Mild Cognitive Impairment, Dementia, and Their Subtypes in Oldest Old Women

Kristine Yaffe, MD; Laura E. Middleton, PhD; Li-Yung Lui, MA, MS; Adam P. Spira, PhD; Katie Stone, PhD; Caroline Racine, PhD; Kristine E. Ensrud, MD; Joel H. Kramer, PsyD

Background: The population of oldest old is increasing, but the prevalence of cognitive impairment is not well characterized in this group.

Objectives: To determine the prevalence of mild cognitive impairment (MCI), dementia, and their subtypes in oldest old women and to examine whether some groups of oldest old women were more likely to have cognitive impairment.

Design: Prospective cohort study.


Participants: A total of 1299 oldest old (≥85 years) women.

Main Outcome Measures: All the women completed a neuropsychological test battery. Those who screened positive for possible cognitive impairment (n=634) were further assessed for a diagnosis of dementia, MCI, or normal cognition. The remaining women (n=665) were considered cognitively normal. Dementia and MCI subtypes were determined using standard criteria.

Results: The women had a mean age of 88.2 years, and 27.0% were 90 years or older; 231 women (17.8%) were diagnosed as having dementia and 301 (23.2%) as having MCI, for a combined cognitive impairment prevalence of 41.0%. Clinical features consistent with Alzheimer disease and mixed dementia were most common, each accounting for 40% of dementia cases. Amnestic multiple domain and nonamnestic single domain were the most common MCI types, accounting for 33.9% and 28.9% of cases, respectively. Cognitive impairment was more frequent in women 90 years or older compared with those 85 to 89 years (dementia, 28.2% vs 13.9%, P<.001; MCI, 24.5% vs 22.7%, P=.02) and was more common in women with less education, a history of stroke, and prevalent depression.

Conclusions: In this large sample of oldest old women, 41.0% had clinically adjudicated cognitive impairment. Subtypes of dementia and MCI were similar to those in younger populations. Women in the fastest growing demographic, the oldest old, should be screened for cognitive disorders, especially high-risk groups.

Arch Neurol. 2011;68(5):631-636

People 85 years or older are often referred to as the oldest old. This group is the fastest growing segment of the US population and is expected to increase in number by 40% during the next decade alone. Because the oldest old account for a significant portion of health care needs and expenditures, the expected rise in this population will have important societal effects on health care costs and caregiving.

Initial evidence suggests that the incidence of all-cause dementia almost doubles with every 5 years of age and that the prevalence of dementia rises from approximately 2% to 3% in those 65 to 75 years to 35% in those 85 years or older. However, cognitive impairment in the oldest old is not well characterized. In particular, few studies have examined mild cognitive impairment (MCI) in the oldest old, and the prevalence of MCI and its subtypes has not been well characterized. The prevalence of MCI and dementia by subtypes has important public health implications because the prognosis, symptoms, and treatment vary according to type. It is also possible that classic risk factors for MCI and dementia in the young-old, such as low education, cardiovascular disease, and an apolipoprotein E ε4 (APOE ε4) allele, may not pertain to the oldest old owing to differential survival or differences in coexisting comorbidities and neuropathologic features.

The objective of this study was to characterize the prevalence of MCI, dementia, and their subtypes in oldest old women. A secondary objective of this study was to examine whether some groups of oldest old women were more likely to have cognitive impairment. We hypothesized that the prevalence of cognitive impairment in the oldest old cohort would be higher than that reported for young-old populations.
but that the proportion with specific dementia and MCI subtypes would be similar.

METHODS

Study participants were women enrolled in the ongoing Study of Osteoporotic Fractures (SOF), a multicenter, prospective, observational study of women 65 years or older at baseline. In brief, 9704 primarily white women were recruited to the SOF between September 19, 1986, and October 31, 1988, from 4 cities and areas in the United States: Baltimore, Maryland; Minneapolis, Minnesota; Portland, Oregon; and Monongahela Valley, Pennsylvania. The women attended clinic visits every 2 to 4 years.

At visit 9 (November 13, 2006, to August 22, 2008), 3 of the 4 SOF sites participated in an ancillary study regarding clinical cognitive status called the Women’s Cognitive Impairment Study of Exceptional Aging (WISE). The 1338 women from the original SOF cohort who completed an expanded cognitive battery as part of the visit 9 protocol and who were based at 1 of the participating sites were part of the WISE. Of the remaining 8366 original participants, 5463 died, 1137 withdrew from the study or were lost to follow-up, 948 were from the nonparticipating site (Baltimore), 35 did not complete visit 9, and 783 were still observed but only by self-administered questionnaire. Of the 1338 women, the 1299 who were 85 years or older constituted the present study sample.

Baseline characteristics included self-reported age, education level, and race/ethnicity. The APOE phenotype was determined using standard procedures for the women enrolled at 1 clinic site. At visit 9, the women had their height, weight, and blood pressure measured, and body mass index was calculated. Participants reported their type of residence (community or nursing home). Self-reported medication use during the previous 30 days was recorded and confirmed by examination of pill bottles (medication and dosage). Participants also reported whether a physician had ever diagnosed them as having a variety of medical conditions, including stroke or transient ischemic attack, dementia or Alzheimer disease (AD), diabetes mellitus, or Parkinson disease. Women who reported a physician-identified heart attack or coronary disease or that they had undergone angioplasty or stenting were classified as having coronary artery disease. As part of the medical history, women were also asked to report on the occurrence of poor memory symptoms in the past week.

Depressive symptoms were evaluated using the 15-item Geriatric Depression Scale. Those with a score of 6 or higher were considered to have symptoms consistent with depression. Functional status was evaluated at visit 9 by caregivers or proxies using the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) and by a scale-based assessment of self-reported ability to perform activities of daily living (ADLs) and instrumental ADLs with or without difficulty. All the women provided written informed consent, and the study was approved by the committee on human research at each study site and at the coordinating center, the University of California at San Francisco.

NEUROPSYCHOLOGICAL TEST BATTERY

Women were administered either a slightly shortened (26-point) or standard (30-point) Mini-Mental State Examination (MMSE) and the Trail Making B Test every 2 to 4 years during the 20-year study. The MMSE is a brief test of global cognitive function that evaluates orientation, concentration, language, praxis, and memory. Trails B is a timed test of executive function in which participants connect a series of alternating numbers and letters.

At visit 9, centrally trained clinic staff administered an expanded neuropsychological test battery to participants. The battery included the Trails B and the Modified Mini-Mental State Examination (3MS), a 100-point extended version of the MMSE that is more sensitive; the California Verbal Learning Test, Second Edition (CVLT-II) Short Form; Digit Span; and category and verbal fluency. The CVLT-II is a test of verbal episodic memory with immediate and 10-minute delayed recall scores. Digit Span is a test of attention with forward and backward scores. Category and verbal fluency measure semantic memory, requiring the participant to say as many words as possible that fit into a given category (for the WISE examination, “vegetables” and words that begin with the letter F) in 1 minute.

CLINICAL COGNITIVE STATUS EVALUATION

Cognitive impairment was determined in a 2-step process. First, women were screened at visit 9 for the following criteria: (1) a score of less than 88 on the 3MS; (2) a score of less than 4 on the CVLT-II delayed recall; (3) a score of 3.6 or greater on the IQCODE; (4) a previous dementia diagnosis; and (5) nursing home residence. The 634 women who screened positive for 1 criterion or more and a random sample of 20 women who screened negative were adjudicated for clinical cognitive status. The remaining women who screened negative were considered cognitively normal.

A randomly selected member of a panel of clinical experts, which included a neurologist (K.Y.), 2 neuropsychologists (C.R. and J.H.K.), and a geropsychologist (A.P.S.), adjudicated the cognitive status of each woman. Information considered for the adjudication included visit 9 neuropsychological test scores, depression scores, functional status, medications, previous cognitive test scores, and medical history. To test interrater reliability, all 4 adjudicators evaluated 20 participants who screened positive for cognitive impairment. The average weighted κ for interrater reliability of diagnoses was 0.77 (93% confidence interval, 0.71-0.84), indicating substantial strength of agreement.

A diagnosis of dementia was made based on Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition) criteria. That is, the development of multiple cognitive deficits that include memory impairment and impairment in at least 1 other cognitive domain that is a decline from the previous level of functioning and is sufficiently severe to cause impairment in function. Impairment in functional status was determined primarily by the IQCODE. If women did not have an informant, functional status was informed by self-reported difficulty to perform ADLs and instrumental ADLs. The likely dementia cause (AD, vascular dementia, dementia due to multiple causes [mixed], or other) was also determined. A diagnosis of AD was made in accord with National Institute of Neurological Disorders and Stroke criteria. Vascular dementia was based on Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition) criteria. Dementia was classified as “other” if the participant had a history consistent with other neuropsychiatric conditions, such as head trauma, Parkinson disease, or active major depression. Finally, adjudicators diagnosed mixed dementia if there was evidence of multiple causes. If the criteria for dementia were met but the type of dementia could not be established, the participant was classified as having an indeterminate type of dementia.

Mild cognitive impairment was diagnosed using modified Petersen criteria, which require cognitive impairment that is insufficient to be dementia and generally intact function. Women with MCI were classified into amnestic or nonamnestic and single or multiple domains based on the cognitive domain(s) with impairment, defined as 1.5 SD poorer than age-appropriate ref-
The ease, and depression), and presence or absence of MCI (combined dementia and MCI) across strata of women, in- necessary. Finally, we compared the prevalence of cognitive impairment (combined dementia and MCI) across strata of women, including education (less than high school vs high school or more), presence or absence of comorbidities (stroke, coronary artery disease, and depression), and presence or absence of APOE ε4 using the χ² test. All the analyses were performed using a commercially available software program (SAS, version 9.2; SAS Institute, Inc, Cary, North Carolina).

### Results

The 1,299 women had an average age of 88.2 years, a mean education of 12.8 years, and a mean baseline shortened MMSE score of 24.9. In this oldest old cohort, 231 women (17.8%) were diagnosed as having dementia and 301 (23.2%) as having MCI, for a combined total of 41.0% with clinical cognitive impairment; the remaining 767 women (59.0%) were cognitively normal (639 from negative screening and 128 from adjudication). Compared with the WISE participants, the 1,012 SOF surviving nonparticipants were slightly older, were less educated, and had lower baseline cognitive scores (P < .05 for all).

### Prevalence of MCI, Dementia, and Their Subtypes by Age Group

The prevalence of MCI was higher in women 90 years or older than in women 85 to 89 years (24.5% vs 22.7%, P = .02). Amnestic multiple domain was the most common subtype of MCI (33.9%), followed by nonamnestic single domain (28.9%) and amnestic single domain (21.9%). Fewer participants were classified as nonamnestic multiple domain (8.6%) or indeterminate type (6.6%). The proportion of oldest old women with each MCI subtype was similar by age group (P = .83) (Table 1). The prevalence of dementia in women 90 years or older was approximately double that in women aged 85 to 89 years (28.2% vs 13.9%, P < .001) (Table 1). Clinical features consistent with AD and mixed dementia were most common (accounting for almost 40% of dementia cases each). Features consistent with vascular dementia and “other” dementia were less common (12.1% and 0.9% of dementia, respectively), and 7.4% were indeterminate. Although the overall prevalence of dementia was higher in women 90 years or older, the distribution of dementia subtypes was similar across age groups (P = .94 for difference by age group). Of the women diagnosed as having dementia, approximately one-quarter reported a previous dementia diagnosis and approximately 20% reported that they currently took dementia medications.

### Participant Characteristics by Cognitive Status

Cognitive impairment (dementia and MCI combined) was more common in women with less than a high school education (55.3% vs 38.4%, P < .001). The prevalence of
cognitive impairment was also higher in women with a history of stroke (51.2% vs 39.4%, P = .003) and with depression (65.2% vs 37.7%, P < .001) but did not differ in those with and without coronary artery disease (P = .96) or an APOE ε4 allele (P = .38) (Figure).

Compared with women with normal cognition, those with dementia were, on average, older, less likely to have completed high school, and more likely to live in a nursing home. In addition, women with dementia were more likely than women with normal cognition to be depressed, to have a history of stroke, and to have an APOE ε4 allele (P < .05 for all pairwise comparisons). Compared with women with normal cognition, women who were diagnosed as having MCI were older and were more likely to be depressed, to live in a nursing home, and to have a history of stroke but were less likely to have completed high school (P < .05 for all pairwise comparisons) (Table 2).

NEUROPSYCHOLOGICAL TEST SCORES BY COGNITIVE STATUS

As expected, women with dementia had the worst scores and women with normal cognition had the best scores on all visit 9 neuropsychological tests (Table 3). These differences across cognitive diagnoses were most noticeable on tests of global cognition, executive function, and memory. For example, the mean score on the 3MS was 92.6 for the normal cognition group, 84.6 for the MCI group, and 72.7 for the dementia group (P < .001 across all groups).

This study is among the few to characterize the prevalence of dementia, MCI, and their subtypes in the oldest old. In this cohort of oldest old women, 41.0% met the criteria for clinically significant cognitive impairment. Cognitive impairment, and particularly dementia, was more common in those 90 years or older than in those 85 to 89 years. However, the distribution of subtypes seemed to be similar across age groups, with AD and mixed dementia being the most common types of dementia and amnestic multiple domain and nonamnestic single domain being the most common forms of MCI.

The observed prevalence estimate for dementia was lower than that in most previous studies, but not all, which could be due to the relative young age of the population compared with other oldest old studies. The mean age of all WISE participants was 88 years, and among those 90 years or older, it was 92 years, whereas the mean age of participants in the 90+ Study was 94 years. In addition, it is probable that the women who survived to SOF visit 9 but did not participate in the WISE were more likely to have dementia than were WISE participants. However, this is likely to be true for previous longitudinal, population-based studies of the oldest old. Finally, although many studies followed a 2-stage protocol for dementia ascertainment similar to the WISE protocol, most previous studies did not include MCI diagnoses. As a result, participants with MCI may have been included among cases with dementia, resulting in higher estimates of dementia, especially where the diagnosis was not formed by clinical evaluation.

The distribution of dementia subtypes is vital for public health planning because the treatment and course of dementia differ by type. In this sample of oldest old women, AD and mixed dementia were the most common types, accounting for almost 80% of dementia cases combined, and vascular dementia accounted for 12.1% of cases. This distribution is similar to that found in a meta-analysis of European studies that stratified by age; AD accounted for 76.6% and vascular dementia accounted for 18.8% of dementia cases among the oldest old, totaling 95.5%.

Table 2. Characteristics of 1299 Oldest Old Women in the WISE by Cognitive Status

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normal (n=767)</th>
<th>MCI (n=301)</th>
<th>Dementia (n=231)</th>
<th>P Valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>87.8 (2.5)</td>
<td>88.5 (2.7)b</td>
<td>89.4 (3.4)b</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Education &lt;high school</td>
<td>11.5</td>
<td>21.3b</td>
<td>19.5</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Nursing home residence, %</td>
<td>2.7</td>
<td>6.7c</td>
<td>19.6b</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>History of stroke, %</td>
<td>10.8</td>
<td>15.4d</td>
<td>17.9b</td>
<td>.009</td>
</tr>
<tr>
<td>Coronal artery disease, %</td>
<td>19.2</td>
<td>18.7</td>
<td>20.0</td>
<td>.93</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>13.0</td>
<td>12.7</td>
<td>13.5</td>
<td>.97</td>
</tr>
<tr>
<td>Depression, %</td>
<td>7.1</td>
<td>18.4b</td>
<td>19.7</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>BMI, mean (SD)</td>
<td>26.2 (4.5)</td>
<td>25.7 (4.3)</td>
<td>25.7 (5.1)</td>
<td>.18</td>
</tr>
<tr>
<td>APOE ε4 allele, %</td>
<td>6.9</td>
<td>4.2</td>
<td>15.9d</td>
<td>.03</td>
</tr>
<tr>
<td>mMMSE score, mean (SD)</td>
<td>24.5 (2.0)</td>
<td>22.1 (3.0)b</td>
<td>18.4 (5.0)b</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviations: APOE, apolipoprotein E; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); MCI, mild cognitive impairment; mMMSE, shortened Mini-Mental State Examination; WISE, Women Cognitive Impairment Study of Exceptional Aging.

a P value by analysis of variance across all groups for continuous variables and by χ² test for categorical variables.
b P < .001 for pairwise comparisons with normal cognitive function.
c P < .01 for pairwise comparisons with normal cognitive function.
d P < .05 for pairwise comparisons with normal cognitive function.
e Only 309 women were tested for APOE ε4.
However, this study also has some important limitations. In addition, the women are well-characterized, and have been closely observed for 20 years. However, this study also has some important limitations. The cognitive diagnoses were made without standard neuroimaging or confirmatory autopsy, and although we gave preference to informant-based variables, such as the IQCODE, we relied on participants’ self-report of medical conditions and, for women who did not have an informant, self-report of functional limitations. Nevertheless, extensive demographics, medical history, and neuropsychological test scores were considered for diagnoses. Surviving women with cognitive impairment may also have been more likely to drop out of the SOF during the 20-year follow-up. As a result of these limitations, it is likely that the prevalence estimates are conservative. Finally, most of the participants were white women, and the prevalence estimates should not be generalized to men or to more diverse populations.

By 1994, the oldest old already represented almost 40% of people with dementia,7 despite accounting for just more than 1% of the population. The absolute and relative growth of the oldest old population in the coming decades will increase the number and proportion of dementia cases among the oldest old. In this study, we found that more than 40% of oldest old women are cognitively impaired and that this rate was higher in those 90 years or older than in those aged 85 to 89 years. The distributions of MCI and dementia subtypes were similar in those 90 years or older than in those aged 85 to 89 years. The distributions of MCI and dementia subtypes were similar to those from the younger Women’s Health Initiative (women ≥65 years), which also found that amnestic multiple-domain MCI was most common; however, in that cohort, amnestic multiple-domain MCI was more common; however, in that cohort, amnestic multiple-domain MCI was the next most common type, followed by amnestic single-domain MCI. It is important to characterize MCI prevalence by subtype because rate of progression to dementia may vary by MCI type. Some studies have suggested that amnestic single-domain MCI is most likely to progress to dementia, whereas multiple-domain and nonamnestic single-domain MCI are least likely; although this is controversial.

Women with low education, a history of stroke, and depression were more likely to have cognitive impairment, similar to previous findings in young-old populations. Although having an APOE ε4 allele did not carry an excess risk of MCI, women with an ε4 allele were more likely to be diagnosed as having dementia, confirming earlier results in the oldest old. However, we found no association between APOE ε2 and preserved cognitive function, unlike in the 90+ Study. Of note, the observed prevalence of ε2 was high, possibly due to enhanced survival in those with an ε2 allele, as previously reported. Although most studies of young-old adults report that diabetes is associated with increased likelihood of dementia or MCI, we did not observe that in the WISE cohort, possibly owing to differential survival. That is, people with diabetes and cognitive impairment may have been less likely to survive to age 85 years.

This study has several strengths. Most important, we studied a large cohort of oldest old women with careful cognitive evaluation. In addition, the women are well characterized and have been closely observed for 20 years. However, this study also has some important limitations. The cognitive diagnoses were made without standard neuroimaging or confirmatory autopsy, and although we gave preference to informant-based variables, such as the IQCODE, we relied on participants’ self-report of medical conditions and, for women who did not have an informant, self-report of functional limitations. Nevertheless, extensive demographics, medical history, and neuropsychological test scores were considered for diagnoses. Surviving women with cognitive impairment may also have been more likely to drop out of the SOF during the 20-year follow-up. As a result of these limitations, it is likely that the prevalence estimates are conservative. Finally, most of the participants were white women, and the prevalence estimates should not be generalized to men or to more diverse populations.

**Accepted for Publication:** November 18, 2010.  
**Author Affiliations:** Departments of Psychiatry (Dr Yaffe), Neurology (Drs Yaffe and Kramer), Epidemiology and Biostatistics (Dr Yaffe), and Neurological Surgery and Radiation Oncology (Dr Racine), School of Medicine, University of California at San Francisco; Department of Psychiatry, Veterans Affairs Medical Center, San Francisco (Dr Yaffe); Heart and Stroke Foundation Center for Stroke Recovery, Sunnybrook Hospital, Toronto, Ontario, Canada (Dr Middleton); Research Institute, California Pacific Medical Center, San Francisco (Dr Stone and Ms Lui); Department of Mental Health, The John Hopkins Bloomberg School of Public Health, Baltimore, Maryland (Dr Spira); and Center for Chronic Disease Out-
comes Research, Veterans Affairs Medical Center, Minneapolis, Minnesota (Dr Ensrud).

Correspondence: Kristine Yaffe, MD, Department of Psychiatry, University of California at San Francisco, 4150 Clement St, PO Box 181, San Francisco, CA 94121 (kristine.yaffe@ucsf.edu).

Author Contributions: Dr Yaffe had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Yaffe, Spira, Stone, and Kramer. Acquisition of data: Yaffe, Racine, and Ensrud. Analysis and interpretation of data: Yaffe, Middleton, Lui, Spira, Stone, Racine, Ensrud, and Kramer. Drafting of the manuscript: Yaffe and Middleton. Critical revision of the manuscript for important intellectual content: Middleton, Lui, Spira, Stone, Racine, Ensrud, and Kramer. Statistical analysis: Yaffe and Middleton. Obtained funding: Yaffe and Stone. Administrative, technical, and material support: Yaffe and Racine. Study supervision: Yaffe and Stone.

Financial Disclosure: None reported.

Funding/Support: This study was supported in part by grant K24 AG 031155 from the National Institute of Aging and an Independent Investigator Award from the Alzheimer’s Association (Dr Yaffe); by a Canadian Institute of Health Research fellowship (Dr Middleton); and by Mentored Research Scientist Development Award K01AG033195 from the National Institute on Aging (Dr Spira). The SOF and the SOF-WISE are supported by grants AG05394, AR35584, AR35583, R01 AG005407, R01 AG05407, AR35582, AR35581, AG018173, AG005665, AG017565, AG000001, AG053629, AG05407, AR35582, AR35583, R01 AG005407, R01 AG027576-22, 2 R01 AG005394-22A1, 2 R01 AG027574-22A1, and 5 R01AG026720-04 from the National Institutes of Health.

REFERENCES