



LUND UNIVERSITY

Prevalence of cerebral amyloid pathology in persons without dementia: a meta-analysis.

Jansen, Willelmin J; Ossenkoppele, Rik; Knol, Dirk L; Tijms, Betty M; Scheltens, Philip; Verhey, Frans R J; Visser, Pieter Jelle; Aalten, Pauline; Aarsland, Dag; Alcolea, Daniel; Alexander, Myriam; Almdahl, Ina S; Arnold, Steven E; Baldeiras, Inês; Barthel, Henryk; van Berckel, Bart N M; Bibeau, Kristen; Blennow, Kaj; Brooks, David J; van Buchem, Mark A; Camus, Vincent; Cavedo, Enrica; Chen, Kewei; Chetelat, Gael; Cohen, Ann D; Drzezga, Alexander; Engelborghs, Sebastiaan; Fagan, Anne M; Fladby, Tormod; Fleisher, Adam S; van der Flier, Wiesje M; Ford, Lisa; Förster, Stefan; Fortea, Juan; Foskett, Nadia; Frederiksen, Kristian S; Freund-Levi, Yvonne; Frisoni, Giovanni B; Froelich, Lutz; Gabryelewicz, Tomasz; Gill, Kiran Dip; Gkatzima, Olymbia; Gómez-Tortosa, Estrella; Gordon, Mark Forrest; Grimmer, Timo; Hampel, Harald; Hausner, Lucrezia; Hellwig, Sabine; Herukka, Sanna-Kaisa; Hildebrandt, Helmut

Published in:

JAMA: The Journal of the American Medical Association

DOI:

[10.1001/jama.2015.4668](https://doi.org/10.1001/jama.2015.4668)

2015

[Link to publication](#)

Citation for published version (APA):

Jansen, W. J., Ossenkoppele, R., Knol, D. L., Tijms, B. M., Scheltens, P., Verhey, F. R. J., Visser, P. J., Aalten, P., Aarsland, D., Alcolea, D., Alexander, M., Almdahl, I. S., Arnold, S. E., Baldeiras, I., Barthel, H., van Berckel, B. N. M., Bibeau, K., Blennow, K., Brooks, D. J., ... Zetterberg, H. (2015). Prevalence of cerebral amyloid pathology in persons without dementia: a meta-analysis. *JAMA: The Journal of the American Medical Association*, 313(19), 1924-1938. <https://doi.org/10.1001/jama.2015.4668>

Total number of authors:

129

General rights

Unless other specific re-use rights are stated the following general rights apply:

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal

LUND UNIVERSITY

PO Box 117
221 00 Lund
+46 46-222 00 00

Original Investigation

Prevalence of Cerebral Amyloid Pathology in Persons Without Dementia

A Meta-analysis

Willemijn J. Jansen, MSc; Rik Ossenkoppele, PhD; Dirk L. Knol, PhD; Betty M. Tijms, PhD; Philip Scheltens, MD, PhD; Frans R. J. Verhey, MD, PhD; Pieter Jelle Visser, MD, PhD; and the Amyloid Biomarker Study Group

IMPORTANCE Cerebral amyloid- β aggregation is an early pathological event in Alzheimer disease (AD), starting decades before dementia onset. Estimates of the prevalence of amyloid pathology in persons without dementia are needed to understand the development of AD and to design prevention studies.

OBJECTIVE To use individual participant data meta-analysis to estimate the prevalence of amyloid pathology as measured with biomarkers in participants with normal cognition, subjective cognitive impairment (SCI), or mild cognitive impairment (MCI).

DATA SOURCES Relevant biomarker studies identified by searching studies published before April 2015 using the MEDLINE and Web of Science databases and through personal communication with investigators.

STUDY SELECTION Studies were included if they provided individual participant data for participants without dementia and used an a priori defined cutoff for amyloid positivity.




DATA EXTRACTION AND SYNTHESIS Individual records were provided for 2914 participants with normal cognition, 697 with SCI, and 3972 with MCI aged 18 to 100 years from 55 studies.

MAIN OUTCOMES AND MEASURES Prevalence of amyloid pathology on positron emission tomography or in cerebrospinal fluid according to AD risk factors (age, apolipoprotein E [*APOE*] genotype, sex, and education) estimated by generalized estimating equations.

RESULTS The prevalence of amyloid pathology increased from age 50 to 90 years from 10% (95% CI, 8%-13%) to 44% (95% CI, 37%-51%) among participants with normal cognition; from 12% (95% CI, 8%-18%) to 43% (95% CI, 32%-55%) among patients with SCI; and from 27% (95% CI, 23%-32%) to 71% (95% CI, 66%-76%) among patients with MCI. *APOE*- $\epsilon 4$ carriers had 2 to 3 times higher prevalence estimates than noncarriers. The age at which 15% of the participants with normal cognition were amyloid positive was approximately 40 years for *APOE* $\epsilon 4\epsilon 4$ carriers, 50 years for $\epsilon 2\epsilon 4$ carriers, 55 years for $\epsilon 3\epsilon 4$ carriers, 65 years for $\epsilon 3\epsilon 3$ carriers, and 95 years for $\epsilon 2\epsilon 3$ carriers. Amyloid positivity was more common in highly educated participants but not associated with sex or biomarker modality.

CONCLUSIONS AND RELEVANCE Among persons without dementia, the prevalence of cerebral amyloid pathology as determined by positron emission tomography or cerebrospinal fluid findings was associated with age, *APOE* genotype, and presence of cognitive impairment. These findings suggest a 20- to 30-year interval between first development of amyloid positivity and onset of dementia.

JAMA. 2015;313(19):1924-1938. doi:10.1001/jama.2015.4668
Corrected on May 19, 2015.

-  Editorial page 1913
-  Related article page 1939
-  Supplemental content at jama.com

Author Affiliations: Author affiliations are listed at the end of this article.

Authors/Group Information: Members of the Amyloid Biomarker Study Group are listed at the end of the article.

Corresponding Author: Willemijn J. Jansen, MSc, Department of Psychiatry and Neuropsychology, School for Mental Health and Neuroscience, Alzheimer Center Limburg, Maastricht University, PO Box 616, 6200 MD, Maastricht, the Netherlands (willemijn.jansen@maastrichtuniversity.nl) and Pieter Jelle Visser, MD, PhD (pj.visser@maastrichtuniversity.nl).

Alzheimer disease (AD) is the most common cause of dementia, with a worldwide prevalence of about 25 million in 2010, expected to be doubled by 2030 because of increased life expectancy.¹ The earliest recognizable pathological event in AD is cerebral amyloid- β aggregation.² This pathology may be present up to 20 years before the onset of dementia.^{3,4} Novel research criteria for AD in individuals without dementia emphasize the presence of amyloid pathology to define the first stage of the disease.^{5,6}

Prevalence estimates of amyloid pathology in persons without dementia are needed to better understand the development of AD and to facilitate the design of AD prevention studies. Initiation of treatment for AD in the prodementia phase, when neuronal damage is still limited, may be crucial to have clinical benefit.⁷ Neuropathological studies have reported prevalences of amyloid pathology in nondemented individuals ranging between 10% and 60%.^{8,9} Studies that assessed amyloid pathology in nondemented individuals during life using biomarkers in cerebrospinal fluid (CSF) or on positron emission tomography (PET) also showed large variability in prevalence estimates (10%-70%).¹⁰⁻¹³ This variability may have resulted from small sample sizes, differences in study design, and participant selection.

The aim of this study was to estimate the prevalence of amyloid pathology as assessed by biomarkers in nondemented individuals with an individual participant meta-analysis. We estimated the prevalence in participants with normal cognition, subjective cognitive impairment (SCI), and mild cognitive impairment (MCI) and investigated the relation with known risk factors for AD-type dementia, including age, sex, education, and *APOE* genotype. We also tested the association of biomarker modality and recruitment strategies with prevalence estimates and compared age-specific estimates of amyloid positivity in participants with normal cognition with the prevalence of AD-type dementia in the general population.

Methods

To identify relevant biomarker studies, the MEDLINE and Web of Science databases were searched for studies published before April 2015. The search terms used for PET studies were *PET* and (*Pittsburgh* or *PiB* or *florbetapir* or *AV-45* or *florbetaben* or *flutemetamol*) and (*amyloid* or *abeta*). The search terms used for CSF studies were (*CSF* or *cerebrospinal fluid*) and (*amyloid* or *abeta*). Titles and abstracts were reviewed and relevant studies were retrieved. Searches were restricted to articles published in the English language. Studies were included if amyloid biomarker data for participants without dementia were reported and an a priori defined cutoff for amyloid abnormality was used. Studies that included participants with neurological, psychiatric, or other diseases that might affect the central nervous system were excluded. We also asked partners from 2 European multicenter collaborative projects, BIOMARKAPD and EMIF-AD, to provide unpublished data (Figure 1).

As most published studies did not provide prevalence estimates according to age and other risk factors, we asked study contact persons to provide participant-level data or tabulated data according to 10-year age categories and unpublished data if available. Tabulated data were converted to participant-level data with the average age in the age category. The quality of primary articles from each study was systematically assessed using relevant criteria from the STROBE¹⁴ and QUADAS¹⁵ guidelines (eTable 1 in the Supplement). All participants gave written informed consent to participate. Studies were approved by the local ethics committees of the participating centers.

Data Collection and Operationalization

Information on study procedures was extracted from the publication or requested from the study contact person and used to create a common set of variables.

Cognitive Status, *APOE*, Sex, and Education

Normal cognition was defined as normal scores on cognitive tests, the absence of cognitive complaints for which medical help was sought, or both. Subjective cognitive impairment was defined as presence of a cognitive complaint with presentation at a health care facility but normal cognition on tests. Mild cognitive impairment was defined according to published criteria.^{16,17} These include a decline in memory or another cognitive domain reported by the patient, informant, or both and objectively verified by neuropsychological testing, in combination with no or minimal impairment in activities of daily living and not meeting criteria for dementia. Mild cognitive impairment was subclassified as amnesic MCI or nonamnesic MCI when possible. Information on *APOE*- $\epsilon 4$ carrier status (yes/no), *APOE* genotype, and years of education was retrieved. To describe the association of *APOE* genotype with age, we reported for each genotype the age at which 15% of the participants with normal cognition were amyloid positive as a proxy for first appearance of abnormal amyloid.

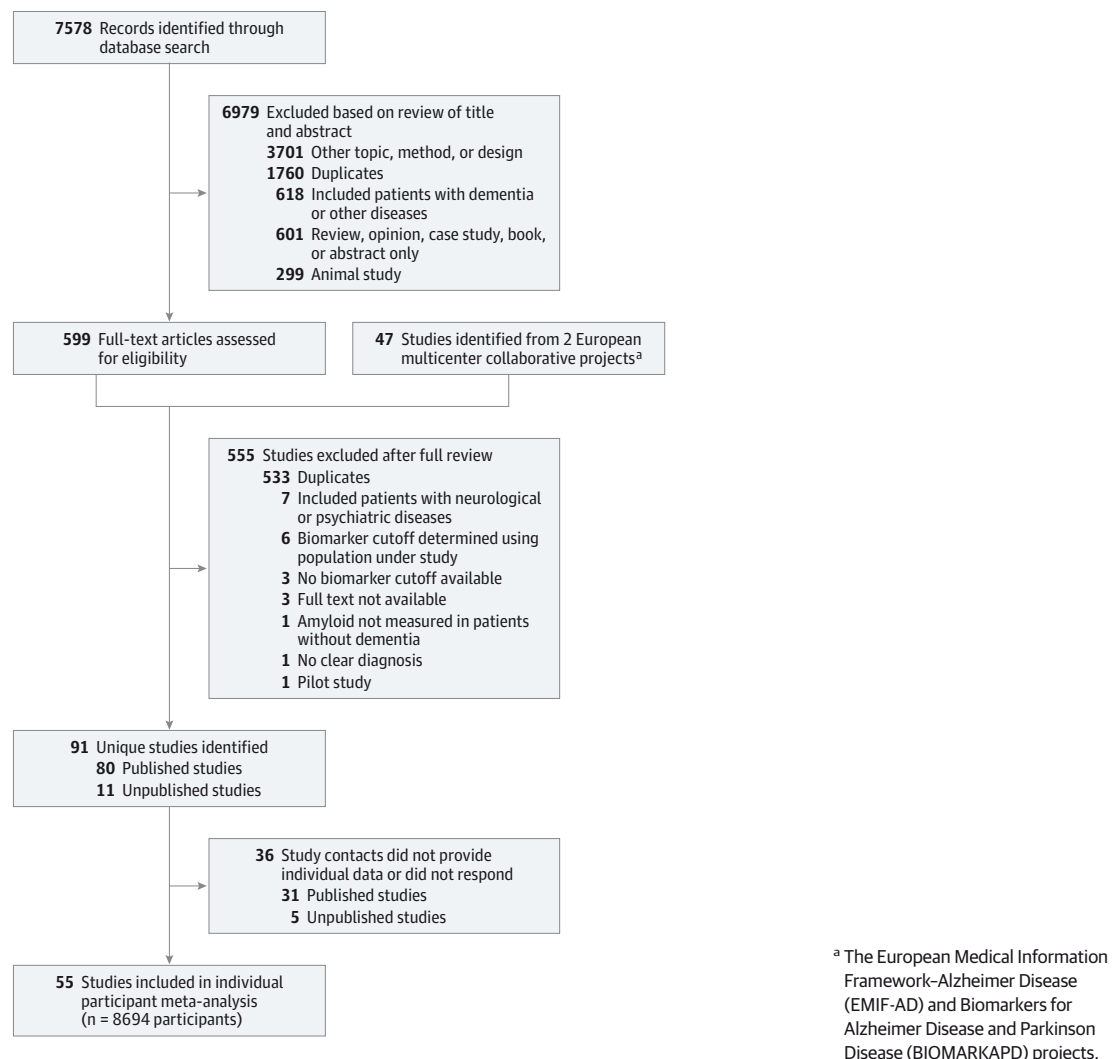
Setting and Recruitment

The study setting was classified as clinical if patients presented with cognitive complaints at a health care facility; research if patients were asked to participate in research by recruitment through advertisements or from other hospital departments; population-based if a random sample of the general population was included; or mixed if participants were recruited from a combination of settings.

Amyloid Assessment

Measurement details documented included amyloid tracer and assessment via visual scales or quantitative measures for PET studies and assay used to measure amyloid- β_{1-42} levels for CSF studies. Positron emission tomography and CSF biomarkers were dichotomized as negative (normal) or positive (abnormal) according to study-specific cutoffs. (See eTables 2 and 3 in the Supplement for measurement details.) For participants who had both PET and CSF amyloid measures, we selected the first amyloid measure in time.

Figure 1. Flow Diagram of Literature Search and Study Selection



Comparison With Prevalence of AD-Type Dementia

Age- and *APOE*-specific prevalence data of AD-type dementia were obtained through a meta-analysis or from published lifetime risk data for AD-type dementia¹⁸ as described in the eMethods in the Supplement.

Number Needed to Screen

To use the prevalence estimates in selecting participants at risk for amyloid positivity for AD prevention studies, numbers needed to screen to identify 1 amyloid-positive participant were calculated as described in the footnote of eTable 6 in the Supplement.

Statistical Analysis

We conducted a meta-analysis with individual participant data, in which original research data were sought directly from study contact persons, combined, and reanalyzed centrally. Generalized estimating equations (GEEs) were used to estimate the prevalence and odds ratios (ORs). Generalized estimating equations allow for analysis of binary correlated

data such that participant-level data on the prevalence from all studies could be modeled while simultaneously accounting for the clustering of participants within studies. We assumed a logit link function for binary outcome with an exchangeable correlation structure to account for within-study correlation. Analyses were performed using SPSS version 20.0 (IBM) with the *genlin* command. They were conducted using the total study population unless specified otherwise.

The main analyses were performed with cognitive status (normal cognition, SCI, MCI), age, sex, education, and *APOE-ε4* genotype as independent variables. Age was entered as a continuous measure centered at the median. Educational level was dichotomized at the median (high, ≥ 14 years, vs moderate to low, < 14 years). Secondary analyses tested associations with biomarker modality, MCI subtype, published vs unpublished studies, setting, and recruitment strategy while adjusting for cognitive status, age, and *APOE-ε4* carrier status. We tested 2-way and 3-way interactions between variables and age as a quadratic term, and

these were retained in the equation in case of a significant Wald statistic as indicated in table footers and figure legends. Analyses were repeated using natural cubic splines with knots at ages 50, 60, 70, and 80 years, but this did not improve the model. Estimated probabilities and 95% confidence intervals from the GEE analyses were used in tables. Probabilities estimated by GEE were compared with the observed probabilities in 5-year age groups.

The extent of between-study variability was investigated in several ways. In the total sample, the random intercept variance related to study was estimated in a random-effects analysis with the independent variables age, *APOE*- ϵ 4 carrier status, cognitive status, and interactions using the *xmlogit* function from Stata version 12.0 (Stata-Corp). This variance was expressed as an intraclass correlation coefficient. In diagnostic and *APOE* subgroups, heterogeneity within 5-year age strata was assessed with the I^2 statistic¹⁹ from a random-effects meta-analysis in Stata version 12.0. An I^2 statistic value greater than 50% was considered indicative for substantial heterogeneity.¹⁹ Center variability across the age range was visualized by plotting the prevalence for studies with more than 50 participants.

Significance level was set at $P < .05$ in 2-sided tests, uncorrected for multiple comparisons. When associations changed after correcting for multiple comparisons with the Bonferroni method, this was mentioned in the text or table. R version 3.1.2 (R Foundation for Statistical Computing) and GraphPad Prism version 6.0 (GraphPad Software) were used for graphs with estimated probabilities and 95% confidence intervals from the GEE analyses.

Results

The literature search resulted in 7578 publications; amyloid was assessed by PET in 890 and by CSF in 6688. From these, 599 were selected for full-text review. We identified 47 studies from the European multicenter projects (Figure 1). A total of 91 unique studies met inclusion criteria; the authors of 55 studies agreed to share data. Contact persons from 54 studies provided participant-level data and 1 provided tabulated data ($n = 137$). Of the 36 studies for which contact persons refused or did not reply, 31 were selected through the literature search and 5 from the European multicenter studies. Characteristics of the 31 excluded published studies did not differ from those of the 55 included studies (eTable 4 in the Supplement).

Study Characteristics

Of the selected studies, 45 were single-center and 10 were multicenter studies. (eTable 5 in the Supplement shows detailed study information.) Forty-one studies provided data for participants with normal cognition, 20 for patients with SCI, and 47 for patients with MCI. Of the MCI studies, 8 classified patients with MCI as amnesic MCI or nonamnesic MCI, 10 studies only included patients with amnesic MCI, and all other studies used a broad MCI definition or did not specify MCI subtype. Information on *APOE*- ϵ 4 carrier status

was provided by 41 studies and information on *APOE* genotype by 37 studies. All studies but 1 specified the sex of the participants. Information on years of education was available from 44 studies. Studies contributing data for participants with normal cognition were performed in a research setting in 95% ($n = 39$, selection through advertisements in 15, from hospitals in 10, and from other or unknown sources in 14) and a mixed setting in 5% ($n = 2$). Forty-six of the studies (98%) that included patients with SCI or MCI were performed in a clinical setting.

Amyloid-PET data were provided by 29 studies. Of these, 22 studies used [¹¹C]Pittsburgh compound-B (PiB), 9 [¹⁸F]florbetapir, 2 [¹⁸F]florbetaben, and 1 [¹⁸F]flutemetamol, including 5 that used multiple tracers. Eleven studies assessed the PET images by visual scales whereas 16 studies used quantitative assessment and 2 studies used both methods. Cerebrospinal fluid amyloid- β_{1-42} data were provided by 31 studies. The Innotech enzyme-linked immunosorbent assay (Fujirebio Europe) was used for CSF analysis in 29 studies and the xMAP Luminex assay in 2 studies. Two studies (1111 participants) provided data on both PET and CSF amyloid measures. Primary studies were assessed with the quality rating criteria, and typically met all criteria, although bias could not be assessed in 37 publications and participant flow remained unclear in 2 publications (eTable 1 in the Supplement).

Participant Characteristics

We included 7583 participants from 55 studies, of whom 2914 (38%) had normal cognition, 697 (9%) SCI, and 3972 (52%) MCI. Amyloid positivity was assessed with PET for 2370 participants (31%; 1346 normal cognition, 35 SCI, 989 MCI) and with CSF for 5213 participants (69%; 1568 normal cognition, 662 SCI, 2983 MCI). Baseline characteristics according to cognitive status are shown in **Table 1**. Participants with missing *APOE* data did not differ in amyloid positivity and sex from participants with *APOE* data but more often had limited education (63%) compared with participants who had these data available (48%, $\chi = 62.5$, $P < .001$). Participants with missing sex or education data did not differ in amyloid positivity, sex or education, and *APOE*- ϵ 4 carrier status from participants with these data.

Prevalence of Amyloid Positivity

Estimated probabilities of amyloid positivity according to cognitive status, *APOE*- ϵ 4 status, and age are displayed in **Figure 2**, **Figure 3A** and **B**, and **Table 2**. Observed prevalence estimates are shown in **Table 3**. The difference between the observed and predicted prevalence rates was less than 10% in more than 90% of the comparisons indicating good model fit. Amyloid positivity was about twice as common in patients with MCI compared with participants with normal cognition (mean difference, 25% [95% CI, 22% to 28%]; $P < .001$) or SCI (mean difference, 23% [95% CI, 14% to 32%]; $P < .001$), while it did not differ between participants with normal cognition and SCI (mean difference, 2% [95% CI, -6% to 10%]; $P = .62$). Amyloid positivity increased with age in all diagnostic groups.

Table 1. Baseline Study Participant Characteristics

Characteristic	Normal Cognition (n = 2914)	SCI (n = 697)	MCI (n = 3972)
Age	(n = 2914)	(n = 697)	(n = 3971)
Mean (SD), y	66.8 (13.2)	64.2 (8.0)	70.2 (8.7)
Age groups, No. (%), y			
<40	140 (4.8)	1 (0.1)	1 (0.0)
40-44	28 (1.0)	3 (0.4)	10 (0.3)
45-49	80 (2.7)	12 (1.7)	31 (0.8)
50-54	178 (6.1)	48 (6.9)	113 (2.8)
55-59	258 (8.9)	158 (22.7)	349 (8.8)
60-64	361 (12.4)	170 (24.4)	541 (13.6)
65-69	530 (18.2)	126 (18.1)	763 (19.2)
70-74	567 (19.5)	103 (14.8)	883 (22.2)
75-79	380 (13.0)	56 (8.0)	745 (18.8)
80-84	263 (9.0)	16 (2.3)	385 (9.7)
85-89	102 (3.5)	4 (0.6)	131 (3.3)
≥90	27 (0.9)	0	19 (0.5)
Sex, No. (%)	(n = 2796)	(n = 697)	(n = 3972)
Female	1537 (55.0)	348 (49.9)	1839 (46.3)
Male	1259 (45.0)	349 (50.1)	2133 (53.7)
Education	(n = 2280)	(n = 364)	(n = 2926)
Mean (SD), y	14.6 (3.6)	12.1 (4.3)	12.5 (4.4)
Education by category, No. (%)	(n = 2280)	(n = 539)	(n = 3099)
<14 y	815 (35.7)	356 (66.0)	1854 (59.8)
≥14 y	1465 (64.3)	183 (34.0)	1245 (40.2)
MMSE score ^a	(n = 2592)	(n = 693)	(n = 3910)
Mean (SD)	29.0 (1.3)	28.4 (1.5)	26.8 (2.5)
Assessment by PET biomarker	1346 (46.2)	35 (5.0)	989 (24.8)
Assessment by CSF biomarker	1568 (53.8)	662 (95.0)	2983 (75.2)
Biomarker abnormal, No. (%)			
Amyloid PET	328 (24.4)	8 (22.8)	523 (52.9)
CSF β amyloid	415 (26.5)	144 (21.8)	1513 (50.7)
APOE-ε4 carrier status, No. (%)	(n = 2289)	(n = 533)	(n = 3118)
APOE-ε4 negative	1614 (70.5)	322 (60.4)	1650 (52.9)
APOE-ε4 positive	675 (29.5)	211 (39.6)	1468 (47.1)
APOE genotype, No. (%)	(n = 2130)	(n = 533)	(n = 2837)
ε2ε2	10 (0.5)	1 (0.2)	5 (0.2)
ε2ε3	255 (12.0)	49 (9.2)	211 (7.4)
ε2ε4	41 (1.9)	13 (2.4)	62 (2.2)
ε3ε3	1228 (57.7)	272 (51.0)	1267 (44.7)
ε3ε4	531 (24.9)	178 (33.4)	991 (34.9)
ε4ε4	65 (3.1)	20 (3.8)	301 (10.6)

Abbreviations: APOE, apolipoprotein E; CSF, cerebrospinal fluid; MCI, mild cognitive impairment; MMSE, Mini Mental State Examination; PET, positron emission tomography; SCI, subjective cognitive impairment.

^a Range 0-30, with 30 as the best score.

APOE-ε4 carriers had 10% to 40% higher absolute prevalence estimates than noncarriers in each diagnostic group (Table 2, Figure 3A and B). At the median age of 70 years, the prevalence estimates were different between all APOE genotypes in participants with normal cognition, except for those of the ε2ε4 and ε3ε4 genotypes, which did not differ from each other (mean difference ε4ε4 vs ε3ε4, 38% [95% CI, 22% to 53%]; $P < .001$, vs ε2ε4, 28% [95% CI, 7% to 49%]; $P = .008$, vs ε3ε3, 60% [95% CI, 44% to 75%]; $P < .001$, vs ε2ε3, 73% [95% CI, 58% to 87%]; $P < .001$; mean difference ε3ε4 vs ε2ε4, 9% [95% CI, -1% to 20%]; $P = .08$, vs ε3ε3, 22% [95% CI, 18% to 26%]; $P < .001$, vs ε2ε3, 35%

[95% CI, 29% to 40%]; $P < .001$; mean difference ε2ε4 vs ε3ε3, 31% [95% CI, 21% to 42%]; $P < .001$, vs ε2ε3, 44% [95% CI, 31% to 57%]; $P < .001$; mean difference ε3ε3 vs ε2ε3, 13% [95% CI, 8% to 17%]; $P < .001$) (Figure 3C).

After correction for multiple comparisons, ε2ε4 and ε4ε4 showed no statistically significant difference ($P = .08$). None of the 10 participants with ε2ε2 were amyloid positive. APOE genotype was associated with the age at onset of amyloid positivity. For example, the age at which 15% of the participants with normal cognition were amyloid positive was approximately 40 years for ε4ε4 carriers, 50 years for ε2ε4 carriers, 55 years for ε3ε4 carriers, 65 years for ε3ε3 carriers,

and 95 years for $\epsilon 2\epsilon 3$ carriers. In patients with SCI, prevalence of amyloid pathology according to *APOE* genotype was similar to participants with normal cognition in all age groups (mean difference, 1% [95% CI, -11% to 12%]; $P = .92$). In patients with MCI, the prevalence differed between genotypes at the median age of 70 years, while again the $\epsilon 2\epsilon 4$ and $\epsilon 3\epsilon 4$ genotypes did not differ from each other; the difference between the $\epsilon 2\epsilon 4$ and $\epsilon 3\epsilon 3$ genotypes was not statistically significant (mean difference $\epsilon 4\epsilon 4$ vs $\epsilon 3\epsilon 4$, 23% [95% CI, 17% to 29%]; $P < .001$, vs $\epsilon 2\epsilon 4$, 33% [95% CI, 14% to 51%]; $P = .001$, vs $\epsilon 3\epsilon 3$, 54% [95% CI, 47% to 60%]; $P < .001$, vs $\epsilon 2\epsilon 3$, 64% [95% CI, 57% to 71%]; $P < .001$; mean difference $\epsilon 3\epsilon 4$ vs $\epsilon 2\epsilon 4$, 10% [95% CI, -9% to 28%]; $P = .31$, vs $\epsilon 3\epsilon 3$, 31% [95% CI, 25% to 37%]; $P < .001$, vs $\epsilon 2\epsilon 3$, 41% [95% CI, 34% to 48%]; $P < .001$; mean difference $\epsilon 2\epsilon 4$ vs $\epsilon 3\epsilon 3$, 21% [95% CI, -1% to 43%]; $P = .06$, vs $\epsilon 2\epsilon 3$, 31% [95% CI, 9% to 53%]; $P = .005$; mean difference $\epsilon 3\epsilon 3$ vs $\epsilon 2\epsilon 3$, 10% [95% CI, 6% to 14%]; $P < .001$) (Figure 3D).

Patients with MCI and the *APOE* $\epsilon 2\epsilon 2$ genotype were not included in the analysis because of the small sample size ($n = 5$, of whom 1 was amyloid positive). The prevalence of amyloid pathology in patients with MCI at age 70 years was 89% (95% CI, 81%-94%) for $\epsilon 4\epsilon 4$ carriers, 66% (95% CI, 60%-72%) for $\epsilon 3\epsilon 4$ carriers, 57% (95% CI, 35%-76%) for $\epsilon 2\epsilon 4$ carriers, 35% (95% CI, 31%-40%) for $\epsilon 3\epsilon 3$ carriers, and 25% (95% CI, 19%-32%) for $\epsilon 2\epsilon 3$ carriers. Table 4 shows the ORs for amyloid positivity of the *APOE* genotypes relative to the $\epsilon 3\epsilon 3$ genotype at age 70 years for participants with normal cognition and MCI.

The prevalence of amyloid pathology at the mean age was 5% higher (95% CI, 1% to 8%; $P = .005$) in participants with an education above the median ($n = 2530$) than in those with education below the median ($n = 2415$) regardless of cognitive status, age, and *APOE*- $\epsilon 4$ carrier status (eFigure 1 in the Supplement). There was no significant association with or interaction between sex and any of the risk factors for amyloid positivity (mean difference, 1% [95% CI, -1% to 3%]; $P = .52$).

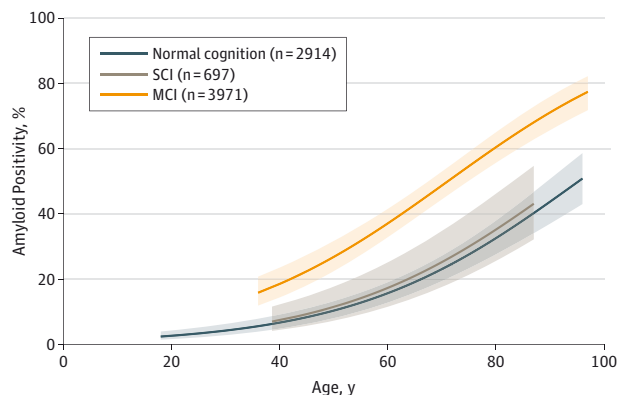
Comparison With Prevalence of AD-Type Dementia

The age-related increase in amyloid positivity in participants with normal cognition paralleled age-specific AD-type dementia prevalence estimates, with an intervening period of about 20 years (Figure 4A). Similarly, *APOE* genotype-specific estimates of amyloid positivity paralleled *APOE* genotype-specific lifetime risks of AD-type dementia with a difference of 25 to 30 years (Figure 4B).

Number Needed to Screen

The numbers of participants needed to screen (NNS) to identify 1 amyloid-positive person are displayed according to age, cognitive status, and *APOE* genotype in eTable 6 in the Supplement. The NNS varied from 1.0 (95% CI, 1.0-1.1), for persons with normal cognition or MCI who were older than 70 years with the *APOE* $\epsilon 4\epsilon 4$ genotype, to 16.7 (95% CI, 11.1-25.0), for persons with normal cognition aged 50 years without an *APOE*- $\epsilon 4$ allele. If *APOE* genotype is unknown, participants need to be screened for this first. The number

Figure 2. Association of Age With Prevalence Estimates of Amyloid Positivity According to Cognitive Status



The prevalence estimates were generated from generalized estimating equations. The model included age and cognitive status as predictors. Shading indicates 95% CIs; SCI, subjective cognitive impairment; MCI, mild cognitive impairment.

of participants for whom *APOE* genotyping needs to be performed to find 1 participant with that particular *APOE* genotype who is amyloid positive varied between 3.5 (95% CI, 2.8-4.3), for persons with normal cognition aged 90 years without an *APOE*- $\epsilon 4$ allele, to 89.6 (95% CI, 64.5-129.0), for persons with normal cognition aged 50 years with the *APOE* $\epsilon 4\epsilon 4$ genotype.

Assessment of Study-Related Heterogeneity

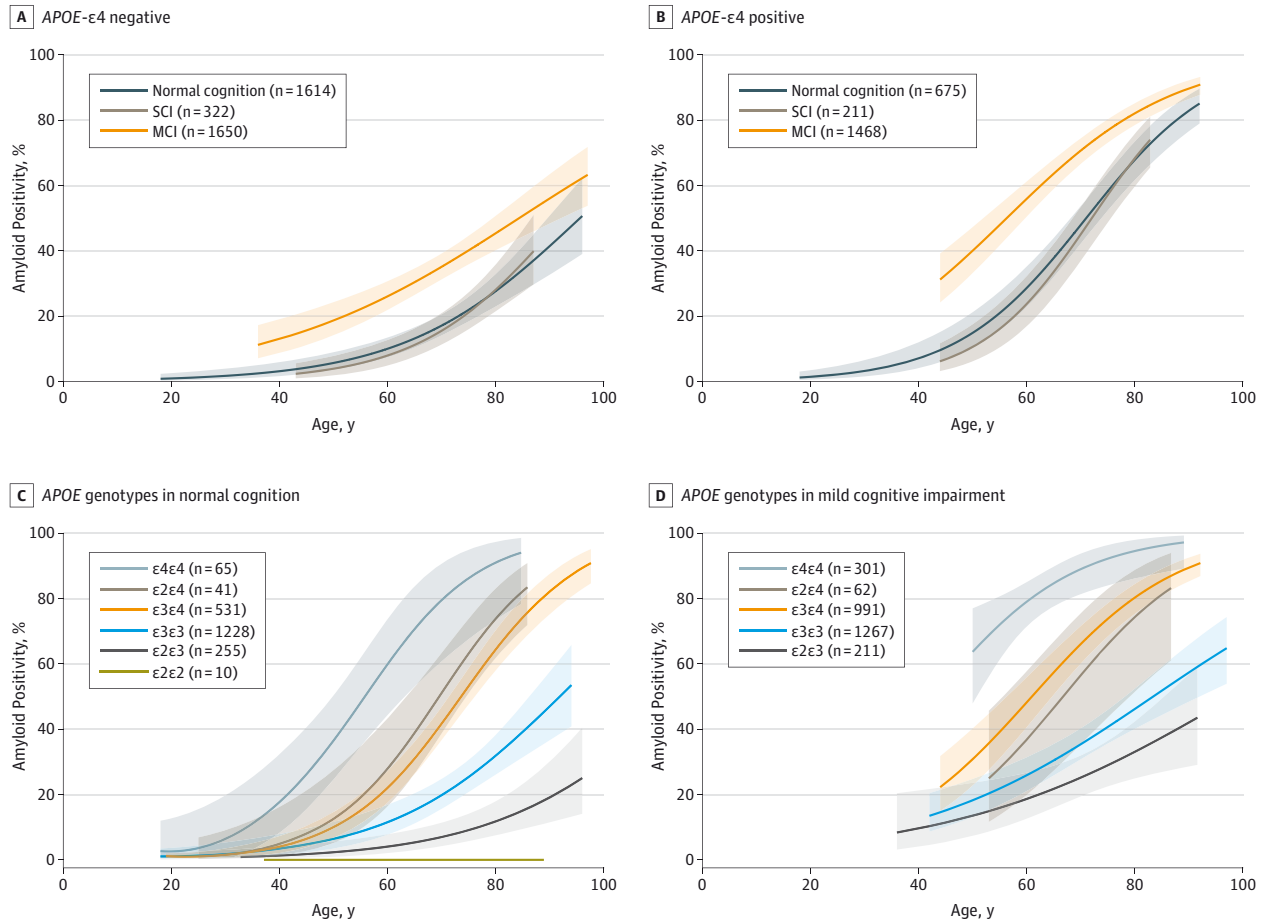
In the total study population, the intraclass correlation coefficient for study-related random intercept variance was 0.085, indicating minor heterogeneity among studies. Within age, *APOE*- $\epsilon 4$, and diagnostic subgroups, heterogeneity was not substantial according to the I^2 statistic, except for 2 of 54 subgroups (50%-60% in age group 65-69 years of SCI *APOE*- $\epsilon 4$ carriers and in age group 75-79 years of MCI *APOE*- $\epsilon 4$ noncarriers) (eTable 7 in the Supplement).

Visual inspection of variability in prevalence estimates across age in studies with at least 50 participants also indicated that between-study variability was small (eFigure 2 in the Supplement).

Post Hoc Analyses

The biomarker used to assess amyloid positivity was not associated with prevalence (mean difference, 0% [95% CI, -7% to 8%]; $P = .87$) for participants with normal cognition or MCI ($n = 6885$). Patients with SCI were excluded because amyloid was measured with PET in only 5% of participants. While adjusting for *APOE*- $\epsilon 4$ carrier status and age, amyloid prevalence at the mean age was higher in patients with amnesic MCI ($n = 1405$) than in patients with nonamnesic MCI ($n = 225$, 58% [95% CI, 48% to 67%] vs 47% [95% CI, 35% to 60%], mean difference, 11% [95% CI, 0% to 21%]; $P = .03$) and higher in patients with nonamnesic MCI than in participants with normal cognition ($n = 2289$, mean difference, 15% [95% CI, 2% to 28%]; $P = .03$). The prevalence

Figure 3. Association of Age With Prevalence Estimates of Amyloid Positivity According to Cognitive Status and Apolipoprotein E (APOE) Genotype



The model for the analyses in panels A and B included age, cognitive status, APOE-ε4 status, an interaction between age and cognitive status, and an interaction between age and APOE-ε4 status as predictors. The models for the analyses in panels C and D included age, cognitive status, APOE genotype, an interaction between age and cognitive status, an interaction between age and APOE genotype, and an interaction between cognitive status and APOE

genotype as predictors. In panel C, none of the 10 participants with ε2ε2 were amyloid positive, and no 95% confidence interval is provided for this group. In panel D, data of participants with ε2ε2 are not shown because of the small sample size (n = 5). Shading indicates 95% CIs; SCI, subjective cognitive impairment; MCI, mild cognitive impairment.

did not differ between amnesic MCI (n = 1405) and MCI patients diagnosed using a broad or unspecified definition of MCI (n = 1487, mean difference, 3% [95% CI, -6% to 13%]; P = .51). Prevalence estimates did not differ for published and unpublished studies (eTable 8 in the Supplement). The prevalence in participants with normal cognition recruited via advertisements (n = 1868) was similar to that of participants recruited from hospital departments (n = 305, mean difference, 4% [95% CI, -13% to 21%]; P = .96).

Discussion

This amyloid biomarker study including individuals without dementia provides prevalence estimates of amyloid pathology over an age range of 18 to 100 years for persons with normal cognition, SCI, and MCI. The age at onset of amyloid positivity was associated with cognitive status and

the APOE genotype. At age 90 years, about 40% of the APOE-ε4 noncarriers and more than 80% of APOE-ε4 carriers with normal cognition were amyloid positive. Amyloid positivity was associated with education but not with sex or biomarker modality. The age-related prevalence of amyloid positivity in participants with normal cognition paralleled the age-related prevalence of AD-type dementia in the general population in an APOE genotype-specific way with a time lag of 20 to 30 years.

Patients with MCI had 20% to 30% higher prevalence estimates of amyloid positivity than those with normal cognition or SCI, supporting the view that MCI is a risk state for AD.¹⁶ Cognitively normal and SCI groups did not differ in amyloid positivity, suggesting that the presence of SCI in a memory clinic population might not be associated with an increased risk for AD. Previous studies in other settings showed inconsistent results regarding differences in amyloid positivity between cognitively normal and SCI participants,^{20,21} indicat-

Table 2. Prevalence Estimates of Amyloid Positivity According to Age, Cognitive Status, and APOE-ε4 Carrier Status^a

Age, y	Normal Cognition, % (95% CI)			SCI, % (95% CI)			MCI, % (95% CI)		
	Total	APOE-ε4-	APOE-ε4+	Total	APOE-ε4-	APOE-ε4+	Total	APOE-ε4-	APOE-ε4+
50	10.4 (8.1-13.3)	5.7 (3.6-8.9)	14.9 (10.2-21.2)	11.6 (7.3-17.8)	3.9 (1.9-7.8)	10.6 (6.2-17.5)	26.9 (22.5-31.7)	18.7 (14.2-24.2)	40.0 (33.2-47.2)
55	12.9 (10.3-16.0)	7.6 (5.2-11.0)	20.9 (15.5-27.5)	14.2 (9.3-21.2)	5.6 (3.1-10.0)	16.1 (10.4-24.0)	31.8 (27.5-36.4)	22.2 (17.8-27.3)	47.9 (41.7-54.2)
60	15.8 (12.9-19.1)	10.0 (7.4-13.5)	28.6 (22.9-35.1)	17.4 (11.6-25.2)	8.0 (4.9-12.7)	23.7 (16.9-32.2)	37.1 (32.9-41.6)	26.1 (21.9-30.7)	55.9 (50.5-61.2)
65	19.2 (16.0-22.9)	13.2 (10.4-16.6)	37.8 (32.0-43.9)	21.1 (14.4-29.7)	11.2 (7.6-16.3)	33.5 (25.9-42.5)	42.8 (38.7-47.1)	30.4 (26.5-34.6)	63.6 (59.0-68.0)
70	23.1 (19.5-27.2)	17.1 (14.1-20.6)	47.9 (42.2-53.7)	25.3 (17.7-34.8)	15.5 (11.3-20.9)	45.0 (36.9-53.4)	48.7 (44.5-53.0)	35.1 (31.3-39.2)	70.7 (66.6-74.4)
75	27.6 (23.4-32.3)	21.9 (18.4-25.9)	58.2 (52.3-63.8)	30.0 (21.4-40.3)	21.2 (16.1-27.3)	57.1 (48.7-65.1)	54.6 (50.2-59.0)	40.1 (35.9-44.6)	76.9 (73.1-80.2)
80	32.6 (27.6-38.0)	27.7 (23.0-32.9)	67.8 (61.6-73.5)	35.2 (25.6-46.2)	28.1 (21.5-35.8)	71.5 (63.0-78.8) ^b	60.4 (55.7-65.0)	45.4 (40.2-50.7)	82.1 (78.5-85.2)
85	38.0 (32.2-44.2)	34.2 (27.7-41.4)	76.2 (69.8-81.6)	40.8 (30.3-52.3)	36.3 (27.3-46.4)	74.0 (65.5-81.0) ^b	66.0 (60.8-70.7)	50.7 (44.3-57.1)	86.3 (82.9-89.2)
90	43.8 (37.0-50.7)	41.5 (32.7-50.8)	82.9 (76.6-87.7)	43.1 (32.2-54.7) ^b	39.9 (29.7-51.0) ^b		71.1 (65.7-75.9)	56.1 (48.3-63.5)	89.1 (85.9-91.7) ^b

Abbreviations: APOE, apolipoprotein E; MCI, mild cognitive impairment; SCI, subjective cognitive impairment.

^a The prevalence estimates were generated from generalized estimating equations. Amyloid positivity in the total group was modeled using age and cognitive status as predictors. Amyloid positivity according to APOE-ε4 status was modeled with age, cognitive status, APOE-ε4 status, an interaction

between age and cognitive status, and an interaction between age and APOE-ε4 status. Table 3 displays the number of participants and observed probabilities of amyloid positivity per age subgroup. No estimate was provided if the 5-year range around the indicated column age included no participants.

^b No participants available with the exact age; prevalence estimated at nearest age.

Table 3. Observed Probabilities of Amyloid Positivity^a

Age Group	Normal Cognition			SCI			MCI		
	Total	APOE-ε4-	APOE-ε4+	Total	APOE-ε4-	APOE-ε4+	Total	APOE-ε4-	APOE-ε4+
47.5-52.4 y	13.2 (15/114)	7.9 (5/63)	17.2 (5/29)	19.2 (5/26)	0.0 (0/8)	0.0 (0/8)	25.0 (16/64)	19.4 (7/36)	44.4 (8/18)
52.5-57.4 y	15.3 (38/249)	6.9 (8/116)	23.1 (15/65)	10.6 (12/113)	8.3 (4/48)	7.3 (3/41)	26.6 (78/293)	22.0 (24/109)	53.8 (42/78)
57.5-62.4 y	12.1 (36/296)	10.0 (16/160)	26.1 (12/46)	16.9 (29/171)	5.2 (5/96)	35.2 (19/54)	39.1 (181/463)	30.4 (58/191)	51.4 (95/185)
62.5-67.4 y	22.6 (110/485)	13.4 (31/232)	40.6 (54/133)	16.8 (24/143)	4.5 (3/66)	30.4 (14/46)	45.5 (303/666)	27.7 (74/267)	67.1 (171/255)
67.5-72.4 y	24.1 (128/530)	17.1 (50/292)	40.7 (55/135)	26.0 (32/123)	16.1 (9/56)	42.9 (12/28)	54.5 (461/845)	35.0 (104/297)	77.1 (272/353)
72.5-77.4 y	32.2 (164/510)	23.3 (70/301)	61.3 (65/106)	44.0 (33/75)	25.0 (7/28)	59.3 (16/27)	57.2 (494/864)	44.4 (154/347)	79.1 (250/316)
77.5-82.4 y	42.0 (111/264)	35.1 (60/171)	65.5 (36/55)	31.8 (7/22)	33.3 (3/9)		62.1 (323/520)	49.2 (117/238)	86.9 (153/176)
82.5-87.4 y	49.0 (103/210)	41.7 (55/132)	76.5 (39/51)	57.1 (8/14)	50.0 (4/8)		60.3 (135/224)	51.4 (57/111)	81.9 (59/72)
87.5-92.4 y	51.0 (25/49)	42.9 (15/35)	87.5 (7/8)				61.4 (35/57)	58.5 (24/41)	100.0 (7/7)

Abbreviations: APOE, apolipoprotein E; MCI, mild cognitive impairment; SCI, subjective cognitive impairment.

^a Data are observed probabilities in % (No. amyloid positive/No. total

subgroup). No estimates were provided if the age group included <5 participants.

ing that further research is needed on this. Patients with nonamnesic MCI had lower prevalence estimates of amyloid positivity than patients with amnesic MCI but higher than participants with normal cognition. This suggests that both amnesic MCI and nonamnesic MCI are associated with an increased risk for AD and that this risk is higher for patients with amnesic MCI. The observation that a substantial number of patients with MCI were not amyloid positive, even at older age, suggests that the MCI phenotype does not always have AD as underlying pathology. Possible non-AD causes in MCI may be hippocampal sclerosis, mild depression, or vascular damage.

Age was a risk factor for amyloid positivity, which is in line with the finding that age is an important risk factor for postmortem amyloid load²² and for AD-type dementia,²³ as also shown in Figure 4A. The prevalence of amyloid positivity in participants with normal cognition aged 50 to 60 years was somewhat higher than found in an earlier population-based study that was not included in our analysis.²⁴ This could relate to differences in recruitment strategy and assessment.

Relative to the APOE-ε3 allele, the APOE-ε4 risk allele was associated with a greater risk for amyloid positivity and de-

Table 4. Odds Ratios for the Association Between APOE Genotype and Amyloid Positivity at Age 70 Years^a

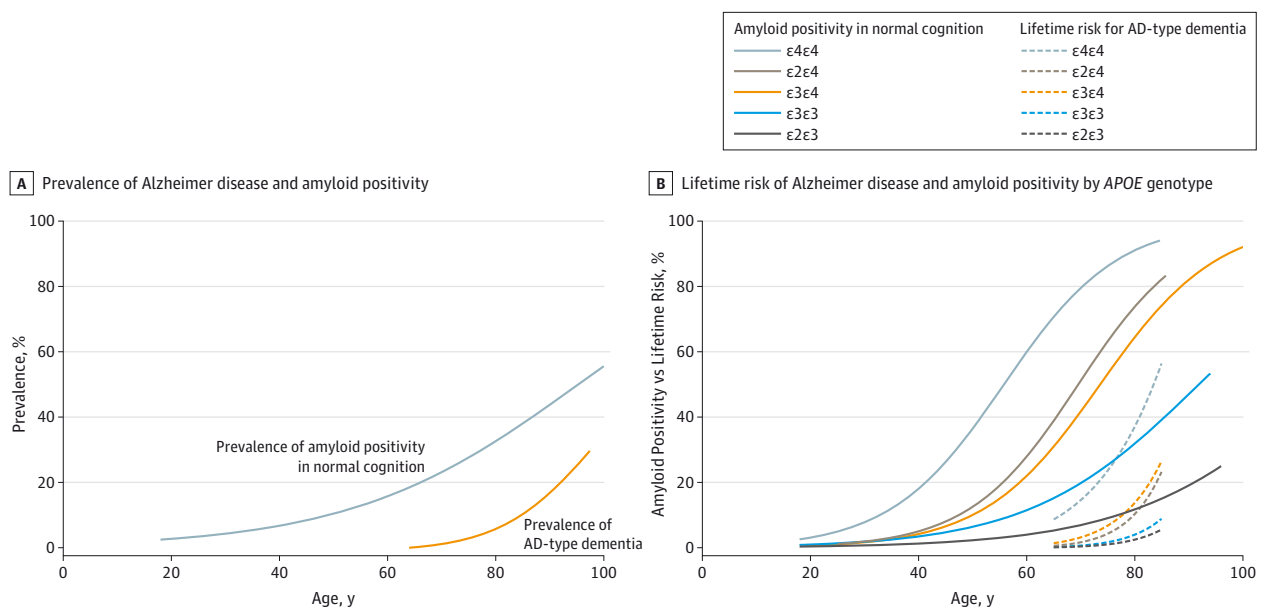
	APOE Genotype				
	ε3ε3	ε2ε3	ε2ε4	ε3ε4	ε4ε4
Normal cognition					
OR (95% CI)	1 [Reference]	0.34 (0.23-0.51)	4.29 (2.67-6.90)	2.94 (2.34-3.70)	18.76 (5.47-64.37)
P value		<.001	<.001	<.001	<.001
No. amyloid positive (%)	275 (22.4)	22 (8.6)	17 (41.5)	213 (40.1)	45 (69.2)
MCI					
OR (95% CI)	1 [Reference]	0.59 (0.48-0.73)	2.38 (0.98-5.81)	3.52 (2.73-4.55)	14.50 (8.14-25.81)
P value		<.001	.06	<.001	<.001
No. amyloid positive (%)	490 (38.7)	57 (27.0)	35 (56.5)	666 (67.2)	261 (86.7)

Abbreviations: APOE, apolipoprotein E; OR, odds ratio; MCI, mild cognitive impairment.

^a The ORs were generated from generalized estimating equations separately in participants with normal cognition and MCI. The models included age, APOE genotype, an interaction between age and APOE genotype, and a quadratic

age term in the normal cognition model as predictors. P values represent the significance of the OR for amyloid positivity compared with the ε3ε3 genotype. The ε2ε2 genotype was excluded because of the small number of participants in this group.

Figure 4. Comparison of the Prevalence of Amyloid Positivity With the Prevalence of and Lifetime Risks for Alzheimer Disease-Type Dementia



The prevalence estimates in panel A were estimated from a meta-analysis of 14 studies (eMethods in the Supplement). The prevalence estimates in panel B of amyloid positivity in participants with normal cognition are plotted against

published lifetime risks for Alzheimer disease (AD)-type dementia by APOE genotype (adapted from Genin et al¹⁸).

creased age at onset, while the APOE-ε2 allele had the opposite associations. This is similar to the relation of APOE genotype with the risk for AD-type dementia and age at onset of AD-type dementia as reported in clinical studies^{25,26} and the APOE genotype-specific lifetime risk for AD as shown in Figure 4B. The high prevalence of amyloid positivity in participants with normal cognition and MCI with ε2ε4 in the present study indicates that the detrimental relation of amyloid positivity with ε4 outweighs the protective association with ε2, in line with clinical AD studies.²⁷ The OR for amyloid pathology of the APOE genotypes relative to the ε3ε3 genotype was similar to the OR for AD-type dementia in case-control

studies.^{18,27} The strong association of the APOE genotype with amyloid positivity emphasizes APOE as an important target for treatment studies.^{28,29}

Highly educated participants had a higher prevalence of amyloid pathology than those with less formal education. This may seem in contrast with the finding that high education level is associated with a lower risk for AD-type dementia³⁰ but is in agreement with the cognitive reserve hypothesis.³¹ According to this hypothesis, nondemented individuals with a high level of education have a greater cognitive reserve such that they can sustain more amyloid pathology before developing dementia. Education itself was not associated with the ex-

tent of pathology at postmortem examination³² but might modify the relationship between AD pathology and expression of dementia,³³ resulting in higher amyloid positivity prevalence in nondemented highly educated participants. An alternative explanation would be that highly educated persons with amyloid pathology may be overrepresented in study participation or clinical care seeking due to self-selection bias.

Our finding that the prevalence of amyloid positivity was the same for men and women is in line with a previous neuropathological study showing no difference in neuritic and diffuse plaque load between men and women.³⁴ This finding is also in agreement with another earlier study,³⁵ as is our finding that there was no interaction between sex and *APOE*- ϵ 4 carrier status on amyloid positivity.

Although PET and CSF are thought to measure different types of amyloid- β ,³⁶ we did not find differences in amyloid positivity estimates for PET and CSF biomarkers. This is in line with published high concordance rates of 84% to 92% between the 2 biomarkers.^{37,38} Also, high levels of agreement have been reported for studies that provided more than 50 participants to our study in whom amyloid was assessed with both PET and CSF.^{39,40}

We pooled data from a large number of studies, and this may have introduced bias because of differences in the methods underlying amyloid assessment, cutoff definition, participant selection, diagnostic criteria, and other aspects of study design. However, in the total study sample; in age, *APOE*, and diagnostic subgroups; and on visual inspection of study-specific prevalences over age, there was limited evidence for study-related heterogeneity, which supports the pooling of data from different studies (eFigure 2 and eTable 7 in the Supplement). Moreover, the Alzheimer's Association Quality Control program for CSF biomarkers reported that overall concordance for diagnostic classification was high between centers despite analytical variance.⁴¹ We also explored the association of a number of study characteristics with the prevalence in post hoc analyses, but no relation was found. An advantage of participant-level analysis over aggregated pooling is that the power to detect subgroup effects is increased,⁴² while the risk for ecological bias is decreased.⁴³

A limitation of this study is that our participants with normal cognition were mostly recruited via advertisements, making this sample vulnerable to self-selection bias⁴⁴ and restricting generalizability to the general population. Participants with SCI and MCI were mostly recruited from clinical settings, rendering them dissimilar from these individuals in the general population. Participants with significant comorbid disorders are usually excluded from participation, and studies often used standardized cognitive screens, which also affects generalizability. Although MCI was not classified as amnesic or non-

amnesic for most participants, our findings indicate that we mostly included amnesic MCI patients because the prevalence estimates in amnesic MCI patients did not differ from those with a broad or unspecified definition of MCI. Still, patients with nonamnesic MCI had a lower prevalence than patients with amnesic MCI, suggesting that this is an important distinction to make in future research. Moreover, our prevalence estimates are based on cross-sectional data. The lifetime risk for individuals without dementia to develop amyloid pathology will be higher than the cross-sectional estimate at any age because amyloid-positive persons may die or progress to dementia at follow-up.

This study has several implications for understanding the development of AD. The observation that key risk factors for AD-type dementia are also risk factors for amyloid positivity in cognitively normal persons provides further evidence for the hypothesis that amyloid positivity in these individuals reflects early AD. Further support for this hypothesis comes from other studies that show that amyloid positivity in nondemented individuals is associated with memory impairment, cognitive decline, increased amyloid deposition and brain atrophy rates, and mortality.⁴⁵⁻⁴⁸ Our study also indicates that development of AD pathology can start as early as age 30 years, depending on the *APOE* genotype. Comparison with prevalence and lifetime risk estimates of AD-type dementia suggests a 20- to 30-year interval between amyloid positivity and dementia, implying that there is a large window of opportunity to start preventive treatments. Still, the exact interval between the onset of amyloid positivity and onset of AD-type dementia needs to be assessed by long-term follow-up studies because not all persons with amyloid pathology will become demented during their lifetime,⁴⁹ and not all individuals with a clinical diagnosis of AD-type dementia have amyloid pathology. Because of the uncertainty about whether and when an amyloid-positive individual without dementia will develop dementia, amyloid positivity in these individuals should not be equated with impending clinical dementia but rather be seen as a risk state. Our prevalence rates can be used as an inexpensive and noninvasive approach to select persons at risk for amyloid positivity.

Conclusions

Among persons without dementia, the prevalence of cerebral amyloid pathology as determined by PET imaging or CSF findings was associated with age, *APOE* genotype, and presence of cognitive impairment. These findings suggest a 20- to 30-year interval between first development of amyloid positivity and onset of dementia.

ARTICLE INFORMATION

Authors/Amyloid Biomarker Study Group

members include the byline authors as well as the following individuals: Pauline Aalten, PhD; Dag Aarsland, MD, PhD; Daniel Alcolea, MD; Myriam Alexander, PhD; Ina S. Almdahl, MD; Steven E. Arnold, MD; Inês Baldeiras, PhD;

Henryk Barthel, MD, PhD; Bart N. M. van Berckel, MD, PhD; Kristen Bibeau, PhD; Kaj Blennow, MD, PhD; David J. Brooks, MD, PhD; Mark A. van Buchem, MD, PhD; Vincent Camus, MD, PhD; Enrica Cavado, MSc; Kewei Chen, PhD; Gael Chetelat, PhD; Ann D. Cohen, PhD; Alexander Drzezga, MD, PhD; Sebastiaan Engelborghs, MD, PhD; Anne M. Fagan, PhD;

Tormod Fladby, MD, PhD; Adam S. Fleisher, MD, MAS; Wiesje M. van der Flier, PhD; Lisa Ford, MD; Stefan Förster, MD, PhD; Juan Fortea, PhD; Nadia Fosskett, MD, PhD; Kristian S. Frederiksen, MD, PhD; Yvonne Freund-Levi, MD, PhD; Giovanni B. Frisoni, MD; Lutz Froelich, MD, PhD; Tomasz Gabryelewicz, MD, PhD; Kiran Dip Gill, PhD; Olympia Gkatzima, MSc; Estrella Gómez-Tortosa, MD, PhD;

Mark Forrest Gordon, MD; Timo Grimmer, MD, PhD; Harald Hampel, MD, PhD; Lucrezia Hausner, MD, PhD; Sabine Hellwig, MD; Sanna-Kaisa Herukka, MD, PhD; Helmut Hildebrandt, PhD; Lianna Ishihara, PhD; Adrian Ivanoiu, MD, PhD; William J. Jagust, MD; Peter Johannsen, MD, PhD; Ramesh Kandimalla, PhD; Elisabeth Kapaki, MD, PhD; Aleksandra Klimkowicz-Mrowiec, MD, PhD; William E. Klunk, MD, PhD; Sebastian Köhler, PhD; Norman Koglin, PhD; Johannes Kornhuber, MD; Milica G. Kramberger, MD, PhD; Koen Van Laere, MD, PhD, DrSc; Susan M. Landau, PhD; Dong Young Lee, MD, PhD; Mony de Leon, EdD; Viviana Lisetti, MSc; Alberto Lleó, MD, PhD; Karine Madsen, MD, PhD; Wolfgang Maier, MD, PhD; Jan Marcusson, MD, PhD; Niklas Mattsson, MD, PhD; Alexandre de Mendonça, MD, PhD; Olga Meulenbroek, PhD; Philipp T. Meyer, MD, PhD; Mark A. Mintun, MD, PhD; Vincent Mok, MD; José Luis Molinuevo, MD, PhD; Hanne H. G. B. Møllergård, PhD; John C. Morris, MD; Barbara Mroczko, MD, PhD; Stefan Van der Mussele, PhD; Duk L. Na, MD, PhD; Andrew Newberg, MD, PhD; Agneta Nordberg, MD, PhD; Arto Nordlund, PhD; Gerald P. Novak, MD; George P. Paraskevas, MD, PhD; Lucilla Parnetti, MD, PhD; Gayan Perera, PhD; Oliver Peters, MD; Julius Popp, MD; Sudesh Prabhakar, MD, PhD; Gil D. Rabinovici, MD; Inez H. G. B. Ramakers, PhD; Lorena Rami, MSc; Catarina Resende de Oliveira, MD, PhD; Juha O. Rinne, MD, PhD; Karen M. Rodrigue, PhD; Eloy Rodríguez-Rodríguez, MD, PhD; Catherine M. Roe, PhD; Uros Rot, MD, PhD; Christopher C. Rowe, MD, PhD; Eckart Rütger, MD, PhD; Osama Sabri, MD, PhD; Pascual Sanchez-Juan, MD, PhD; Isabel Santana, MD, PhD; Marie Sarazin, MD, PhD; Johannes Schröder, MD, PhD; Christin Schütte, MSc; Sang W. Seo, MD, PhD; Femke Soetewey, MSc; Hilka Soininen, MD, PhD; Luiza Spuru, MD, PhD; Hanne Struyfs, MSc; Charlotte E. Teunissen, PhD; Magda Tsolaki, MD, PhD; Rik Vandenberghe, MD, PhD; Marcel M. Verbeek, PhD; Victor L. Villemagne, MD, PhD; Stephanie J. B. Vos, PhD; Linda J. C. van Waalwijk van Doorn, MSc; Gunhild Waldemar, MD, DMSc; Anders Wallin, MD, PhD; Åsa K. Wallin, MD, PhD; Jens Wiltfang, MD, PhD; David A. Wolk, MD; Marzena Zboch, MD, PhD; Henrik Zetterberg, MD, PhD.

Affiliations of Authors/Amyloid Biomarker Study

Group: Department of Psychiatry and Neuropsychology, School for Mental Health and Neuroscience, Alzheimer Center Limburg, Maastricht University, Maastricht, the Netherlands (Aalten, Köhler, Ramakers, Vos); Department of Neurology and Alzheimer Center, VU University Medical Center, Neuroscience Campus Amsterdam, Amsterdam, the Netherlands (van der Flier); Department of Radiology and Nuclear Medicine, VU University Medical Center, Neuroscience Campus Amsterdam, Amsterdam, the Netherlands (van Berckel); Department of Neurology, Memory and Aging Center, University of California, San Francisco (Rabinovici); Helen Wills Neuroscience Institute, University of California, Berkeley (Jagust, Landau); Department of Epidemiology and Biostatistics, VU University Medical Center, Amsterdam, the Netherlands (van der Flier); Center for Age-Related Medicine, Stavanger University Hospital, Stavanger, Norway (Aarsland); Neurology Department, Hospital de Sant Pau, Barcelona, Spain (Alcolea, Fortea, Lleó); Roche Products, Welwyn Garden City, United Kingdom (Alexander, Foskett, Perera); Department of Neurology, Akershus University Hospital,

Lørenskog, Norway (Almdahl, Fladby, Møllergård); Department of Neurology, University of Pennsylvania, Philadelphia (Arnold, Wolk); Center for Neuroscience and Cell Biology, Faculty of Medicine, Hospital Center University of Coimbra, Portugal (Baldeiras, Resende de Oliveira, Santana); Department of Nuclear Medicine, University of Leipzig, Leipzig, Germany (Barthel, Sabri); GlaxoSmithKline, Worldwide Epidemiology, Research Triangle Park, North Carolina (Bibeau); Institute of Neuroscience and Physiology, Sahlgrenska Academy at University of Gothenburg, Mölndal, Sweden (Blennow, Nordlund, A. Wallin, Zetterberg); Division of Neuroscience, Medical Research Council Clinical Sciences Centre, Imperial College London, London, United Kingdom (Brooks); Department of Radiology, Leiden University Medical Center, Leiden, the Netherlands (van Buchem); CHRU de Tours, CIC INSERM 1415, INSERM U930, and Université François Rabelais de Tours, Tours, France (Camus); Laboratory of Epidemiology, Neuroimaging and Telemedicine, IRCCS San Giovanni di Dio Fatebenefratelli, Brescia, Italy (Cavedo, Frisoni); Sorbonne University, University Pierre et Marie Curie, Paris 06, Institut de la Mémoire et de la Maladie d'Alzheimer (IM2A) and Institut du Cerveau et de la Moelle épinière (ICM), UMR S 1127, Hôpital de la Pitié-Salpêtrière Paris and CATI Multicenter Neuroimaging Platform, Paris, France (Cavedo); Banner Alzheimer's Institute, Phoenix, Arizona (Chen, Fleisher); Institut National de la Santé et de la Recherche Médicale (Inserm), U1077, Caen, France (Chetelat); University of Pittsburgh School of Medicine, Department of Psychiatry, Pittsburgh, Pennsylvania (Cohen, Klunk); Department of Nuclear Medicine, University of Cologne, Cologne, Germany (Drzezga); Reference Center for Biological Markers of Dementia (BIODEM), University of Antwerp, Antwerp, Belgium (Engelborghs, Van der Mussele, Soetewey, Struyfs); Knight Alzheimer's Disease Research Center, Department of Neurology, Washington University School of Medicine, St Louis, Missouri (Fagan, Morris, Roe); Eli Lilly, Indianapolis, Indiana (Fleisher); Department of Neurosciences, University of California, San Diego (Fleisher); Janssen Research and Development, Titusville, New Jersey (Ford, Novak); Department of Nuclear Medicine, Technischen Universität München, Munich, Germany (Förster); Memory Clinic, Danish Dementia Research Center, Rigshospitalet, Copenhagen, Denmark (Johannsen); Department of Geriatrics, Institution of NVS, Section of Clinical Geriatrics, Karolinska Institutet, Stockholm, Sweden (Freund-Levi); Department of Geriatric Psychiatry, Central Institute of Mental Health, Medical Faculty Mannheim, University of Heidelberg, Mannheim, Germany (Froelich, Hausner); Department of Neurodegenerative Disorders, Mossakowski Medical Research Centre Polish Academy of Sciences, Warsaw, Poland (Gabryelewicz); Postgraduate Institute of Medical Education and Research (PGIMER), Department of Biochemistry, Research Block-A, Chandigarh, India (Gill, Kandimalla); Third Department of Neurology, Aristotle University of Thessaloniki, Thessaloniki, Greece (Gkatzima, Tsolaki); Department of Neurology, Fundación Jiménez Díaz, Madrid, Spain (Gómez-Tortosa); Boehringer Ingelheim Pharmaceuticals, Ridgefield, Connecticut (Gordon); Department of Psychiatry and Psychotherapy, Klinikum rechts der Isar der Technischen Universität München, Munich, Germany

(Grimmer); AXA Research Fund and UPMC Chair Sorbonne Universités, Université Pierre et Marie Curie, Paris 06, Institut de la Mémoire et de la Maladie d'Alzheimer and INSERM U1127, Institut du Cerveau et de la Moelle épinière (ICM), Département de Neurologie, Hôpital de la Pitié-Salpêtrière, Paris, France (Hampel); Department of Psychiatry, Alzheimer Memorial Center and Geriatric Psychiatry Branch, Ludwig-Maximilian University, Munich, Germany (Hampel); Center of Geriatrics and Gerontology, University Hospital Freiburg, Freiburg, Germany (Hellwig); Center for Neurology, Hospital of Bremen-Ost, Bremen, Germany (Hildebrandt, Schütte); GlaxoSmithKline, Worldwide Epidemiology, Epidemiology, Genetic Epidemiology and Neurology, United Kingdom (Ishihara); Memory Clinic and Neurochemistry Laboratory, Saint Luc University Hospital, Institute of Neuroscience, Université catholique de Louvain, Brussels, Belgium (Ivanoiu); Radiation Oncology, Emory University, Atlanta, Georgia (Kandimalla); First Department of Neurology, Neurochemistry Unit and Cognitive and Movement Disorders Clinic, National and Kapodistrian University of Athens, Eginition Hospital, Athens, Greece (Kapaki, Paraskevas); Jagiellonian University College of Medicine, Krakow, Poland (Klimkowicz-Mrowiec); Piramal Imaging, Berlin, Germany (Koglin); Department of Psychiatry and Psychotherapy, Friedrich-Alexander University of Erlangen-Nuremberg, Erlangen, Germany (Kornhuber); Center for Cognitive Impairments, University Medical Centre Ljubljana, Ljubljana, Slovenia (Kramberger, Rot); Laboratory for Cognitive Neurology and Alzheimer Research Centre KU Leuven, Catholic University Leuven, Leuven, Belgium (Vandenberghe); Department of Neuropsychiatry, Seoul National University, College of Medicine, Seoul, South Korea (Lee); School of Medicine, Center for Brain Health, New York University, New York (de Leon); Section of Neurology, Center for Memory Disturbances, University of Perugia, Perugia, Italy (Lisetti, Parnetti); Neurobiology Research Unit, Copenhagen University Hospital, Copenhagen, Denmark (Madsen); Department of Psychiatry and Psychotherapy, University of Bonn, German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany (Maier); Geriatric Medicine, Department of Clinical and Experimental Medicine, University of Linköping, Linköping, Sweden (Marcusson); Institute of Molecular Medicine and Faculty of Medicine, University of Lisbon, Portugal (de Mendonça); Department of Geriatric Medicine, Radboud Alzheimer Center, Radboud University Medical Center, Nijmegen, the Netherlands (Meulenbroek); Department of Nuclear Medicine, University Hospital Freiburg, Freiburg, Germany (Meyer); Avid Radiopharmaceuticals, Philadelphia, Pennsylvania (Mintun); Lui Che Woo Institute of Innovative Medicine, Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Hong Kong SAR, China (Mok); Alzheimer's Disease and Other Cognitive Disorders Unit, IDIBAPS, Clinic University Hospital, Barcelona, Spain (Molinuevo, Rami); Department of Neurodegeneration Diagnostics, Leading National Research Centre in Białystok (KNOW), Medical University of Białystok, Białystok, Poland (Mroczko); Department of Neurology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea (Na, Seo); Myrna Brind Center of Integrative Medicine, Thomas Jefferson University and Hospital, Philadelphia, Pennsylvania

(Newberg); Dept NVS, Center for Alzheimer, Translational Alzheimer Neurobiology, Karolinska Institutet, and Geriatric Medicine, Karolinska University Hospital, Stockholm, Sweden (Nordberg); Department of Psychological Medicine, Institute of Psychiatry, Kings College London, London, United Kingdom (Perera); Department of Psychiatry and Psychotherapy, Charité Berlin, German Center for Neurodegenerative Diseases (DZNE), Berlin, Germany (Peters); Department of Psychiatry, Service of Old Age Psychiatry and Department of Clinical Neurosciences, Leenaards Memory Centre, University Hospital of Lausanne, Lausanne, Switzerland (Popp); Postgraduate Institute of Medical Education and Research (PGIMER), Department of Neurology, Nehru Hospital, Chandigarh, India (Prabhakar); Turku PET Centre and Division of Clinical Neurosciences Turku, University of Turku and Turku University Hospital, Turku, Finland (Rinne); Center for Vital Longevity, University of Texas at Dallas (Rodrigue); Neurology Service, Universitary Hospital Marqués de Valdecilla, IDIVAL, Santander, Spain (Rodríguez-Rodríguez, Sanchez-Juan); Department of Nuclear Medicine and Centre for PET, Austin Health, Melbourne, Australia (Rowe, Villemagne); Department of Psychiatry and Psychotherapy, University Medical Center, Georg-August University, Göttingen, Germany (Rüther, Wiltfang); Neurologie de la Mémoire et du Langage, Centre Hospitalier Sainte-Anne, Université Paris 5, Paris, France (Sarazin); Sektion Gerontopsychiatrie, Universität Heidelberg, Heidelberg, Germany (Schröder); Department of Neurology, University of Eastern Finland and Kuopio University Hospital, Kuopio, Finland (Herukka, Soininen); Department of Geriatrics-Gerontology-Gerontopsychiatry, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania (Spiru); Neurochemistry Laboratory and Biobank, Department of Clinical Chemistry, Neuroscience Campus Amsterdam, VU University Medical Center, Amsterdam, the Netherlands (Teunissen); Departments of Neurology and Laboratory Medicine, Donders Institute for Brain, Cognition and Behaviour, Radboud Alzheimer Center, Radboud University Medical Center, Nijmegen, the Netherlands (Verbeek, van Waalwijk van Doorn); Danish Dementia Research Center, Department of Neurology, Rigshospitalet, University of Copenhagen, Denmark (Frederiksen, Waldemar); Clinical Memory Research Unit, Clinical Sciences Malmö, Lund University, Lund, Sweden (Mattsson, Å. K. Wallin); Alzheimer Center, Wrocław Medical University, Scinawa, Poland (Zboch); UCL Institute of Neurology, Queen Square, London, United Kingdom (Zetterberg); Memory Clinic and LANVIE-Laboratory of Neuroimaging of Aging, University Hospitals, and University of Geneva, Geneva, Switzerland (Frisoni); Department of Imaging and Pathology, Catholic University Leuven, Leuven, Belgium (Van Laere).

Author Affiliations: Department of Psychiatry and Neuropsychology, School for Mental Health and Neuroscience, Alzheimer Center Limburg, Maastricht University, Maastricht, the Netherlands (Jansen, Verhey, Visser); Department of Neurology and Alzheimer Center, VU University Medical Center, Neuroscience Campus Amsterdam, Amsterdam, the Netherlands (Ossenkoppele, Tijms, Scheltens, Visser); Department of Radiology and Nuclear Medicine, VU University Medical Center, Neuroscience Campus Amsterdam, Amsterdam,

the Netherlands (Ossenkoppele); Department of Neurology, Memory and Aging Center, University of California, San Francisco (Ossenkoppele); Helen Wills Neuroscience Institute, University of California, Berkeley (Ossenkoppele); Department of Epidemiology and Biostatistics, VU University Medical Center, Amsterdam, the Netherlands (Knol).

Author Contributions: Ms Jansen and Dr Visser had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Jansen, Ossenkoppele, Verhey, Visser.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Jansen, Visser.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Jansen, Knol, Visser.

Administrative, technical, or material support: All authors.

Study supervision: Visser.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Scheltens reported having received grants from GE Healthcare, Piramal, and Merck, paid to his institution. Dr Verhey reported having received compensation as a speaker and consultant for Nutricia Advanced Medical Food. Dr Visser reported having received grants from EU/EFPIA Innovative Medicines Initiative Joint Undertaking, EU Joint Programme-Neurodegenerative Disease Research (JPND), ZonMw, and Bristol-Myers Squibb; having served as member of the advisory board of Roche Diagnostics; and having received nonfinancial support from GE Healthcare. Dr Aarsland reported having received research support or honoraria from Astra-Zeneca, H. Lundbeck, Novartis Pharmaceuticals, and GE Health. Dr Alexander reported being an employee of Roche Products. Dr Barthel reported having received speaker and consultant honoraria as well as travel expenses from Piramal Imaging (Berlin) and personal fees from Siemens Healthcare. Dr Bibeau reported being a share-holding employee of GlaxoSmithKline. Dr Blennow reported having received personal fees (advisory board) from Roche Diagnostics, IBL International, Novartis, and Eli Lilly. Dr Brooks reported having served as consultant for GE Healthcare. Dr Camus reported having received grants from the French Ministry of Health. Dr Chen reported having received grants from the National Institutes of Health (NIH). Dr Drzezga reported having received speaker honoraria and consulting fees from GE Healthcare, AVID/Lilly, and Piramal. Dr Fagan reported having received grants from NIH, Fred Simmons and Olga Mohan, and Charles and Joanne Knight Alzheimer's Research Initiative of the Washington University Knight Alzheimer's Disease Research Center; having received personal fees from IBL International, Roche, and AbbVie; and having a patent, 6,465,195 B2, "Predictive diagnostic for Alzheimer's disease," issued and a patent, PCT/US09/050255, "A risk factor and new therapeutic target for Alzheimer's disease," pending. Dr Fladby reported having a patent "Methods and compositions for monitoring phagocytic activity," PCT/US2011/062233, pending. Dr Fleisher reported having been a full-time employee of the Banner Alzheimer's Institute; being a full-time employee of Eli Lilly; maintaining a

voluntary faculty appointment at the University of California, San Diego; having been a member of data and safety monitoring boards for Merck, Pfizer, and the National Institute of Aging (NIA); having received grant funding from NIA and Avid Radiopharmaceutical; and having been a consultant for Eli Lilly, Grifols, Avid Radiopharmaceuticals, and Siemens Imaging. Dr van der Flier reported having received grants from Boehringer Ingelheim, Piramal Imaging, and Roche. Dr Förster reported having received personal fees (consultancy) from Piramal, Bayer, and GE. Dr Foskett reported being a full-time employee of Roche Prod and holding Roche shares and share options. Dr Frisoni reported having received grants and/or personal fees from Lilly, Bristol-Myers Squibb, Bayer, Lundbeck, Elan, AstraZeneca, Pfizer, Taurx, Wyeth, GE, Baxter, Avid, Roche, Piramal, and the Alzheimer's Association. Dr Gill reported having received grants from the Indian Council of Medical Research, New Delhi, India. Dr Gordon reported being a salaried employee of Boehringer Ingelheim Pharmaceuticals. Dr Grimmer reported having received personal fees from Eli Lilly. Dr Hampel reported having received grants, personal fees, and/or nonfinancial support from Boehringer-Ingelheim, Bristol-Myers Squibb, Elan, Novartis, Eisai, Pfizer, sanofi-aventis, Roche Pharmaceuticals and Diagnostics, GE Healthcare, Avid, Eli Lilly, GlaxoSmithKline Biologicals, Jung-Diagnostics, and Cytox and having a patent, "Method for predicting whether subjects with mild cognitive impairment (MCI) will develop Alzheimer's disease," pending; a patent, "3-Hydroxykynurenin im Serum als diagnostischer Marker für die Demenz vom Alzheimer-Typ," pending; a patent, "Neurodegenerative markers for psychiatric conditions," pending; a patent, "Ratio Aβ42/40 im Plasma in der Früh- und Differentialdiagnose der Alzheimer Krankheit," pending; a patent "Liquordiagnostisches in vitro Verfahren zur Diagnose von Demenz Erkrankungen und neuroinflammatorischen Erkrankungen," pending; and a patent, "In vitro Verfahren zur Diagnose von neurodegenerativen Erkrankungen," pending. Dr Hellwig reported having received grants from GE Healthcare and Medical Faculty, University of Freiburg. Dr Ishihara reported being an employee and shareholder of GlaxoSmithKline. Dr Jagust reported having received personal fees from Banner Alzheimer Institute/Genentech, Synarc/Bioclinica, and Novartis. Dr Kandimalla reported having received grants from the Indian Council of Medical Research, India. Dr Kapaki reported having received grants from the European Union (European Regional Development Fund [ERDF]) and Greek national funds through the Operational Program "Competitiveness and Entrepreneurship" of the National Strategic Reference Framework (NSRF) Research Funding Program: Joint Programming Neurodegenerative Disease, "Biomarkers for Alzheimer's disease and Parkinson's disease." Dr Klunk reported being a co-inventor of the amyloid imaging tracer PiB and, as such, having a financial interest in the license agreement. (PiB intellectual property is owned by the University of Pittsburgh, and GE Healthcare holds a license agreement with the University of Pittsburgh based on the PiB technology described in this article. Dr Klunk receives "inventors share" payments from the University of Pittsburgh based on income from that license.) Dr Koglin reported having received personal fees from employment at Piramal Imaging, who is marketing Neuraceq

(florbetaben F18) as an amyloid-beta PET imaging agent. Dr Kornhuber reported having received grants from German Federal Ministry of Education and Research (BMBF): Kompetenznetz Demenzen (O1GIO420) and German Federal Ministry of Education and Research (BMBF): The Frontotemporo-Lobar Degeneration Consortium (FTDL-C), O1GI1007A and having a patent, PCT/EP2004/003963, "Diagnosis of Alzheimer's disease," issued; a patent, EP 1811304 A1, "Large A β -peptide binding particles (LAPS) in diagnosis and therapy of Alzheimer's dementia," issued; a patent, WO2007/082750 A1, "Immunoglobulin-bound Ab-peptides and immunoglobulins-binding Ab-peptides in diagnosis and therapy of Alzheimer's dementia," issued; a patent, EP 2437067A2, "Methods of differentially diagnosing dementias," issued; and a patent, "New formulations for diagnosis of Alzheimer's disease," pending. Dr Van Laere reported having received grants from Merck, Janssen Pharmaceuticals, and GE Healthcare. Dr Landau reported having received grants from NIH and personal fees from Biogen Idec, Genentech, and Synarc. Dr Leo reported having received grants from Instituto de Salud Carlos III (Fondo de Investigación Sanitaria, PI10/O1878; PI13/O1532; PI11/2425; PI11/3035 and the CIBERNED program). Dr Madsen reported having received grants from the Lundbeck Foundation, Danish Medical Research Council, and Rigshospitalet. Dr Meyer reported having received money from GE Healthcare for an ongoing research study (IIT). Dr Mintun reported being an employee of Avid Radiopharmaceuticals, a wholly owned subsidiary of Eli Lilly. Dr Morris reported having received grants from NIH (P50AG005681, P01AG003991, P01AG026276, U19AG032438). Dr Mroczko reported having received grants and personal fees from the Leading National Research Centre (KNOW), Medical University of Białystok, Poland. Dr Novak reported being an employee of Janssen Research and Development and holding stock in the same. Dr Paraskevas reported having received grants from European Union (European Regional Development Fund [ERDF]) and Greek national funds through the Operational Program "Competitiveness and Entrepreneurship" of the National Strategic Reference Framework (NSRF) Research Funding Program: Joint Programming Neurodegenerative Disease, "Biomarkers for Alzheimer's disease and Parkinson's disease." Dr Peters reported having received grants and/or personal fees from Lilly, Roche, Genentech, Lundbeck, Affiris, Piramal, Novartis, and Trx-Pharmaceuticals. Dr Popp reported having received grants from the Swiss National Science Foundation. Dr Rabinovici reported having received grants from Avid Radiopharmaceuticals and personal fees from GE Healthcare and Piramal. Dr Rinne reported having received grants from Sigrid Juselius Foundation and Turku University Hospital clinical grants. Dr Rot reported having received grants from JPND BIOMARKAPD. Dr Rowe reported having received grants from Avid Radiopharmaceuticals, Piramal Imaging, AstraZeneca, GE Healthcare, Avid/Lilly, Navidea, CSIRO, NHMRC, Alzheimer's Association, and an anonymous foundation and having had a patent licensed for PET image processing. Dr Sabri reported having received grants and/or personal fees from Piramal Imaging, Bayer Healthcare, and Siemens Healthcare. Dr Sarazin reported having received personal fees from Novartis (lecture) and

Allianz (lecture). Dr Soinin reported having received grants from the Academy of Finland, European Union 7ThFP 601055 VPH-DARE, Kuopio University Hospital VTR, and University of Eastern Finland. Dr Teunissen reported being a member of the international advisory board at Innogenetics and Roche; having received free kit-reagents for experiments from IBL, Innogenetics, Mesoscale Discovery, Invitrogen, Euroimmun, and FluidX; and having research contracts at Probiobrug, IBL, and Abbott. Dr Vandenberghe reported having received clinical trial agreements with GEHC, Merck, Forum, and Roche; grants from Research Foundation-Flanders (FWO) and KU Leuven; and nonfinancial support from GEHC. Dr Verbeek reported having served on an advisory board for Roche. Dr Waldemar reported being a board member of the Lundbeck Foundation. Dr Anders Wallin reported having received speakers' bureau fees from Esai and Triolab and serving on the advisory board for Nutrica and Esai. Dr Wolk reported having received personal fees from GE Healthcare and Piramal Pharma and grants from Avid Radiopharmaceuticals. The authors received compensation (ie, salary) as employees of their respective organizations. No other disclosures were reported.

Funding/Support: The research leading to these results has received support from the Innovative Medicines Initiative Joint Undertaking under EMIF grant agreement No. 115372, resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies' in-kind contribution. BIOMARKAPD is an EU Joint Programme-Neurodegenerative Disease Research (JPND) project. The project is supported through national funding organizations under the aegis of JPND (<http://www.jpnd.eu>). In the Netherlands, this is ZonMw. The DESCRIPA study was funded by the European Commission within the 5th framework program (QLRT-2001-2455). The EDAR study was funded by the European Commission as part of the 6th framework programme (contract No. 37670). This research was performed within the framework of the Center for Translational Molecular Medicine (CTTM) (<http://www.ctmm.nl>), project LeARN (grant O2N-101). The AIBL study was funded in part by the study partners (Australian Commonwealth Scientific Industrial and Research Organization [CSIRO], Edith Cowan University [ECU], Mental Health Research Institute [MHRI], Alzheimer's Australia [AA], National Ageing Research Institute [NARI], Austin Health, CogState, Hollywood Private Hospital, Sir Charles Gardner Hospital). The study also received support from the National Health and Medical Research Council (NHMRC) and the Dementia Collaborative Research Centres program (DCRC2), as well as ongoing funding from the Science and Industry Endowment Fund (SIEF). Data collection and sharing for this project was funded by the Alzheimer's Disease Neuroimaging Initiative (ADNI) (National Institutes of Health grant U01 AG024904) and the US Department of Defense ADNI (W81XWH-12-2-0012). ADNI is funded by the National Institute on Aging and the National Institute of Biomedical Imaging and Bioengineering and through generous contributions from the following: Alzheimer's Association; Alzheimer's Drug Discovery Foundation; BioClinica; Biogen Idec; Bristol-Myers Squibb Company; Eisai; Elan Pharmaceuticals;

Eli Lilly; F. Hoffmann-La Roche and its affiliated company Genentech; GE Healthcare; Innogenetics; IXICO; Janssen Alzheimer Immunotherapy Research & Development; Johnson & Johnson Pharmaceutical Research & Development; Medpace; Merck; Meso Scale Diagnostics; NeuroRx Research; Novartis Pharmaceuticals; Pfizer; Piramal Imaging; Servier; Synarc; and Takeda Pharmaceutical. The Canadian Institutes of Health Research is providing funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the National Institutes of Health (<http://www.fnih.org>). The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer's Disease Cooperative Study at the University of California, San Diego. ADNI data are disseminated by the Laboratory for Neuro Imaging at the University of Southern California. The Dementia Competence Network (DCN) has been supported by a grant from the German Federal Ministry of Education and Research (BMBF): Kompetenznetz Demenzen (O1GIO420). Additional funding related to the randomized clinical trials came from Janssen-Cilag and Merz Pharmaceuticals. The latter funds were exclusively used for personnel, pharmaceuticals, blistering and shipment of medication, and monitoring and as capitation fees for recruiting centers. Funding source for the Chandigarh study is the Indian Council of Medical Research (ICMR), India. Funding for the St Louis contribution was provided by the National Institute on Aging (P50 AG005681, P01 AG003991, and P01 AG026276); Fred Simmons and Olga Mohan, and the Charles and Joanne Knight Alzheimer's Research Initiative of the Washington University Knight Alzheimer's Disease Research Center. The Tours study received financial support of the French Ministry of Health grant PHRC-N 2008 1004 and the EC-FP6-project DiMI, LSHB-CT-2005-512146. The Caen study was funded by Agence Nationale de la Recherche, Programme Hospitalier de Recherche Clinique, Région Basse Normandie, and Institut National de la Santé et de la Recherche Médicale (Inserm). The research leading to the Munich contribution to the Mattsson multicenter study has received funding from the program "Investissements d'avenir" (ANR-10-IAIHU-06). The study from Pittsburgh was supported by National Institutes of Health grants (P50 AG005133, R37 AG025516, P01 AG025204). The New York contributions to the Mattsson multicenter study were in part supported by P30 AG008051, R01 AG13616, R01 AG022374, and R01 AG12101. Data from Brescia in this article were collected by Translational Outpatient Memory Clinic (TOMC) working group at IRCCS Fatebenefratelli in Brescia, Italy. Contributors to the TOMC are G. Amicucci, S. Archetti, L. Benussi, G. Binetti, L. Bocchio-Chiavetto, C. Bonvicini, E. Canu, F. Caobelli, E. Cavedo, E. Chittò, M. Cotelli, M. Gennarelli, S. Galluzzi, C. Geroldi, R. Ghidoni, R. Giubbini, U. P. Guerra, G. Kuffenschin, G. Lussignoli, D. Moretti, B. Paghera, M. Parapini, C. Porter, M. Romano, S. Rosini, I. Villa, R. Zanardini, and O. Zanetti. The JPND Project is supported in Italy by the Italian Ministry of Health. The assembling of the TU Munich data set was supported in part by the German research foundation (Deutsche Forschungsgemeinschaft) (HE 4560/1-2, DR 445/3-1 and DR 445/4-1 to A.D.), and by a KKF grant for clinical research of the Technische Universität München (to A.D. and T.G.). The Florbetaben phase 2 study from which data

were derived for this multicenter evaluation was sponsored by Bayer Healthcare/Piramal Imaging (Berlin, Germany). This work was supported by the University of Antwerp Research Fund; the Alzheimer Research Foundation (SAO-FRA); the Research Foundation Flanders (FWO); the Agency for Innovation by Science and Technology (IWT); the Belgian Science Policy Office Interuniversity Attraction Poles (IAP) program; and the Flemish Government-initiated Methusalem excellence grant.

Role of the Funder/Sponsor: The sponsors had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. The authors' respective organizations were given the opportunity to review the manuscript for medical and scientific accuracy as well as intellectual property considerations.

Disclaimer: Any views expressed in this publication represent the personal opinions of the authors and not those of their respective employers.

Additional Contributions: We acknowledge Gabriel Miltenberger-Miltényi and André Janeiro (Institute of Molecular Medicine, Lisbon) for quantification of CSF biomarkers assembled in the Lisbon contribution. Neither individual was compensated for the contribution besides salary. Multicenter studies involved in this project included the following: European Medical Information Framework-Alzheimer Disease (EMIF-AD); Biomarkers for Alzheimer Disease and Parkinson Disease (BIOMARKAPD); Alzheimer's Disease Neuroimaging Initiative (ADNI); Australian Imaging, Biomarkers & Lifestyle (AIBL) study; Avid Pharmaceuticals multicenter study for the AV45-A17 Study Group; Development of Screening Guidelines and Clinical Criteria for Predementia AD (DESCRIPA) study; German Dementia Competence Network (DCN); European Beta Amyloid Oligomers in the Early Diagnosis of AD and as Marker for Treatment Response (EDAR) study; Florbetaben (FBB) Phase 2 multicenter study; Leiden Alzheimer-Research Nederland (LeARN) project; Mattsson et al (2009) multicenter study; Multicenter study by UK Hospitals and University Hospital of Turku. Part of the data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (<http://adni.loni.usc.edu>). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf. Additional information is available in the Supplement.

Correction: This article was corrected online May 19, 2015, to fix curves in Figure 3C.

REFERENCES

- World Health Organization. Dementia: a public health priority. http://www.who.int/mental_health/publications/dementia_report_2012/en/. Accessed April 27, 2015.
- Bateman RJ, Xiong C, Benzinger TL, et al; Dominantly Inherited Alzheimer Network. Clinical and biomarker changes in dominantly inherited Alzheimer's disease. *N Engl J Med*. 2012;367(9):795-804.
- Jack CR Jr, Holtzman DM. Biomarker modeling of Alzheimer's disease. *Neuron*. 2013;80(6):1347-1358.
- Fagan AM, Xiong C, Jaselecc MS, et al; Dominantly Inherited Alzheimer Network. Longitudinal change in CSF biomarkers in autosomal-dominant Alzheimer's disease. *Sci Transl Med*. 2014;6(226):226ra30.
- Sperling RA, Aisen PS, Beckett LA, et al. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. 2011;7(3):280-292.
- Dubois B, Feldman HH, Jacova C, et al. Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria. *Lancet Neurol*. 2014;13(6):614-629.
- Sperling RA, Jack CR Jr, Aisen PS. Testing the right target and right drug at the right stage. *Sci Transl Med*. 2011;3(111):111cm33.
- Murayama S, Saito Y. Neuropathological diagnostic criteria for Alzheimer's disease. *Neuropathology*. 2004;24(3):254-260.
- Bennett DA, Schneider JA, Bienias JL, Evans DA, Wilson RS. Mild cognitive impairment is related to Alzheimer disease pathology and cerebral infarctions. *Neurology*. 2005;64(5):834-841.
- Lin Y-T, Cheng J-T, Yao Y-C, et al. Increased total TAU but not amyloid-beta(42) in cerebrospinal fluid correlates with short-term memory impairment in Alzheimer's disease. *J Alzheimers Dis*. 2009;18(4):907-918.
- Rowe CC, Ellis KA, Rimajova M, et al. Amyloid imaging results from the Australian Imaging, Biomarkers and Lifestyle (AIBL) study of aging. *Neurobiol Aging*. 2010;31(8):1275-1283.
- Randall C, Mosconi L, de Leon M, Glodzik L. Cerebrospinal fluid biomarkers of Alzheimer's disease in healthy elderly. *Front Biosci (Landmark Ed)*. 2013;18:1150-1173.
- Klunk WE. Amyloid imaging as a biomarker for cerebral β -amyloidosis and risk prediction for Alzheimer dementia. *Neurobiol Aging*. 2011;32(suppl 1):S20-S36.
- Vandenbroucke JP, von Elm E, Altman DG, et al; STROBE Initiative. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. *Epidemiology*. 2007;18(6):805-835.
- Whiting P, Rutjes AW, Reitsma JB, Bossuyt PM, Kleijnen J. The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. *BMC Med Res Methodol*. 2003;3:25.
- Petersen RC. Mild cognitive impairment as a diagnostic entity. *J Intern Med*. 2004;256(3):183-194.
- Winblad B, Palmer K, Kivipelto M, et al. Mild cognitive impairment: beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. *J Intern Med*. 2004;256(3):240-246.
- Genin E, Hannequin D, Wallon D, et al. APOE and Alzheimer disease: a major gene with semi-dominant inheritance. *Mol Psychiatry*. 2011;16(9):903-907.
- Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327(7414):557-560.
- Chételat G, Villemagne VL, Bourgeat P, et al; Australian Imaging Biomarkers and Lifestyle Research Group. Relationship between atrophy and beta-amyloid deposition in Alzheimer disease. *Ann Neurol*. 2010;67(3):317-324.
- Amariglio RE, Becker JA, Carmasin J, et al. Subjective cognitive complaints and amyloid burden in cognitively normal older individuals. *Neuropsychologia*. 2012;50(12):2880-2886.
- Bennett DA, Schneider JA, Arvanitakis Z, et al. Neuropathology of older persons without cognitive impairment from two community-based studies. *Neurology*. 2006;66(12):1837-1844.
- Matthews F, Brayne C; Medical Research Council Cognitive Function and Ageing Study Investigators. The incidence of dementia in England and Wales: findings from the five identical sites of the MRC CFA Study. *PLoS Med*. 2005;2(8):e193.
- Jack CR Jr, Wiste HJ, Weigand SD, et al. Age-specific population frequencies of cerebral β -amyloidosis and neurodegeneration among people with normal cognitive function aged 50-89 years: a cross-sectional study. *Lancet Neurol*. 2014;13(10):997-1005.
- Morris JC, Roe CM, Xiong C, et al. APOE predicts amyloid-beta but not tau Alzheimer pathology in cognitively normal aging. *Ann Neurol*. 2010;67(1):122-131.
- Suri S, Heise V, Trachtenberg AJ, Mackay CE. The forgotten APOE allele: a review of the evidence and suggested mechanisms for the protective effect of APOE ϵ 2. *Neurosci Biobehav Rev*. 2013;37(10 pt 2):2878-2886.
- Farrer LA, Cupples LA, Haines JL, et al; APOE and Alzheimer Disease Meta Analysis Consortium. Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease: a meta-analysis. *JAMA*. 1997;278(16):1349-1356.
- Liao F, Hori Y, Hudry E, et al. Anti-ApoE antibody given after plaque onset decreases A β accumulation and improves brain function in a mouse model of A β amyloidosis. *J Neurosci*. 2014;34(21):7281-7292.
- Boehm-Cagan A, Michaelson DM. Reversal of apoE4-driven brain pathology and behavioral deficits by bexarotene. *J Neurosci*. 2014;34(21):7293-7301.
- Evans DA, Hebert LE, Beckett LA, et al. Education and other measures of socioeconomic status and risk of incident Alzheimer disease in a defined population of older persons. *Arch Neurol*. 1997;54(11):1399-1405.
- Stern Y. Cognitive reserve and Alzheimer disease. *Alzheimer Dis Assoc Disord*. 2006;20(3)(suppl 2):S69-S74.
- Serrano-Pozo A, Qian J, Monsell SE, Frosch MP, Betensky RA, Hyman BT. Examination of the clinicopathologic continuum of Alzheimer disease in the autopsy cohort of the National Alzheimer Coordinating Center. *J Neuropathol Exp Neurol*. 2013;72(12):1182-1192.

33. Roe CM, Mintun MA, Ghoshal N, et al. Alzheimer disease identification using amyloid imaging and reserve variables: proof of concept. *Neurology*. 2010;75(1):42-48.
34. Barnes LL, Wilson RS, Bienias JL, Schneider JA, Evans DA, Bennett DA. Sex differences in the clinical manifestations of Alzheimer disease pathology. *Arch Gen Psychiatry*. 2005;62(6):685-691.
35. Jack CR Jr, Wiste HJ, Weigand SD, et al. Age, sex, and APOE ϵ 4 effects on memory, brain structure, and β -amyloid across the adult life span [published online March 16, 2015]. *JAMA Neurol*. doi:10.1001/jamaneurol.2014.4821.
36. Schöll M, Wall A, Thordardottir S, et al. Low PiB PET retention in presence of pathologic CSF biomarkers in Arctic APP mutation carriers. *Neurology*. 2012;79(3):229-236.
37. Zwan M, van Harten A, Ossenkopppele R, et al. Concordance between cerebrospinal fluid biomarkers and [11C]PiB PET in a memory clinic cohort. *J Alzheimers Dis*. 2014;41(3):801-807.
38. Palmqvist S, Zetterberg H, Blennow K, et al. Accuracy of brain amyloid detection in clinical practice using cerebrospinal fluid β -amyloid 42: a cross-validation study against amyloid positron emission tomography. *JAMA Neurol*. 2014;71(10):1282-1289.
39. Landau SM, Lu M, Joshi AD, et al; Alzheimer's Disease Neuroimaging Initiative. Comparing positron emission tomography imaging and cerebrospinal fluid measurements of β -amyloid. *Ann Neurol*. 2013;74(6):826-836.
40. Fagan AM, Mintun MA, Mach RH, et al. Inverse relation between in vivo amyloid imaging load and cerebrospinal fluid A β 42 in humans. *Ann Neurol*. 2006;59(3):512-519.
41. Mattsson N, Andreasson U, Persson S, et al; Alzheimer's Association QC Program Work Group. CSF biomarker variability in the Alzheimer's Association quality control program. *Alzheimers Dement*. 2013;9(3):251-261.
42. Debray TP, Moons KG, Abo-Zaid GM, Koffijberg H, Riley RD. Individual participant data meta-analysis for a binary outcome: one-stage or two-stage? *PLoS One*. 2013;8(4):e60650.
43. Thomas D, Radji S, Benedetti A. Systematic review of methods for individual patient data meta-analysis with binary outcomes. *BMC Med Res Methodol*. 2014;14:79.
44. Brodaty H, Mothakunnel A, de Vel-Palumbo M, et al. Influence of population versus convenience sampling on sample characteristics in studies of cognitive aging. *Ann Epidemiol*. 2014;24(1):63-71.
45. Hedden T, Oh H, Younger AP, Patel TA. Meta-analysis of amyloid-cognition relations in cognitively normal older adults. *Neurology*. 2013;80(14):1341-1348.
46. van Harten AC, Visser PJ, Pijnenburg YA, et al. Cerebrospinal fluid A β 42 is the best predictor of clinical progression in patients with subjective complaints. *Alzheimers Dement*. 2013;9(5):481-487.
47. Vos SJ, Xiong C, Visser PJ, et al. Preclinical Alzheimer's disease and its outcome: a longitudinal cohort study. *Lancet Neurol*. 2013;12(10):957-965.
48. Villemagne VL, Burnham S, Bourgeat P, et al; Australian Imaging Biomarkers and Lifestyle (AIBL) Research Group. Amyloid β deposition, neurodegeneration, and cognitive decline in sporadic Alzheimer's disease: a prospective cohort study. *Lancet Neurol*. 2013;12(4):357-367.
49. Savva GM, Wharton SB, Ince PG, Forster G, Matthews FE, Brayne C; Medical Research Council Cognitive Function and Ageing Study. Age, neuropathology, and dementia. *N Engl J Med*. 2009;360(22):2302-2309.