Prevalence and Outcomes of Amyloid Positivity Among Persons Without Dementia in a Longitudinal, Population-Based Setting

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IMPORTANCE Brain amyloid deposition is a marker of Alzheimer disease (AD) pathology. The population-based prevalence and outcomes of amyloid positivity in a population without dementia are important for understanding the trajectory of amyloid positivity to clinically significant outcomes and for designing AD prevention trials.

OBJECTIVE To determine prevalence and outcomes of amyloid positivity in a population without dementia.

DESIGN, SETTING, AND PARTICIPANTS In the prospective, population-based Mayo Clinic Study of Aging in Olmsted County, Minnesota, participants without dementia were randomly selected from the county population and were clinically and cognitively evaluated at baseline and every 15 months from August 1, 2008, to September 18, 2018. They were also invited to undergo carbon\textsuperscript{11}-Pittsburgh compound B positron emission tomography (PET) imaging.

EXPOSURES Amyloid positivity (defined as a standardized uptake value ratio $>1.42$ on PET).

MAIN OUTCOMES AND MEASURES Prevalence of amyloid positivity in the Olmsted County population without dementia and risk of progression from no cognitive impairment (ie, normal cognition for age) to incident amnestic MCI (aMCI) and from MCI or aMCI to incident AD dementia.

RESULTS Of 3894 participants, 1671 underwent PET imaging and were included in the study; 2198 did not undergo imaging, and 25 were excluded for other reasons. The mean (SD) age of participants was 71.3 (9.8) years; 892 (53.4%) were men, and 179 (10.7%) had prevalent MCI. The prevalence of amyloid positivity without cognitive impairment in the population without dementia increased from 2.7% (95% CI, 0.5% to 4.9%) in persons aged 50 to 59 years to 41.3% (95% CI, 33.4% to 49.2%) in those aged 80 to 89 years at baseline. Prevalence of amyloid-positive MCI in the population without dementia increased from 0% in persons aged 50 to 59 years to 16.4% (95% CI, 10.3% to 22.5%) in those aged 80 to 89 years. The incident aMCI risk increased more than 2-fold in participants without cognitive impairment who were amyloid positive vs those who were amyloid negative (hazard ratio [HR], 2.26; 95% CI, 1.52 to 3.35; $P < .001$). The risk of AD dementia was 1.86 (95% CI, 0.89 to 3.88; $P = .10$) for amyloid-positive participants with MCI vs amyloid-negative participants with MCI, 1.63 (95% CI, 0.78 to 3.41; $P = .20$) for participants with aMCI who were amyloid positive vs amyloid negative, and 2.56 (95% CI, 1.35 to 4.88; $P = .004$) for amyloid-positive participants who were either without cognitive impairment or had aMCI vs those who were amyloid negative. Global cognitive and memory domain z scores declined significantly in amyloid-positive individuals during follow-up. The mean (SD) follow-up time from baseline was 3.7 (1.9) years to incident aMCI and 3.8 (2.0) years to incident AD dementia.

CONCLUSIONS AND RELEVANCE Population-based prevalence of amyloid-positive status and progression rates of amyloid positivity provide valid information for designing AD prevention trials and assessing the public health outcomes of AD prevention and interventions.
he National Institutes on Aging-Alzheimer’s Association and the International Working Group has established stages of preclinical Alzheimer disease (AD) and defined mild cognitive impairment (MCI) due to AD (and its subset, prodromal AD) with elevated brain amyloid as the key biomarker for AD pathology. Our group has published frequencies of the National Institute on Aging-Alzheimer’s Association biomarker groups in Mayo Clinic Study of Aging (MCSA) participants who either had no cognitive impairment or had amnestic MCI (aMCI). Whereas frequencies describe the proportion of individuals in a study who have a condition, prevalence represents the number of individuals in a defined population with a disease or condition. Prevalence of amyloid positivity in the population without dementia provides reliable and valid estimates of the burden of AD pathology, which are useful for sample size estimations in designing primary and secondary AD prevention trials in persons without dementia.

Despite this, there are relatively few population-based estimates of amyloid positivity in the population without dementia. Jansen et al reported the prevalence of amyloid positivity in persons without dementia from a meta-analysis of clinic-based, volunteer-based studies in hospital departments and population-based studies. Because of differences in study designs and recruitment strategies, the estimates are potentially prone to bias. Ossenkoppele et al estimated amyloid positivity prevalence among persons with dementia, but because participants had dementia prior to the initiation of the study, the estimates cannot be used in estimating sample sizes for primary and secondary prevention AD trials. Our first objective was therefore to estimate the prevalence of amyloid positivity in a population without dementia.

Current AD trials are focused on primary and secondary prevention in persons without dementia. Population-based studies on outcomes of preclinical AD, MCI due to AD, and prodromal AD are informative for estimating effect sizes, rates of progression, duration of trials, and interpreting the efficacy of clinical trial interventions. Our group has published studies on the progression in participants with preclinical AD in a small sample during a very short duration. Van Harten et al examined the predictive role of preclinical AD for cognitive decline in memory clinic participants, and Hansson et al assessed progression from biomarker-positive MCI (using tau protein in cerebrospinal fluid or amyloid β) to AD dementia in a small sample of memory clinic participants. Clinic-based studies, however, typically overestimate rates of progression because participants may have more advanced disease than the general population. Studies of cognitive decline have been conducted among Alzheimer’s Disease Neuroimaging Initiative (ADNI) participants. However, the ADNI cohort is a highly select convenience sample focused on the symptomatic phase of the disease, and it excludes participants with clinical evidence of cerebrovascular disease. Therefore ADNI estimates may not represent the general population without dementia. Thus, the second objective of this study was to estimate outcomes of amyloid positivity in a large, prospective, population-based cohort.

**Methods**

The MCSA cohort was established in 2004 to identify risk factors for MCI and dementia, and the design has been published in detail. Briefly, researchers enumerated the Olmsted County, Minnesota, population aged 70 to 89 years on October 1, 2004, using the Rochester Epidemiology Project, a medical records–linkage system. Participants were then selected for the study using an age-stratified and sex-stratified random sampling scheme. Exclusion criteria included terminal illness, hospice admission, or dementia. Recruitment of people aged 50 to 69 years began in 2012 to determine the timing of onset of brain pathology and cognitive impairment. Recruitment of persons with dementia began in 2014 to allow potential imaging of these participants.

The institutional review boards of the Mayo Clinic and the Olmsted Medical Center approved all study protocols. Written informed consent was obtained from all participants.

**Evaluation of Participants**

A study coordinator assessed sociodemographic factors, memory, and the Beck Depression Inventory (BDI) in participants and administered the Clinical Dementia Rating Scale and Functional Activities Questionnaire to a study partner (defined as someone who knew the participant well). A physician assessed global cognition and performed a neurological examination to identify potential causes of cognitive impairment. Participants underwent cognitive testing to assess performance in memory (Wechsler Memory Scale–Revised Logical Memory II and Visual Reproduction II Tests and the Auditory Verbal Learning Test, all of which were implemented with delayed recall); attention-executive function (Trail Making Test Part B, the Digit Symbol Substitution Test from Wechsler Adult Intelligent Scale–Revised); language (Boston Naming Test, category fluency); and visuospatial skills (Block Design and Picture Completion Tests from Wechsler Adult Intelligent Scale–Revised). Raw scores from each test were transformed into age-adjusted scores using normative data, aver-
aged, and scores were scaled to compute domain z scores. In addition, the raw test scores at each evaluation were averaged and scaled to create a domain z score to allow comparisons across domains; the 4 domain z scores were averaged and scaled to calculate a global cognitive z score.

**Diagnostic Assessment**
Mild cognitive impairment was diagnosed by a combination of (1) cognitive concern by participant, study partner, and/or physician, (2) impairment in 1 or more cognitive domain, (3) essentially normal functional activities, and (4) absence of dementia. The diagnosis was characterized as amnestic MCI (aMCI) if impairment occurred in the memory domain and non-amnestic if impairment occurred only in 1 or more non-memory domains. Dementia (including AD dementia) was based on published criteria. Persons were considered cognitively unimpaired if they did not meet criteria for MCI (whether amnestic or nonamnestic) or dementia.

**Other Covariates**
Weight and height were measured at each evaluation, and apolipoprotein E (ApoE) ε4 status was determined. To obtain information on potential causes of nonparticipation bias at baseline, the medical records of participants and nonparticipants were abstracted for vascular diseases (ie, diabetes, hypertension, dyslipidemia, coronary artery disease, atrial fibrillation, congestive heart failure, and stroke).

**Prospective Follow-up**
Participants were evaluated every 15 months to identify incident MCI and dementia. Trained nurses reviewed the medical records of participants lost to follow-up for incident physician-diagnosed AD dementia.

**Imaging**
Participants underwent magnetic resonance imaging and a computed tomographic scan for attenuation correction. Amyloid positron emission tomography (PET) imaging was initiated in 2008 and consisted of four 5-minute dynamic frames acquired 40 to 60 minutes after injection of carbon-11-Pittsburgh compound B. The regions of interest were derived from automatically labeled regions of interest from an MRI template. An amyloid PET standardized uptake value ratio (SUVR) was calculated from the voxel number weighted average of the median uptake in the parietal, temporal, prefrontal, orbitofrontal, anterior and posterior cingulate, and precuneus regions of interest, referenced to the cerebellar gray crus region. Amyloid positivity was defined as SUVR greater than 1.42. The first PET result on or after August 1, 2008, was considered the baseline for each participant.

**Statistical Analyses**
We compared the characteristics of participants without cognitive impairment who were positive or negative for amyloid and participants with MCI who were positive or negative for amyloid using χ² (categorical) and Wilcoxon rank sum (continuous) tests. We estimated the proportions of amyloid-positive participants who were cognitively unimpaired or had MCI in the sample without dementia. To adjust for nonparticipation bias in the MCSA cohort, we used logistic regression models to assess the effects of age, sex, and education on (1) probability of participation and (2) probability of undergoing imaging tests. We combined these 2 sets of probabilities, then used the reciprocal of the probability for each individual as weights (inverse probability weighting [IPW]) to adjust the proportions of amyloid positivity for nonparticipation bias.

**Results**

**Baseline Characteristics**
Of 1671 participants without dementia who underwent amyloid imaging between August 1, 2008, and September 18, 2017, the mean (SD) age was 71.3 (9.9) years; 892 (53.4%) were men, 470 (28.3%) were ε4 carriers, and 179 (10.7%) had prevalent MCI (Table 1). The ApoE ε4 allele was more frequently found in people who were amyloid positive than in those who were amyloid negative, whether without cognitive impairment (amyloid positive: 182 of 434 [41.9%] vs amyloid negative: 221 of 1058 [20.9%]) or with MCI (amyloid positive: 56 of 110 [50.9%] vs amyloid negative: 11 of 69 [16%]; P < .05). Global

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cognitive and memory z scores were lowest in participants who were amyloid-positive and had MCI. Compared with participants with amyloid imaging, nonparticipants (n = 2198) were older (nonparticipants: mean [SD] age, 72.5 (8.8) years vs participants: 70.8 (9.9) years; P < .001); were more frequently women (nonparticipants: 1134 of 2198 [51.6%] vs participants: 779 of 1671 [46.6%]; P = .002); had lower mean years of education (nonparticipants: mean [SD], 14.2 (2.7) years vs participants: 14.7 (2.6) years; P < .001); were more frequently found to have hypertension (nonparticipants: 1554 of 2198 [70.7%] vs participants: 1008 of 1671 [60.4%]; P < .001); were more frequently found to have strokes (nonparticipants: 85 of 2198 [3.9%] vs participants: 42 of 1671 [2.5%]; P = .02); and had lower global cognitive z scores (nonparticipants: mean [SD], −0.156 [1.01] vs participants: 0.20 [0.96]; P < .001). They did not differ in regard to frequencies of ApoE ε4 allele (nonparticipants: 594 of 2198 [28.2%] vs participants: 470 of 1671 [28.3%]; P = .92), depressive symptoms (nonparticipants: 158 of 2198 [7.3%] vs participants: 121 of 1671 [7.3%]; P = .96) or prevalent MCI (nonparticipants: 217 of 2198 [9.9%] vs participants: 179 of 1671 [10.7%]; P = .39).

The IPW-adjusted, population-standardized prevalence of amyloid-positive, cognitively unimpaired status in the population without dementia in both sexes combined increased from 2.7% (95% CI, 0.5% to 4.9%) in the age group from 50 to 59 years to 41.3% (95% CI, 33.4% to 49.2%) in participants aged 80 to 89 years (Table 2). The prevalence of amyloid-positive MCI in the population without dementia in both sexes combined increased from 0% at ages 50 to 59 years to 16.4% (95% CI, 10.3% to 22.5%) at ages 80 to 89 years. The total prevalence of amyloid positivity across all ages was 22.0% (18.9% to 30.5%). Age-specific estimates by sex followed the same pattern, with a higher total prevalence of amyloid positivity in women (25.6%; 95% CI, 20.8% to 30.5%) compared with men.
During the follow-up period, 1519 participants had 1 or more clinical and prodromal AD for both sexes combined, in women, the estimates were slightly attenuated with adjustment for ApoE ε4 (Table 3).

Incident aMCI
In unadjusted models, all HRs of incident aMCI were elevated more than 2-fold (Table 3). In models adjusted by age, sex, and education, the HR was 2.26 (95% CI, 1.52 to 3.35; P < .001) for both sexes combined (Figure 1A), 1.96 (95% CI, 1.05 to 3.67; P = .04) in women, and 2.42 (95% CI, 1.46 to 4.04; P < .001) in men. The estimates were slightly attenuated with adjustment for ApoE ε4 (Table 3).

Incident AD Dementia
In unadjusted models, the HR of AD dementia was significantly elevated for amyloid-positive participants with MCI (preclinical AD) or aMCI (prodromal AD) and for amyloid-positive participants with either no cognitive impairment or MCI (preclinical and prodromal AD) for both sexes combined, in women, and in men (Table 3). In models adjusted for age, sex, and education, HRs were nonsignificantly elevated for amyloid-positive participants with MCI (Figure 1B) and aMCI (Figure 1C), respectively. However, the proportions in ages 50 to 89 years combined were higher than prevalence. When stratified by ApoE ε4 status, the prevalence of amyloid positivity was higher in ε4 carriers and older participants (eFigure in the Supplement). The prevalence of amyloid-positive participants without cognitive impairment among ε4 carriers vs noncarriers was 18.5% (95% CI, 14.0% to 23.1%) vs 7.5% (95% CI, 5.3% to 9.5%), respectively, in the age group 50 to 69 years, and 53.1% (95% CI, 46.7% to 59.6%) vs 32.2% (95% CI, 26.5% to 37.9%), respectively, in ages 70 to 89 years. The prevalence of amyloid-positive participants with MCI in ε4 carriers and noncarriers was 2.2% (95% CI, 0.2% to 4.2%) and 0.3% (95% CI, 0.0% to 0.7%), respectively, in the age group 50 to 69 years, and 20.4% (95% CI, 14.9% to 25.8%) and 10.5% (95% CI, 5.9% to 15.0%), respectively, in the age group 70 to 89 years. By sex, the prevalence of amyloid-positive ε4 carriers without cognitive impairment and noncarriers was higher in women (29.5% [95% CI, 24.6% to 34.4%] in ε4 carriers and 17.1% [95% CI, 13.8% to 21.6%] in noncarriers) than in men (24.3% [95% CI, 18.3% to 30.3%] in ε4 carriers and 18.8% [95% CI, 9.0% to 27.7%] in noncarriers) (eTable in the Supplement). The prevalence of amyloid-positive participants with MCI in ε4 carriers was higher in women than in men (women: 8.7% [95% CI, 5.3% to 12.1%] vs men: 3.1% [95% CI, 1.4% to 4.9%]), but there was no sex difference in noncarriers and no interaction of ApoE ε4 with sex.

Clinical Outcomes During Follow-up
During the follow-up period, 1519 participants had 1 or more evaluations: 1377 among participants without cognitive impairment and 142 in participants with MCI; 152 had no follow-up visits (Table 1). In this period, a higher proportion of the 137 deaths occurred in amyloid-positive participants: 54 of 434 amyloid-positive participants without cognitive impairment (13.4%) died vs 52 of 1058 amyloid-negative, cognitively unimpaired participants (4.9%), and 19 of 110 amyloid-positive participants with MCI (17.3%) died vs 8 of 69 amyloid-negative participants with MCI (4.9%).

During a mean (SD) follow-up period of 3.7 (1.9) years, 63 of 434 amyloid-positive participants without cognitive impairment (14.5%) vs 44 of 1058 amyloid-negative participants without cognitive impairment (4.2%) developed incident aMCI. During a mean (SD) follow-up of 3.8 (2.0) years, 3 of 1058 amyloid-negative individuals without cognitive impairment (0.3%); 14 of 434 amyloid-positive individuals without cognitive impairment (3.2%); 10 of 69 amyloid-negative and 52 of 1058 amyloid-negative individuals with MCI (14.5%); and 36 of 110 amyloid-positive individuals with MCI (32.7%) developed AD dementia.

Table 2. Prevalence of Imaging Biomarkers by Cognitive Status, 10-Year Age Groups, and Sex

<table>
<thead>
<tr>
<th>Age Category</th>
<th>Men and Women</th>
<th>Women</th>
<th>Men</th>
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<tr>
<td>Amyloid-positive participants without cognitive impairment, y</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>50-59</td>
<td>6 (2.4)</td>
<td>4 (3.3)</td>
<td>2 (1.6)</td>
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<tr>
<td>60-69</td>
<td>88 (18.6)</td>
<td>53 (23.0)</td>
<td>35 (14.4)</td>
</tr>
<tr>
<td>70-79</td>
<td>191 (32.7)</td>
<td>91 (32.3)</td>
<td>100 (33.1)</td>
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<td>80-89</td>
<td>149 (41.2)</td>
<td>62 (43.1)</td>
<td>87 (39.9)</td>
</tr>
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<td>All age groups</td>
<td>434 (26.0)</td>
<td>210 (27.0)</td>
<td>224 (25.1)</td>
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<tr>
<td>Amyloid-positive participants with MCI, y</td>
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</tr>
<tr>
<td>50-59</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>60-69</td>
<td>6 (1.3)</td>
<td>4 (1.7)</td>
<td>2 (0.82)</td>
</tr>
<tr>
<td>70-79</td>
<td>41 (7.0)</td>
<td>23 (8.2)</td>
<td>18 (6.0)</td>
</tr>
<tr>
<td>80-89</td>
<td>63 (17.4)</td>
<td>28 (19.4)</td>
<td>35 (16.1)</td>
</tr>
<tr>
<td>All</td>
<td>110 (6.6)</td>
<td>55 (7.1)</td>
<td>55 (6.2)</td>
</tr>
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</table>

* Observed frequencies (unadjusted) are represented in parentheses to demonstrate the (potential) impact of the weighting approach on the estimates of prevalence.

**Prevalence estimates for both sexes combined were standardized by age to the Olmsted County, Minnesota, population. Estimates for men and women pooled across age strata and sex were standardized by both age and sex to the Olmsted County, Minnesota, population.

(17.8%; 95% CI, 14.2% to 21.4%). The age-specific proportions of amyloid positivity in participants without cognitive impairment and participants with MCI (percentages in Table 2) were comparable with prevalence. However, the proportions in ages 50 to 89 years combined were higher than prevalence.
Impairment. Consistent with the concept of amyloid-positive participants who were either cognitively unimpaired or had aMCI (2.56; 95% CI, −0.079 to −0.019; Figure 2A). Similarly, slopes for memory domain z scores declined more greatly for amyloid-positive individuals without cognitive impairment (−0.048; 95% CI, −0.062 to −0.035) vs amyloid-negative individuals without cognitive impairment (0.037; 95% CI, 0.027 to 0.046) and declines were also greater in amyloid-positive individuals with MCI (−0.126; 95% CI, −0.156 to −0.096) than in amyloid-negative individuals with MCI (−0.025; 95% CI, −0.063 to 0.013; Figure 2B).

**Discussion**

Among study participants without dementia, the prevalence of amyloid positivity increased with age and was higher in women than in men. Prevalence estimates for ages 50 to 89 years combined were lower than observed proportions (unadjusted or unweighted). Hazard ratios were significantly elevated for the progression of amyloid-positive participants without cognitive impairment to aMCI and the progression of amyloid-positive participants or participants with aMCI to probable AD dementia, and were nonsignificantly elevated for the progression of amyloid-positive individuals from MCI and aMCI to AD dementia. Progression rates were higher for amyloid-positive participants than for amyloid-negative participants with no cognitive impairment or with aMCI as prodromal AD dementia.

### Cognitive Decline

In mixed-effects models, global cognitive and memory domain z scores declined more for amyloid-positive individuals than for amyloid-negative participants. Slopes for global cognitive z scores were greater in amyloid-positive individuals without cognitive impairment (−0.076; 95% CI, −0.086 to −0.065) than in amyloid-negative individuals without cognitive impairment (0.005; 95% CI, −0.002 to 0.012) and amyloid-positive individuals with MCI (−0.180; 95% CI, −0.204 to −0.156) vs amyloid-negative individuals with MCI (−0.049; 95% CI, −0.079 to −0.019; Figure 2A).

### Table 3. Risk of Progression to Incident Amnestic MCI and AD Dementia in Amyloid-Positive Individuals

(Compared With Amyloid-Negative Individuals)

<table>
<thead>
<tr>
<th>Progression</th>
<th>All, HR (95% CI)</th>
<th>P Value</th>
<th>Women, HR (95% CI)</th>
<th>P Value</th>
<th>Men, HR (95% CI)</th>
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</tr>
<tr>
<td>Model 1</td>
<td>3.44 (2.34 to 5.06)</td>
<td>&lt;.001</td>
<td>3.15 (1.71 to 5.82)</td>
<td>&lt;.001</td>
<td>3.60 (2.19 to 5.92)</td>
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<td>2.26 (1.52 to 3.35)</td>
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<td>1.96 (1.05 to 3.67)</td>
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<td>2.42 (1.46 to 4.04)</td>
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<tr>
<td>Model 1</td>
<td>2.60 (1.29 to 5.25)</td>
<td>.01</td>
<td>4.11 (0.96 to 17.6)</td>
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<td>Model 1</td>
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<td>.16</td>
<td>1.20 (0.49 to 2.92)</td>
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<td>2.44 (0.53 to 12.58)</td>
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<td>0.80 (0.25 to 2.68)</td>
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<td>From no cognitive impairment or aMCI to AD dementia</td>
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<td>4.26 (1.22 to 14.80)</td>
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<td>1.54 (0.64 to 3.71)</td>
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</table>

**Abbreviations:** AD, Alzheimer disease; amMCI, amnestic mild cognitive impairment; ApoE, apolipoprotein E; HR, hazard ratios; MCI, mild cognitive impairment.

*a Progression from preclinical AD to amnestic MCI.
*b Progression from preclinical AD to amnestic MCI.
*c Progression from MCI associated with AD (including both amnestic MCI and nonamnestic MCI) to probable AD dementia.
*d Progression from prodromal AD to probable AD dementia.
*e Progression from preclinical and prodromal AD to probable AD dementia.

<table>
<thead>
<tr>
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<th>Model 3</th>
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<tr>
<td>&lt;.001</td>
<td>.003</td>
<td>.34</td>
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A. Progression from unimpaired status to amnestic mild cognitive impairment (aMCI) in amyloid-positive vs amyloid-negative participants. B. Progression from mild cognitive impairment (MCI) to Alzheimer disease (AD) dementia in amyloid-positive vs amyloid-negative participants. C. Progression from aMCI to AD dementia in amyloid-positive vs amyloid-negative participants. D. Progression from no cognitive impairment or aMCI to AD dementia in amyloid-positive vs amyloid-negative participants. Models were adjusted for age, sex, and education using time from baseline as the time scale. At 3 years, the percentage free of aMCI was 88.0% of amyloid-positive participants who were initially cognitively unimpaired vs 96.2% of amyloid-negative participants who were initially cognitively unimpaired; the percentage free of AD dementia was 73.9% of amyloid-positive people who initially had MCI vs 90.8% of amyloid-negative people with the same condition; the corresponding rates for aMCI were 68.3% vs 90.8%, respectively, after censoring.

Valid and reliable population-based estimates of prevalence and outcomes are important for estimating what the impact of an approved anti-amyloid drug would be in a general population. Estimation of effect sizes from a population-based, sample without dementia may lead to more realistic expectations for anti-amyloid agents. In contrast, estimates of effect sizes derived from clinic-based studies and volunteer participants are subject to selection bias and may lead to inflated estimates of time to event. Such studies may overestimate progression rates, because these participants may have a higher likelihood of a family history of dementia or may be more symptomatic and therefore may progress at a higher rate than the general population. On the other hand, clinical trial cohorts are likely to have less comorbidity than a population-based study such as this one. This study focused on persons without dementia because current primary and secondary AD prevention trials are designed to prevent progression in persons without dementia. The unadjusted proportions in the age group 50 to 89 years were lower than prevalence because of differences in participation rates by age, sex, and education or because of oversampling of the people in the age group 80 to 89 years, who likely have more pathology, to ensure adequate power to detect significant differences in prospective studies.

Despite the nonsignificant associations by sex for incident AD dementia, the higher prevalence of amyloid positivity in women and sex differences in risk of progression for amyloid-positive individuals who are either cognitively unimpaired or have MCI may have implications for reporting clinical trial results by sex. Although we did not find a significant interaction of amyloid positivity with sex, higher rates of progression in amyloid-positive women with MCI compared with men may be partly because of the higher prevalence of
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Figure 2. Changes in Global Cognitive Domain and Memory Domain z Scores

A and B. Slopes for global cognitive domain z scores and memory domain z scores for participants who were amyloid positive and cognitively unimpaired; amyloid negative and cognitively unimpaired; amyloid positive with MCI; and amyloid negative with MCI. All slopes were centered on age, sex, and education. Slopes for all groups declined significantly except the global z score for participants who were amyloid negative and cognitively unimpaired and the memory z score for amyloid negative participants with MCI; the memory z score for amyloid-negative participants without cognitive impairment increased significantly.

amyloid positivity in women, particularly among women ε4 carriers compared with men. This is consistent with amyloid as a mediator of the effects of ApoE ε4 and the reduced HRs after adjustment for ApoE ε4 allele in the models. The HRs for progression from amyloid-positive, cognitively unimpaired status to aMCI were higher in men than in women, consistent with our previous study on incident MCI. We speculate that perhaps other factors (eg, vascular conditions) may play a greater role in progression at the preclinical AD stage in men, whereas amyloid may play a greater role in progression from preclinical or prodromal AD to AD dementia in women. These preliminary findings need to be validated in larger population-based, prospective studies. However, they suggest that potential sex differences should be taken into account in clinical trial design.

Our prevalence estimates are consistent with studies reporting an increase in amyloid positivity with age and ApoE ε4 allele carriage. Jansen et al reported a 10% to 12% prevalence of amyloid positivity in persons aged 50 to 59 years who had no cognitive impairment, which is higher than the 2.4% prevalence observed in this study, and that could be because of the large proportion of volunteers or to more accurate characterization from using both PET and cerebrospinal fluid amyloid test results in the previous study. Landau et al reported frequencies of amyloid positivity of 29% in persons without cognitive impairment, 42% in people with early MCI, and 62% in those with late MCI among participants of the ADNI study. Consistent with the highly selective ADNI cohort, these estimates are much higher than the population-based estimates in this study.

These prospective findings suggest that clinic-based studies and studies based primarily on volunteers may overestimate progression. The Australian Imaging, Biomarkers, and Lifestyle Study of Aging, which is based on volunteers and has a much higher proportion of ApoE ε4 carriers than the general population, reported a 4.5-fold increased risk of progression from cognitively unimpaired status to MCI or AD in persons who were amyloid positive compared with amyloid-negative persons. Vos et al reported HRs ranging from 4.6 to 33.8 for progression from preclinical AD stages 1 to 3 to symptomatic AD dementia among 311 volunteers in a Washington University School of Medicine study. It is unclear if tau and cerebrospinal fluid amyloid makers could have contributed to better characterization of amyloid-positive individuals. Similarly, the clinic-based Amsterdam Dementia Cohort of 132 patients with subjective memory complaints reported declines in memory and cognitive z scores that were higher than in those in the MCSA cohort. Nordberg et al reported increased progression to probable AD dementia in amyloid-positive participants with MCI in an European multicenter study. In 445 amyloid-positive participants without cognitive impairment of the ADNI study, Donohue et al reported longitudinal declines in the Preclinical Alzheimer Cognitive Composite, Mini–Mental State Examination, and Clinical Dementia Rating sum of boxes scores; however, lack of a decline in logical memory raises questions about possible selection bias. In a comparative study on frequencies and outcomes of biomarkers in the MCSA cohort (n = 126) vs the ADNI-1 cohort (n = 58) by Petersen et al, ADNI-1 participants had significantly higher frequencies of ApoE ε4 allele (ADNI-1: 32 of 58 [55%] vs MSCA: 49 of 126 [38.9%]), amyloid–neurodegeneration (ADNI-1: 32 of 58 [55%] vs MSCA: 54 of 126 [42.9%]), and higher rates of progression from aMCI to dementia (ADNI-1: 14 of 58 [29%] vs MSCA: 14 of 26 [51%]). Despite the small numbers in some of these studies, higher estimates compared with the present findings show the issues...
worth noting when using information from clinic-based and volunteer studies, including the ADNI study, to design clinical trials.

The strengths of our study include the large sample size, high prevalence of amyloid positivity, and population-based, natural history design. The prospective design and high retention of participants provide reliable and valid information on longitudinal outcomes. The medical records linkage system enabled adjustment for nonparticipation bias and identification of incident dementia outcomes in persons lost to follow-up.

Limitations
Potential limitations of our study include nonparticipation bias, which was mitigated by IPW adjustments. By design, prevalence of amyloid positivity are generalizable to the population without dementia only. Neurodegeneration was not considered, but the frequencies and outcomes of the National Institutes on Aging-Alzheimer’s Association stages in MCSA participants who have no cognitive impairment or had MCI have been published.5,6,10 The present cohort was 98% white; given the homogeneity of the cohort, the findings may not be generalizable to studies with participants of races/ethnicities with a higher prevalence of risk factors, who therefore may have higher rates of progression.

Conclusions
The study findings may be informative for design of primary and secondary AD prevention trials. The sex differences in outcomes remain to be validated.

REFERENCES
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