 of 14) to define depression in keeping with traditional cutpoint.[10]

Statistical analysis. We first compared basic demographic and other baseline characteristics between individuals with and without baseline SMCs using t tests, χ^2, or Fisher exact tests as appropriate. We then conducted logistic regression models to investigate whether baseline SMCs predicted clinically significant cognitive impairment (MCI/dementia vs normal cognition) 18 years later. We conducted this analysis using an unadjusted model as well as a model adjusting for demographics (age, education), baseline mMMSE score, and participant characteristics that significantly differed between groups ($p < 0.05$). We also explored whether the association between SMCs and risk of cognitive impairment changed over time. Similar to our primary analyses, we used logistic regression models to investigate the association between SMCs at each time point (years 2, 6, 10, 16) and later diagnosis of cognitive impairment, unadjusted and adjusted for the same factors as above measured at each respective time point. These models were conducted among participants who had complete SMC data across all time points and who were cognitively normal at the examined time point as determined using the same age- and education-based mMMSE cutoffs as defined above (year 2: n = 1,025; year 6: n = 990; year 10: n = 977; year 16: n = 943).

RESULTS

At baseline, 8.0% of participants (n = 89) endorsed SMCs. Demographics and other participant characteristics are compared between those with and without baseline SMCs in table 1. Compared to those without baseline SMCs, women with SMCs had lower education ($p = 0.01$), greater myocardial infarction history ($p = 0.01$), and higher depressive symptoms ($p < 0.001$).

Table 1 Baseline characteristics by presence of SMCs among 1,107 older women

Characteristic	Baseline SMCs (n = 89)	No SMCs at baseline (n = 1,018)	p Value
Age, y	70.5 (2.8)	70.3 (2.9)	0.43
Education			
<High school	25.8	13.8	
High school graduate	38.2	46.5	0.01
Some college/college graduate	36.0	39.8	
Hypertension	31.5	29.2	0.65
Diabetes	3.4	2.3	0.46
Stroke	0	0.8	0.99
Myocardial infarction	7.4	2.5	0.01
Body mass index, kg/m^2	26.1 (4.3)	26.5 (4.2)	0.41
Depressive symptoms (GDS total of 14)[a]	2.0 (2.4)	0.9 (1.4)	<0.001
mMMSE score, total of 26	25.3 (1.0)	25.3 (1.0)	0.89

Abbreviations: GDS = Geriatric Depression Scale; mMMSE = modified Mini-Mental State Examination; SMC = subjective memory complaint.
Data are mean (SD) or %. Characteristics were measured at year 2 (at the same time as baseline SMC assessment), except for education, hypertension, diabetes, and mMMSE, which were measured at year 1.
[a] GDS total score was taken out of 14, excluding the memory item, which was used to assess SMCs.

Women with baseline SMCs were more likely to be diagnosed with cognitive impairment at year 20 compared to women without baseline SMCs (52.8% vs 38.0%; $\chi^2 = 7.5$, $p = 0.01$). As shown in table 2, baseline SMCs were significantly associated with increased risk of cognitive impairment 18 years later even after adjustment for demographics, baseline mMMSE score, history of myocardial infarction, and depressive symptoms (adjusted odds ratio [OR] = 1.7, 95% confidence interval [CI] 1.1–2.8, $p = 0.03$). In a sensitivity analysis, we excluded 26 participants with baseline depression, and the effect of SMCs was unchanged (fully adjusted OR = 1.7, 95% CI 1.01–2.8, $p = 0.046$).

The figure displays the association between SMCs assessed at varying time points before the diagnostic evaluation and risk of cognitive impairment.

Table 2 Association between baseline SMCs and cognitive impairment 18 years later among 1,107 older women

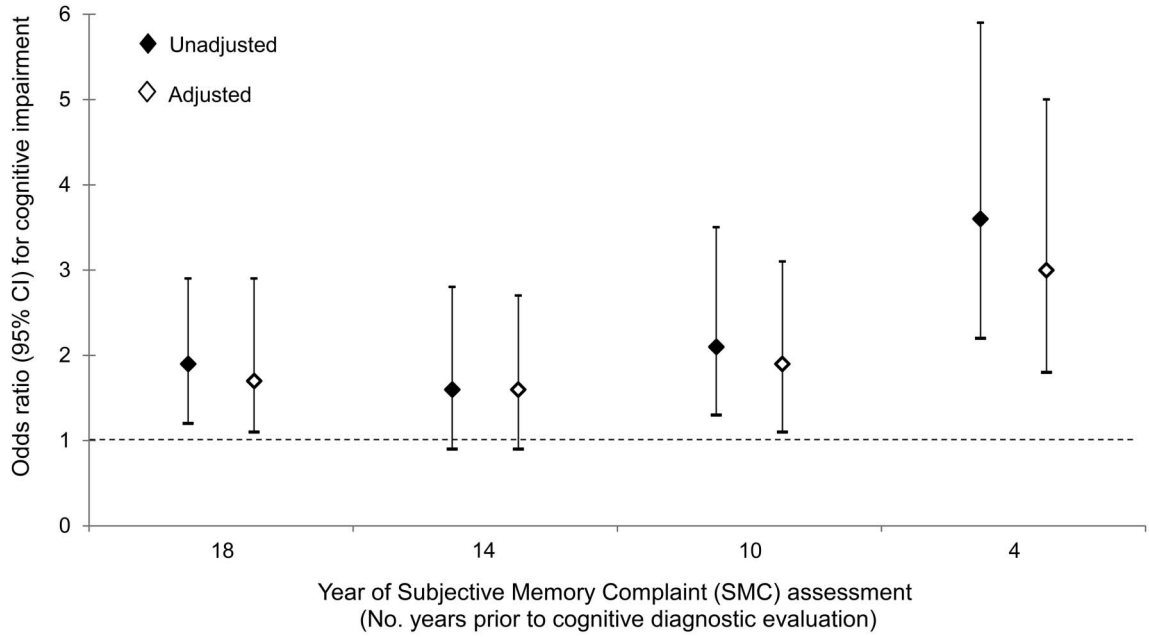
Baseline SMCs	% with cognitive impairment 18 y later	Model 1 (unadjusted) OR (95% CI), p value	Model 2 (adjusted)[a]
No SMCs (n = 1,018)	38.0	Reference	Reference
SMCs (n = 89)	52.8	1.8 (1.2–2.8), p = 0.007	1.7 (1.1–2.8), p = 0.03

Abbreviations: CI = confidence interval; OR = odds ratio; SMC = subjective memory complaint.
[a] Adjusted for demographics (age, education), baseline modified Mini-Mental State Examination score, history of myocardial infarction, and depressive symptoms.

Although SMCs measured 14 years before the diagnostic evaluation were not significantly associated with cognitive impairment (adjusted OR = 1.6, 95% CI 0.9–2.7, $p = 0.12$), the adjusted OR was in the same direction and of similar magnitude as the significant association between SMCs measured 18 years before the diagnostic evaluation (adjusted OR = 1.7, 95% CI 1.1–2.9, $p = 0.03$) and SMCs measured 10 years before the diagnostic evaluation (adjusted OR = 1.9, 95% CI 1.1–3.1, $p = 0.01$). The association between SMCs and cognitive impairment was greatest at the last time point, i.e., SMCs measured 4 years before the diagnostic evaluation (adjusted OR = 3.0, 95% CI 1.8–5.0, $p < 0.001$).

In sensitivity analyses among individuals with complete SMC data who remained cognitively normal at year 16 (n = 943), we explored the independent effects of SMCs at particular time points and the effects of individuals' pattern of SMC endorsement over time. For the former, we included all 4 SMC assessment time points as predictors in a logistic regression model, adjusted for the same covariates as above. There was a significant overall effect of endorsing SMCs at some point on likelihood of cognitive impairment ($p < 0.001$) and significant heterogeneity of effects among the SMC time points ($p = 0.02$). Pairwise comparisons revealed that the last SMC time point (4 years before the cognitive diagnostic evaluation) was most strongly associated with cognitive impairment compared with other SMC time points (the last SMC time point was significantly different from every other time point [all $p < 0.05$]; there were no other significant pairwise differences [all $p > 0.05$]). To explore individuals' pattern of SMC endorsement over time, we first compared risk of cognitive impairment between individuals who endorsed SMCs at 0, 1, vs ≥2 out of the 4 SMC assessment visits. Compared with those who never endorsed SMCs, individuals who endorsed SMCs at one or more visits were more likely to be diagnosed with cognitive impairment (SMCs at only 1 visit [10.7% of participants; n = 101]: adjusted OR = 2.1, 95% CI 1.3–3.2, $p = 0.001$; SMCs at ≥2 visits [7.3% of participants; n = 69]: adjusted OR = 2.0, 95% CI 1.2–3.4, $p = 0.01$). We then classified individuals as endorsing patterns of (1) persistent SMCs—those who endorsed SMCs at baseline and ≥1 additional visit (n = 47), (2) incident SMCs—those who denied SMCs at baseline but endorsed SMCs at ≥1 later visit (n = 91), (3) transient SMCs—those who endorsed SMCs at baseline but denied SMCs at all other visits (n = 32), vs (4) those who never endorsed SMCs (n = 773). Compared with individuals who never endorsed SMCs, individuals with incident SMCs (adjusted OR = 2.4, 95%

Figure SMCs at varying time points before the diagnostic evaluation and risk of cognitive impairment



Additional details by timepoint of SMC assessment:

	18 years before	14 years before	10 years before	4 years before
N	1025	990	977	943
% of participants with SMC	8.2%	5.6%	7.3%	8.3%
% with cognitive impairment at diagnostic evaluation	No SMC: 37.2% SMC: 52.4%	No SMC: 37.7% SMC: 49.1%	No SMC: 36.2% SMC: 54.9%	No SMC: 34.1% SMC: 65.4%

Results of logistic regression analyses examining the association between SMCs assessed at varying time points before the diagnostic evaluation and risk of cognitive impairment. Adjusted models include adjustment for demographics (age, education) as well as mMMSE score, history of myocardial infarction, and depressive symptoms as measured at each SMC assessment time point. At each time point, individuals with an impaired mMMSE score at that time point were excluded (using −1.5 SD age- and education-based cutoffs). CI = confidence interval; mMMSE = modified Mini-Mental State Examination; SMC = subjective memory complaint.

CI 1.5–3.9, $p < 0.001$) and persistent SMCs (adjusted OR = 1.9, 95% CI 1.01–3.5, $p = 0.046$) were more likely to develop cognitive impairment. The effect of transient SMCs was not statistically significant (adjusted OR = 1.4, 95% CI 0.7–3.0, $p = 0.36$).

DISCUSSION We investigated the long-term association between SMCs and cognitive outcomes among older women and found that SMCs were significantly associated with cognitive impairment nearly 2 decades later. We also examined the association between SMCs assessed repeatedly over time and subsequent diagnosis of cognitive impairment and found that the strongest association was present when SMCs were assessed just a few years in advance of participants' clinical cognitive diagnostic evaluation. While women with SMCs 18 years before the diagnostic evaluation had 1.7 times greater odds of receiving an impaired diagnosis, women with SMCs 4 years before the diagnostic evaluation had 3 times greater odds of receiving an impaired diagnosis. As further evidence of the significance of SMCs, we found that even women who endorsed SMCs at only one point in time were at increased risk of cognitive impairment and that patterns of persistent SMCs and incident SMCs over time were both significantly associated with risk of cognitive impairment. Our findings provide further evidence that SMCs in aging warrant close attention as a possible early warning sign of future cognitive problems, even several years in advance. Indeed, a recent study quantified that older adults with SMCs who went on to develop MCI progressed to this diagnosis an average of 9.2 years after they first endorsed SMCs,[20] documenting a prolonged prodromal period between SMCs and the development of cognitive impairment.

Our results add further support to the possibility that SMCs may be an early symptom of an underlying neurodegenerative process, such as AD. That the association between SMCs and risk of cognitive impairment was present very early (i.e., for SMCs endorsed nearly 20 years before our cognitive diagnostic evaluation) and was strongest for SMCs

closest in time to the diagnostic evaluation, this timing pattern suggests that SMCs may signal an insidious disease process as it first emerges and continues to unfold. This would be consistent with the long, prodromal period of AD, during which amyloid deposition, thought to be the beginnings of the AD neuropathology cascade, is present many years before the clinical manifestation of objective cognitive impairment.[21] Moreover, neuroimaging studies corroborate this possibility in finding that older adults with SMCs have greater amyloid burden[3,4] and patterns of atrophy similar to older adults with amnestic MCI and AD.[22,23] Nevertheless, SMCs may not be specific to AD but could also precede objective cognitive impairment in the context of the gradual accumulation of other neuropathology in aging, such as cerebrovascular disease.[24,25] Despite the above possibilities and our findings, it should be noted that the associations we observed (particularly for early years of SMC assessment) are somewhat modest. There may be other reasons for an older adult to endorse SMCs that do not necessarily lead to the development of MCI or dementia.

Strengths of the present study include our ability to investigate the predictive utility of SMCs over an extended follow-up period of 18 years and to examine SMCs assessed repeatedly over time. In addition, our study benefits from the completion of a comprehensive clinical cognitive diagnostic evaluation to determine participants' cognitive status (normal, MCI, dementia). Nevertheless, there are some limitations in the assessment of cognitive status in our study. Because the clinical cognitive diagnostic evaluation was only conducted at the final time point, we cannot be certain exactly when individuals first met diagnostic criteria for MCI/dementia. Our utilization of global cognitive screen (mMMSE) scores to exclude individuals with cognitive impairment at baseline and at subsequent SMC assessment time points reduces the likelihood that significant cognitive impairment was present at those time points. However, it is possible that more subtle cognitive deficits were not detected by these screens. An additional limitation is that we cannot be certain of the extent to which survival bias may have influenced our results. Women included in the present study were generally healthier than those who were not, were less likely to endorse SMCs, and were required to have completed a 20th year of study participation. While some survival bias in our study is therefore likely, it is perhaps even more compelling that we found long-term associations between SMCs and cognitive impairment among this relatively healthier cohort, as survival bias would most likely bias our findings toward an underestimate of risk. Particularly as included women were less likely to have SMCs than those not included, some women with SMCs may have actually been lost to follow-up before year 20 related to the development of cognitive impairment. Further limitations include that our findings cannot be generalized to men or to other racial/ethnic groups.

It is important to consider that we investigated SMCs among community-dwelling older women participating in a population-based study. SMCs endorsed by women in the general population may reflect a different phenomenon than what occurs when older adults are concerned enough about their cognition to present to a clinic for SMCs. Moreover, because we assessed SMCs using one yes/no question, we likely did not capture many complexities inherent in asking an older adult to evaluate his or her own cognitive functioning. As highlighted by the 2014 Subjective Cognitive Decline Initiative Workgroup,[2] valuable data may be gleaned from a more comprehensive assessment that asks individuals to appraise their functioning in multiple cognitive domains both in comparison to their peers and relative to their own prior ability levels. However, it appears notable that, despite the simplicity of our SMC measure and despite studying women from the general population rather than clinic patients, we still found an association between SMCs and risk of cognitive impairment. Therefore, our results support the idea that clinical providers, even in primary care settings, should consider incorporating assessment of SMCs into their routine checkups of older patients, as endorsement of SMCs may be informative even when the patient's primary reason for presenting to clinic is not their cognition. Our results also raise the possibility that even a relatively brief SMC assessment could be a valuable screening tool, perhaps in the form of a questionnaire administered in the waiting room to help minimize provider burden. Moreover, as we found associations between SMCs and risk of cognitive impairment among individuals with unimpaired scores on a global cognitive screen, we recommend that providers should not be entirely reassured by a "normal" cognitive screen performance but instead take care to monitor individuals with SMCs over time for possible cognitive decline.

SMCs among cognitively normal older women appear to be an early indicator of risk of cognitive impairment and may be a subtle signal of an underlying neurodegenerative disease process such as AD that is still in its earliest stages. Early detection of AD and other dementias is likely needed to enable potential interventions to be applied as early in the disease course as possible. Our results suggest that dementia prevention research trials should target older women

with SMCs as a high-risk group, in order to attempt to intervene among those who may be showing the earliest symptoms of neurodegeneration.

AUTHOR CONTRIBUTIONS

Dr. Kaup designed and conceptualized the study, conducted data analysis, interpreted the data, and drafted and revised the manuscript. Dr. Nettiksimmons assisted with data analysis and data interpretation and reviewed and revised the manuscript. Dr. LeBlanc assisted with data interpretation and reviewed and revised the manuscript. Dr. Yaffe designed and conceptualized the study, interpreted the data, reviewed and revised the manuscript, and supervised the study. All authors have approved the manuscript.

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