Prevalence Estimates of Amyloid Abnormality Across the Alzheimer Disease Clinical Spectrum

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Prevalence Estimates of Amyloid Abnormality Across the Alzheimer Disease Clinical Spectrum

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IMPORTANCE One characteristic histopathological event in Alzheimer disease (AD) is cerebral amyloid aggregation, which can be detected by biomarkers in cerebrospinal fluid (CSF) and on positron emission tomography (PET) scans. Prevalence estimates of amyloid pathology are important for health care planning and clinical trial design.

OBJECTIVE To estimate the prevalence of amyloid abnormality in persons with normal cognition, subjective cognitive decline, mild cognitive impairment, or clinical AD dementia and to examine the potential implications of cutoff methods, biomarker modality (CSF or PET), age, sex, *APOE* genotype, educational level, geographical region, and dementia severity for these estimates.

DESIGN, SETTING, AND PARTICIPANTS This cross-sectional, individual-participant pooled study included participants from 85 Amyloid Biomarker Study cohorts. Data collection was performed from January 1, 2013, to December 31, 2020. Participants had normal cognition, subjective cognitive decline, mild cognitive impairment, or clinical AD dementia. Normal cognition and subjective cognitive decline were defined by normal scores on cognitive tests, with the presence of cognitive complaints defining subjective cognitive decline. Mild cognitive impairment and clinical AD dementia were diagnosed according to published criteria.

EXPOSURES Alzheimer disease biomarkers detected on PET or in CSF.

MAIN OUTCOMES AND MEASURES Amyloid measurements were dichotomized as normal or abnormal using cohort-provided cutoffs for CSF or PET or by visual reading for PET. Adjusted data-driven cutoffs for abnormal amyloid were calculated using gaussian mixture modeling. Prevalence of amyloid abnormality was estimated according to age, sex, cognitive status, biomarker modality, *APOE* carrier status, educational level, geographical location, and dementia severity using generalized estimating equations.

RESULTS Among the 19 097 participants (mean [SD] age, 69.1 [9.8] years; 10 148 women [53.1%]) included, 10 139 (53.1%) underwent an amyloid PET scan and 8958 (46.9%) had an amyloid CSF measurement. Using cohort-provided cutoffs, amyloid abnormality prevalences were similar to 2015 estimates for individuals without dementia and were similar across PET- and CSF-based estimates (24%; 95% CI, 21%-28%) in participants with normal cognition, 27% (95% CI, 21%-33%) in participants with subjective cognitive decline, and 51% (95% CI, 46%-56%) in participants with mild cognitive impairment, whereas for clinical AD dementia the estimates were higher for PET than CSF (87% vs 79%; mean difference, 8%; 95% CI, 0%-16%; $P = .04$). Gaussian mixture modeling–based cutoffs for amyloid measures on PET scans were similar to cohort-provided cutoffs and were not adjusted. Adjusted CSF cutoffs resulted in a 10% higher amyloid abnormality prevalence than PET-based estimates in persons with normal cognition (mean difference, 9%; 95% CI, 3%-15%; $P = .004$), subjective cognitive decline (9%; 95% CI, 3%-15%; $P = .005$), and mild cognitive impairment (10%; 95% CI, 3%-17%; $P = .004$), whereas the estimates were comparable in persons with clinical AD dementia (mean difference, 4%; 95% CI, −2% to 9%; $P = .18$).

CONCLUSIONS AND RELEVANCE This study found that CSF-based estimates using adjusted data-driven cutoffs were up to 10% higher than PET-based estimates in people without dementia, whereas the results were similar among people with dementia. This finding suggests that preclinical and prodromal AD may be more prevalent than previously estimated, which has important implications for clinical trial recruitment strategies and health care planning policies.

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Supplemental content

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Pathologic change in Alzheimer disease (AD) is characterized by cerebral amyloid aggregation, as indicated by amyloid biomarkers on positron emission tomography (PET) scans or in cerebrospinal fluid (CSF).[1,2] With emerging disease-modifying antiamyloid therapies, estimating the prevalence of amyloid abnormality in persons across the AD clinical spectrum is important to reduce screening failure rates and improve recruitment efficiency.[3-5] Previous studies analyzed 56 Amyloid Biomarker Study cohorts to estimate age, sex, educational level, and apolipoprotein E (*APOE*; GenBank 348)–associated prevalence of amyloid abnormality on PET scans and in CSF in 7583 individuals without dementia and on PET scans in 1359 individuals with clinical AD dementia.[6,7] Much more biomarker data have become available in recent years, providing the possibility of increasing estimate robustness and examining previously unaddressed factors that could alter amyloid abnormality prevalence estimates.

One such factor is the method for defining amyloid abnormality cutoffs. In a previous analysis, cohort-provided cutoffs were used; however, different methods to calculate amyloid abnormality cutoffs were applied.[8-10] Moreover, values from a specific CSF amyloid-β 42 analysis tool appeared to have gradually increased over the past 2 decades such that older available CSF amyloid-abnormality cutoffs may have been too conservative.[11-13] Therefore, we recalculated the cutoffs using an unbiased mixture modeling approach and examined whether these adjusted cutoffs affected amyloid abnormality prevalence estimates. Furthermore, in a previous study, amyloid abnormality in persons with clinical AD dementia was assessed only with PET measures,[7] whereas CSF measures are now available for this group in the Amyloid Biomarker Study. The large number of participants in this combined analysis of Amyloid Biomarker Study cohort data enabled us to study whether PET and CSF prevalence estimates differed in persons with both measurements. We also examined whether amyloid abnormality prevalence differed by geographical region or between individuals with mild, moderate, or severe dementia, which could be important factors to consider in trial planning.

In this study, we aimed to refine the 2015 results by estimating the prevalence of amyloid abnormality in persons with normal cognition, subjective cognitive decline, mild cognitive impairment, or clinical AD dementia and examining the potential implications of cutoff methods, biomarker modality (CSF or PET), age, sex, *APOE* genotype, educational level, geographical region, and dementia severity for these estimates.

Key Points

Question What is the prevalence of amyloid abnormality assessed in cerebrospinal fluid or on positron emission tomography scans across the clinical Alzheimer disease (AD) spectrum?

Findings This cross-sectional study of 19 097 individuals across the AD spectrum found that, in persons without dementia, the cerebrospinal fluid–based amyloid abnormality prevalence estimate that used data-driven cutoffs was 10% higher than the positron emission tomography–based prevalence estimate that used cohort-provided cutoffs.

Meaning Findings from this study suggest that preclinical and prodromal AD may be more prevalent today than previously anticipated; these updated estimates may inform health care planning and recruitment strategies for clinical trials of AD therapies.

Methods

Participants

This cross-sectional study included participants from the 85 cohorts of the Amyloid Biomarker Study, an ongoing, worldwide data-pooling initiative that started in 2013.[6,7] A flow diagram of the included studies and participants is shown in eFigure 1 in the Supplement. None of the 85 included studies required evidence of amyloid abnormality as an eligibility criterion to enroll in the study. Written informed consent was obtained from all participants in each study, and data were deidentified by the respective cohorts. The study protocol for each cohort was approved by the local ethics committee at each site. The present study was approved by the Medical Ethics Committee of the Maastricht University Medical Center, which declared that the Medical Research Involving Human Subjects Act (WMO) does not apply to the study and waived the informed consent requirement because deidentified data were used. We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

The present pooled analysis consisted of 19 097 participants, of whom 9908 had normal cognition, which was defined by normal scores on cognitive tests and/or absence of cognitive complaints; 1524 had subjective cognitive decline defined by cognitive complaints without objective confirmation on tests; 5405 had mild cognitive impairment[14,15]; and 2260 had clinical AD dementia. Clinical AD dementia was subcategorized as follows according to Mini-Mental State Examination scores (range 0-30, with higher scores indicating better performance): mild (score: ≥20; n = 1525), moderate (score: 11-20; n = 488), or severe (score: ≤10; n = 61). The characteristics of all cohorts are shown in eTable 1 in the Supplement, and an overview of data availability is provided in eTable 2 in the Supplement. Compared with the 2015 analyses of the Amyloid Biomarker Study cohorts, the present study included more people, with 7804 persons without dementia and 737 persons with clinical AD dementia from 29 new cohorts as well as 1205 additional cases from 10 cohorts, who also participated in the 2015 studies (which involved 812 persons without dementia and 737 persons with clinical AD dementia).

Data collection was performed from January 1, 2013, to December 31, 2020. Race and ethnicity data were not collected because this study used existing data, and many of the cohorts we analyzed did not collect this information.

Amyloid Abnormality Cutoffs

Amyloid measures per cohort are detailed in eTables 3 and 4 in the Supplement. We selected the biomarker modality that resulted in the greatest number of participants per cohort for

the primary analyses. Both PET amyloid and CSF amyloid were measured at baseline, and the interval between diagnosis and biomarker assessment did not exceed 6 months.

We calculated cohort-specific, data-driven cutoffs independent of diagnosis to ascertain amyloid abnormality using gaussian mixture modeling in those cohorts that provided continuous amyloid values. Gaussian mixture modeling–based cutoffs may better capture amyloid abnormality than clinical diagnosis–based cutoffs.[12,13,16] We evaluated the number of distributions that provided the best fit on the data using the R function boot.comp (R Foundation for Statistical Computing). Next, we visually inspected the normality of distributions and chose the cutoff as the value where 2 fitted normal distributions intersected. When there were more than 2 distributions, we forced the data into 2 distributions or chose the cutoff of 2 of the 3 distributions after visual inspection (eTable 3 in the Supplement). When there was a single distribution, cohort-provided cutoffs were used.

Statistical Analysis

Descriptive data were analyzed using independent-samples, unpaired, 2-tailed *t* tests for continuous variables and χ^2 tests for categorical variables. Differences in observed percentages were analyzed using McNemar tests. Amyloid abnormality was the dichotomous outcome variable (normal or abnormal) in generalized estimating equations[17] using the genlin command in SPSS, version 26 (IBM). We assumed a logit-link function with an exchangeable correlation structure. The outcome of amyloid abnormality was defined using cohort-provided cutoffs and adjusted cutoffs.

We performed 6 analyses. First, we examined the prevalence of amyloid abnormality defined using cohort-provided cutoffs according to age, diagnosis, and biomarker modality, testing up to 3-way interactions with a forward selection method. Second, we repeated the analyses after cutoff adjustments. Third, we assessed the characteristics of participants who had discordant amyloid-positive results based on cohort-provided vs adjusted cutoffs. Fourth, we conducted separate analyses based on adjusted cutoffs to examine the dependencies on sex; educational level; *APOE* ε4 carrier status (carrier vs noncarrier); *APOE* genotype (ε2ε2, ε2ε3, ε2ε4, ε3ε3, ε3ε4, or ε4ε4); and geographical region of amyloid abnormality prevalence, which were tested with up to 3-way interactions with age, cognitive status, *APOE* ε4 carrier status, and biomarker modality using forward selection. Interaction terms were retained in the model if they appeared significant by the Wald statistical test; a 2-sided $P < .05$ indicated statistical significance. From these separate analyses, we excluded small subgroups of participants with ε2ε2 (44 with normal cognition, 2 with subjective cognitive decline, 6 with mild cognitive impairment, and 1 with clinical AD dementia) and 16 participants with subjective cognitive decline and ε2ε4. Among persons with clinical AD dementia, we examined the association of amyloid abnormality with *APOE* ε4 gene dose (0/1/2 alleles) instead of *APOE* genotype, because the ε2ε2 (0.2%), ε2ε3 (2.5%), and ε2ε4 (2.5%) genotypes were infrequent. Fifth, we investigated whether amyloid abnormality prevalence depended on mild, moderate, or severe AD dementia. Sixth, we assessed PET-CSF concordance for participants who had values for both measurements available.

We performed all 6 analyses separately in persons without dementia (normal cognition, subjective cognitive decline, or mild cognitive impairment) and in persons with clinical AD dementia because the 2015 studies were also conducted in these groups separately[6,7] and because age and biomarker modality associations differed for these groups. Age was included as a continuous variable centered at the median (70 years). Educational level was dichotomized at the median (14 years). Cohorts were subdivided into geographical regions: North America, Europe, Asia, and Australia.

Probabilities and 95% CIs that were estimated by generalized estimating equations were used in figures and tables. Statistical comparisons were reported at the mean age unless otherwise specified.

Results

Of the 19 097 participants included in the study, 10 148 were women (53.1%) and 8949 were men (46.9%) with a mean (SD) age of 69.1 (9.8) years. Participant characteristics according to cognitive status and biomarker modality are shown in **Table 1**. A total of 3858 participants (20.2%) had missing data for *APOE* ε4 carrier status, 132 (0.7%) for sex, and 1803 (9.4%) for educational level (eTable 5 in the Supplement). Participants with missing data were excluded from the respective subanalyses. Of the 19 097 total participants, 1571 (8.2%) underwent both CSF and PET measurements. The characteristics of persons who underwent PET vs CSF measurement are shown in eTable 6 in the Supplement.

A total of 10 139 of 19 097 participants (53.1%) in 50 cohorts underwent an amyloid-PET measurement (26 quantitative reading, 23 visual reading, and 1 combined), and 15 of 26 cohorts provided continuous amyloid load values. In addition, 8958 participants (46.9%) in 51 cohorts had an amyloid-CSF measurement; 50 cohorts provided continuous values, and 2 of these cohorts did not provide study-specific cutoffs.

Of the 50 cohorts with continuous CSF values, 27 showed a bimodal distribution, and 7 showed 3 distributions. In 19 subsets, gaussian mixture modeling of CSF amyloid values did not show distinctive distributions such that the cutoffs could be determined; eTable 7 in the Supplement shows methodological considerations for the cohorts without distinctive distributions. Compared with cohort-provided cutoffs, the adjusted cutoffs in the 34 cohorts with distinctive distributions were higher in 24 cohorts (n = 6299 participants; mean Innotest difference, 108.44 pg/mL), lower in 3 cohorts (n = 741 participants; mean Innotest difference, 48.24 pg/mL), and did not differ in 7 cohorts. Furthermore, 3832 participants (42.8%) had abnormal amyloid with cohort-provided cutoffs and 4467 participants (49.9%) had abnormal amyloid with adjusted cutoffs (mean difference, 7.1%; $P < .001$) (eTable 8 in the Supplement).

Of the 50 cohorts with PET values, 14 provided continuous PET values, 10 of which had a bimodal distribution and 4 did not show distinctive distributions because of small sample

Table 1. Description and Availability of Data According to Cognitive Status and Biomarker Modality

Variable	No. (%)								
	Total sample	Normal cognition		Subjective cognitive decline		Mild cognitive impairment		AD dementia	
		PET modality	CSF modality	PET modality	CSF modality	PET modality	CSF modality	PET modality	CSF modality
Age, y									
No.	19 097 (100)	7105 (37.2)	2803 (14.7)	448 (2.4)	1076 (5.6)	1281 (6.7)	4124 (21.6)	1305 (6.8)	955 (5.0)
Mean (SD)	69.1 (9.8)	69.8 (9.6)	66.0 (12.5)	67.2 (7.6)	65.8 (8.2)	72.7 (9.0)	69.8 (8.4)	69.4 (9.2)	69.5 (9.1)
<40	296 (1.6)	166 (2.3)	121 (4.3)	0	1 (0.1)	1 (0.1)	3 (0.1)	2 (0.2)	2 (0.2)
40-44	79 (0.4)	21 (0.3)	38 (1.4)	0	5 (0.5)	2 (0.2)	11 (0.3)	2 (0.2)	0
45-49	227 (1.2)	41 (0.6)	116 (4.1)	1 (0.2)	18 (1.7)	5 (0.4)	34 (0.8)	9 (0.7)	3 (0.3)
50-54	636 (3.3)	109 (1.5)	196 (7.0)	20 (4.5)	67 (6.2)	26 (2.0)	122 (3.0)	47 (3.6)	49 (5.1)
55-59	1296 (6.8)	155 (2.2)	263 (9.4)	51 (11.4)	166 (15.4)	65 (5.1)	341 (8.3)	166 (12.7)	89 (9.3)
60-64	2046 (10.7)	349 (4.9)	346 (12.3)	90 (20.1)	216 (20.1)	132 (10.3)	585 (14.2)	183 (14.0)	145 (15.2)
65-69	5039 (26.4)	2692 (37.9)	532 (19.0)	118 (26.3)	236 (21.9)	221 (17.3)	804 (19.5)	248 (19.0)	188 (19.7)
70-74	4406 (23.1)	1920 (27.0)	510 (18.2)	98 (21.9)	196 (18.2)	291 (22.7)	969 (23.5)	235 (18.0)	187 (19.6)
75-79	2958 (15.5)	974 (13.7)	335 (12.0)	48 (10.7)	129 (12.0)	266 (20.8)	805 (19.5)	235 (18.0)	166 (17.4)
80-84	1478 (7.7)	475 (6.7)	221 (7.9)	14 (3.1)	36 (3.3)	158 (12.3)	359 (8.7)	124 (9.5)	91 (9.5)
85-89	479 (2.5)	111 (1.6)	116 (4.1)	6 (1.3)	6 (0.6)	73 (5.7)	86 (2.1)	48 (3.7)	33 (3.5)
90-94	136 (0.7)	79 (1.1)	9 (0.3)	2 (0.4)	0	34 (2.7)	5 (0.1)	5 (0.4)	2 (0.2)
95-99	15 (0.1)	8 (0.1)	0	0	0	6 (0.5)	0	1 (0.1)	0
100-104	5	4 (0.1)	0	0	0	1 (0.1)	0	0	0
Amyloid, abnormal with adjusted cutoff	8244 (43.2)	1818 (25.6)	904 (32.3)	111 (24.8)	312 (29.0)	730 (57.0)	2413 (58.5)	1118 (85.7)	838 (87.7)
APOE ε4 carrier status									
Carrier	5951 (31.2)	2172 (30.6)	686 (24.5)	110 (24.6)	314 (29.2)	330 (25.8)	1548 (37.5)	450 (34.5)	341 (35.7)
Unknown	3858 (20.2)	801 (11.3)	414 (14.8)	92 (20.5)	205 (19.1)	527 (41.1)	828 (20.1)	577 (44.2)	414 (43.4)
APOE genotype									
ε2ε2	53 (0.3)	32 (0.5)	12 (0.4)	1 (0.2)	1 (0.1)	0	6 (0.1)	0	1 (0.1)
ε2ε3	1241 (6.5)	628 (8.8)	243 (8.7)	40 (8.9)	55 (5.1)	53 (4.1)	212 (5.1)	2 (0.2)	8 (0.8)
ε2ε4	289 (1.5)	144 (2.0)	43 (1.5)	4 (0.9)	12 (1.1)	12 (0.9)	64 (1.6)	2 (0.2)	8 (0.8)
ε3ε3	6932 (36.3)	3325 (46.8)	1264 (45.1)	196 (43.8)	299 (27.8)	278 (21.7)	1419 (34.4)	28 (2.1)	123 (12.9)
ε3ε4	3962 (20.7)	1758 (24.7)	509 (18.2)	93 (20.8)	179 (16.6)	198 (15.5)	1069 (25.9)	28 (2.1)	128 (13.4)
ε4ε4	783 (4.1)	215 (3.0)	61 (2.2)	13 (2.9)	19 (1.8)	54 (4.2)	342 (8.3)	6 (0.5)	73 (7.6)
Unknown	5837 (30.6)	1003 (14.1)	671 (23.9)	101 (22.5)	511 (47.5)	686 (53.6)	1012 (24.5)	1239 (94.9)	614 (64.3)
Sex									
Female	10 148 (53.1)	4111 (57.9)	1555 (55.5)	268 (59.8)	536 (49.8)	595 (46.4)	1956 (47.4)	633 (48.5)	494 (51.7)
Male	8817 (46.2)	2876 (40.5)	1248 (44.5)	180 (40.2)	540 (50.2)	686 (53.6)	2168 (52.6)	660 (50.6)	459 (48.1)
Unknown	132 (0.7)	118 (1.7)	0	0	0	0	0	12 (0.9)	2 (0.2)
Educational level									
Mean (SD), y	14.0 (4.23)	16.0 (3.19)	13.6 (4.20)	15.3 (4.16)	13.3 (3.96)	12.8 (4.53)	11.8 (4.31)	12.8 (3.96)	12.0 (4.36)
Lower level, <14 y	8629 (45.2)	2112 (29.7)	1262 (45.0)	162 (36.2)	574 (53.3)	748 (58.4)	2476 (60.0)	781 (59.8)	514 (53.8)
Unknown	1803 (9.4)	171 (2.4)	498 (17.8)	29 (6.5)	47 (4.4)	103 (8.0)	644 (15.6)	92 (7.0)	219 (22.9)
MMSE									
No.	18 252 (95.6)	6835 (96.2)	2572 (91.8)	442 (98.7)	1023 (95.1)	1264 (98.7)	4042 (98.0)	1232 (94.4)	842 (88.2)
Mean (SD)	27.4 (3.32)	28.9 (1.23)	28.9 (1.60)	29.0 (1.25)	28.6 (1.55)	26.4 (2.84)	26.6 (2.64)	21.6 (4.65)	21.6 (4.79)

(continued)

Table 1. Description and Availability of Data According to Cognitive Status and Biomarker Modality (continued)

Variable	No. (%)								
	Total sample	Normal cognition		Subjective cognitive decline		Mild cognitive impairment		AD dementia	
		PET modality	CSF modality	PET modality	CSF modality	PET modality	CSF modality	PET modality	CSF modality
Geographical region									
North America	9256 (48.5)	6216 (87.5)	982 (35.0)	162 (36.2)	95 (8.8)	461 (36.0)	805 (19.5)	303 (23.2)	232 (24.3)
Asia	599 (3.1)	83 (1.2)	54 (1.9)	26 (5.8)	0	185 (14.4)	9 (0.2)	233 (17.9)	9 (0.9)
Europe	8803 (46.1)	595 (8.4)	1767 (63.0)	260 (58.0)	981 (91.2)	514 (40.1)	3310 (80.3)	662 (50.7)	714 (74.8)
Australia	439 (2.3)	211 (3.0)	0	0	0	121 (9.4)	0	107 (8.2)	0

Abbreviations: AD, Alzheimer disease; *APOE*, apolipoprotein E; CSF, cerebrospinal fluid; MMSE, Mini-Mental State Examination; PET, positron emission tomography.

sizes (<28 participants). The difference between cohort-provided cutoffs and adjusted cutoffs was less than 0.1 SUVR (standardized uptake value ratio) for 7 cohorts (lower in 3 cohorts [n = 5055 participants], higher in 3 cohorts [n = 1275 participants], and no difference in 1 cohort [n = 279 participants]) and was less than 0.4 SUVR for 3 cohorts (lower in 2 cohorts [n = 312 participants] and higher in 1 cohort [n = 279 participants]). In these 10 cohorts, 2174 participants (30.2%) had abnormal amyloid with the cohort-provided cutoff and 2146 participants (29.8%) had abnormal amyloid with the adjusted cutoff (mean difference, 0.4%; $P = .07$). Given this nonsignificant difference and the limited number of cohorts with continuous data, amyloid abnormality on PET scans was defined using cohort-provided cutoffs for quantitatively rated scans.

Amyloid Abnormality Prevalence in Normal Cognition, Subjective Cognitive Decline, and Mild Cognitive Impairment

With cohort-provided cutoffs for both PET and CSF measures, amyloid abnormality prevalence estimates in normal cognition, subjective cognitive decline, and mild cognitive impairment were similar to the 2015 estimates. Specifically, prevalence estimates increased with older age, were similar for participants with normal cognition and subjective cognitive decline at any age (mean difference, 2%; 95% CI, −7% to 2%; $P = .31$), were approximately 25% higher in participants with mild cognitive impairment vs normal cognition and subjective cognitive decline (mean difference, 25%-27%; 95% CI, 19%-30%; $P < .001$), and were similar for PET and CSF (mean difference, 0% [95% CI, −4% to 4%; $P = .99$]; normal cognition: 24% [95% CI, 21%-28%]; subjective cognitive decline: 27% [95% CI, 21%-33%]; and mild cognitive impairment: 51% [95% CI, 46%-56%]) (**Figure 1**; eFigure 2A and eTable 9 in the Supplement).

With adjusted CSF cutoffs, CSF-based amyloid abnormality estimates were, on average, 10% higher than PET-based estimates in persons with normal cognition (CSF vs PET mean difference, 9%; 95% CI, 3%-15%; $P = .004$), subjective cognitive decline (9%; 95% CI, 3%-15%; $P = .005$), and mild cognitive impairment (10%; 95% CI, 3%-17%; $P = .004$) and were similarly associated with age compared with cohort-provided cutoffs (**Table 2** and Figure 1; eFigure 2B in the Supplement). Given this association of biomarker modality with the prevalence of amyloid abnormality when adjusted CSF cutoffs were included, we included biomarker modality in further analyses. **Table 3** shows observed amyloid abnormality prevalence.

Amyloid abnormality estimates had a steeper increase with age among *APOE* ε4 carriers than noncarriers, regardless of clinical diagnosis and biomarker modality (**Figure 2**A and B; eTable 10 in the Supplement). Similarly, *APOE* ε4ε4 carriers aggregated amyloid at the youngest age, followed by ε3ε4, ε2ε4, ε3ε3, and ε2ε3 (eFigure 3A and B, eFigure 4 in the Supplement). The PET-based amyloid abnormality prevalence was 10% (95% CI, 4%-16%; $P = .001$) higher in ε3ε4 compared with ε2ε4 (normal cognition: 46% vs 36%; subjective cognitive decline: 44% vs 34%; mild cognitive impairment: 66% vs 56%), whereas in the 2015 study, these groups had similar amyloid abnormality frequencies. Of the 44 *APOE* ε2ε2 carriers with normal cognition, 5 had an abnormal amyloid marker. In *APOE* ε4ε4 carriers, CSF-based estimates were 15% (95% CI, 5%-25%; $P = .005$) higher than PET-based estimates, whereas this difference was approximately 8% for the other *APOE* genotypes (modality × *APOE* $P = .008$). Sex was not associated with amyloid abnormality prevalence (PET in female vs male: normal cognition, 25% vs 25%; subjective cognitive decline, 27% vs 27%; mild cognitive impairment, 50% vs 50%; CSF in female vs male: normal cognition, 34% vs 33%; subjective cognitive decline, 36% vs 36%; mild cognitive impairment, 60% vs 60%; $P = .45$), and there were no interactions between sex and age, diagnosis, biomarker modality, or *APOE* ε4 carrier status. Higher educational level was associated with higher prevalence of amyloid abnormality regardless of age, cognitive status, *APOE* ε4 carrier status, and biomarker modality (mean difference, 2%-3%; 95% CI, 1%-5%; $P = .001$) (eFigure 5A and B in the Supplement). Amyloid abnormality prevalence was similar across geographical regions (eg, PET in normal cognition: North America, 24% [95% CI, 21%-29%]; Asia, 24% [95% CI, 16%-35%]; Europe, 24% [95% CI, 18%-31%]; Australia, 29% [95% CI, 27%-32%]; $P = .12$).

Amyloid Abnormality Prevalence in Clinical AD Dementia

With cohort-provided cutoffs, amyloid abnormality estimates were higher with PET vs CSF biomarkers (87% vs 79%; mean difference, 8%; 95% CI, 0%-16%; $P = .04$) and decreased with age (from 91% at age 50 years to 83% at age 90 years for PET vs from 84% at age 50 years to 72% at age 90 years

Figure 1. Estimated Prevalence of Amyloid Abnormality Based on Cohort-Provided Positron Emission Tomography (PET) Cutoffs and Adjusted Cerebrospinal Fluid (CSF) Cutoffs and Based on Adjusted CSF Cutoffs, Cohort-Provided CSF Cutoffs, and Cohort-Provided PET Cutoffs by Biomarker Modality, Cognitive Status, and Age

In panel A, the solid lines represent the estimated prevalence of amyloid abnormality based on cohort-provided PET cutoffs, and the dotted lines represent the estimated prevalence based on adjusted CSF cutoffs. For the CSF modality shown in panel B, the solid lines represent the estimated prevalence of amyloid abnormality based on adjusted CSF cutoffs, and the dotted lines represent the estimated prevalence based on cohort-provided CSF cutoffs. For the PET modality, the solid lines represent the estimated prevalence based on cohort-provided PET cutoffs. Amyloid abnormality for cohort-provided PET cutoffs and adjusted CSF cutoffs in groups with normal cognition, subjective cognitive decline, and mild cognitive impairment was modeled using age (statistical significance: $P < .001$), biomarker modality (statistical significance: $P = .004$), and cognitive status (statistical significance: $P < .001$) as risk factors; amyloid abnormality in the group with Alzheimer disease (AD) dementia was modeled[6,7] using age (statistical significance: $P = .08$) and biomarker modality (statistical significance: $P = .18$) as risk factors. Amyloid abnormality for cohort-provided CSF cutoffs in groups with with normal cognition, subjective cognitive decline, and mild cognitive impairment was modeled using age (statistical significance: $P < .001$), biomarker modality (statistical significance: $P > .99$), and cognitive status (statistical significance: $P < .001$) as risk factors; and in the group with AD dementia was modeled using age (statistical significance: $P = .03$) and biomarker modality (statistical significance: $P = .02$) as risk factors. Shaded areas indicate 95% CIs.

Table 2. Estimated Mean Prevalence and 95% CI of Amyloid Abnormality Based on Adjusted Cutoffs and Comparison With 2015 Estimates According to Biomarker Modality, Cognitive Status, and Age[a]

	Mean prevalence (95% CI), %											
	Normal cognition			Subjective cognitive decline			Mild cognitive impairment			Clinical AD dementia		
Prevalence by age, y	2015 Estimate[b]	PET modality	CSF modality	2015 Estimate[b]	PET modality	CSF modality	2015 Estimate[b]	PET modality	CSF modality	2015 Estimate[b]	PET modality	CSF modality
20	NR	3.8 (1.9-7.3)	5.6 (3.1-10.0)	NA	NA	NA	NA	NA	NA	NA	NA	NA
25	NR	4.7 (2.5-8.7)	6.7 (3.9-11.3)	NA	NA	NA	NA	NA	NA	NA	NA	90.9 (78.8-96.4)
30	NR	5.7 (3.2-10.0)	8.5 (5.2-13.4)	NA	NA	NA	NA	NA	NA	NA	NA	NA
35	NR	7 (4.1-11.5)	10.2 (6.7-15.3)	NA	NA	NA	NA	NA	24.8 (17.4-34.0)	NA	NA	89.5 (78.9-95.1)
40	NR	8.4 (5.3-13.2)	12.3 (8.5-17.6)	NA	NA	13.3 (8.4-20.4)	NA	20.6 (13.5-30.3)	29.8 (22.4-38.4)	NA	91.5 (84.9-95.4)	NA
45	NR	10.2 (6.8-15.0)	14.8 (10.7-20.1)	NA	NA	16.5 (11.0-23.9)	NA	24.0 (16.5-33.4)	34.3 (27.2-42.2)	NA	90.9 (84.9-94.6)	87.8 (78.8-93.3)
50	10.4 (8.1-13.3)	12.3 (8.7-17.2)	17.6 (13.4-22.9)	11.6 (7.3-17.8)	14.3 (9.4-21.0)	19.6 (13.7-27.2)	26.9 (22.5-31.7)	29.8 (22.3-38.5)	39.2 (32.6-46.3)	93.0 (90.0-95.0)	90.0 (84.9-93.5)	87.1 (78.6-92.5)
55	12.9 (10.3-16.0)	14.8 (11.0-19.6)	20.9 (16.5-26.1)	14.2 (9.3-21.2)	16.5 (11.3-23.3)	23.1 (16.9-30.8)	31.8 (27.5-36.4)	33.9 (26.6-42.0)	44.3 (38.4-50.4)	NA	89.2 (84.7-92.5)	86.1 (78.4-91.4)
60	15.8 (12.9-19.1)	17.6 (13.8-22.3)	24.6 (20.1-29.8)	17.4 (11.6-25.2)	19.6 (14.1-26.5)	27 (20.4-34.9)	37.1 (32.9-41.6)	39.2 (32.5-46.4)	49.6 (44.3-54.8)	91.0 (89.0-93.0)	88.4 (84.5-91.5)	85.1 (78.1-90.2)
65	19.2 (16.0-22.9)	20.9 (17.0-25.3)	28.7 (23.9-34.0)	21.1 (14.4-29.7)	23.1 (17.4-30.0)	31.4 (24.4-39.3)	42.8 (38.7-47.1)	44.3 (38.3-50.6)	54.8 (50.1-59.5)	NA	87.6 (84.0-90.5)	84.1 (77.5-89.0)
70	23.1 (19.5-27.2)	24.6 (20.8-28.8)	33.2 (28.0-38.8)	25.3 (17.7-34.8)	27 (21.1-33.9)	36.1 (28.7-44.2)	48.7 (44.5-53.0)	49.6 (44.2-55.0)	60.0 (55.5-64.3)	88.0 (86.0-90.0)	86.6 (83.1-89.5)	82.9 (76.6-87.8)
75	27.6 (23.4-32.3)	28.7 (24.8-32.9)	38 (32.2-44.2)	30.0 (21.4-40.3)	31.4 (25.2-38.2)	41.1 (33.2-49.5)	54.6 (50.2-59.0)	54.8 (50.0-59.6)	64.9 (60.3-69.3)	NA	85.7 (81.8-88.8)	81.7 (75.4-86.8)
80	32.6 (27.6-38.0)	33.2 (29.1-37.6)	43.1 (36.4-50.0)	35.2 (25.6-46.2)	36.1 (29.6-43.1)	46.2 (37.7-55.0)	60.4 (55.7-65.0)	59.9 (55.3-64.4)	69.5 (64.5-74.1)	84.0 (81.0-87.0)	84.6 (80.0-88.4)	80.5 (73.7-85.9)
85	38.0 (32.2-44.2)	38.0 (33.3-42.9)	48.3 (40.6-56.0)	40.8 (30.3-52.3)	41.0 (34.2-48.3)	51.5 (42.3-60.6)	66.0 (60.8-70.7)	64.9 (60.1-69.3)	73.8 (68.3-78.6)	NA	83.5 (77.7-88.1)	79.2 (71.5-85.2)
90	43.8 (37.0-50.7)	43.1 (37.5-48.8)	53.6 (44.8-62.1)	43.1 (32.2-54.7)	46.3 (38.8-54.0)	53.6 (44.1-62.8)	71.1 (65.7-75.9)	69.5 (64.4-74.2)	76.9 (71.1-81.8)	79.0 (73.0-85.0)	82.4 (75.0-87.9)	77.9 (69.0-84.8)
95	NA	48.3 (41.6-55.0)	57.2 (47.7-66.2)	NA	NA	NA	NA	73.9 (68.4-78.8)	80.4 (74.3-85.4)	NA	81.2 (71.9-87.9)	NA
100	NA	54.1 (46.5-62.5)	NA	NA	NA	NA	NA	77.9 (72.0-82.9)	NA	NA	NA	NA

Abbreviations: AD, Alzheimer disease; CSF, cerebrospinal fluid; NA, not available; NR, not reported; PET, positron emission tomography.

[a] Prevalence estimates were generated from generalized estimating equations. Amyloid abnormality in groups with normal cognition, subjective cognitive decline, and mild cognitive impairment was modeled using age (statistical significance: $P < .001$), biomarker modality (statistical significance: $P = .004$), and cognitive status (statistical significance: $P < .001$) as risk factors. Amyloid abnormality in the AD dementia group was modeled using age (statistical significance: $P = .08$) and biomarker modality (statistical significance: $P = .18$) as risk factors. For some ages, a slightly younger or older age (SD, 3 years) was selected when the exact age was not available.

[b] 2015 Estimates from Jansen et al[6] or Ossenkoppele et al.[7]

for CSF; $P = .03$) (Figure 1; eFigure 2A and eTable 9 in the Supplement).

With adjusted CSF cutoffs, CSF-based amyloid abnormality estimates increased and became similar to PET-based estimates (mean difference, 4%; 95% CI, −2% to 9%; $P = .18$; further analyses were not corrected for biomarker modality). The decrease of amyloid abnormality prevalence with older age became no longer significant (Table 2, Figure 1; eFigure 2B and eTable 11 in the Supplement).

APOE ε4 carrier status was associated with higher amyloid abnormality prevalence, with a mean prevalence of 80% for noncarriers, 87% for heterozygotes, and 97% for homozygotes (mean difference: noncarriers vs heterozygotes, 7% [95% CI, −7% to 21%; $P = .33$]; noncarriers vs homozygotes, 17% [95% CI,

Table 3. Observed Mean Prevalence of Amyloid Abnormality According to Biomarker Modality, Cognitive Status, and Age[a]

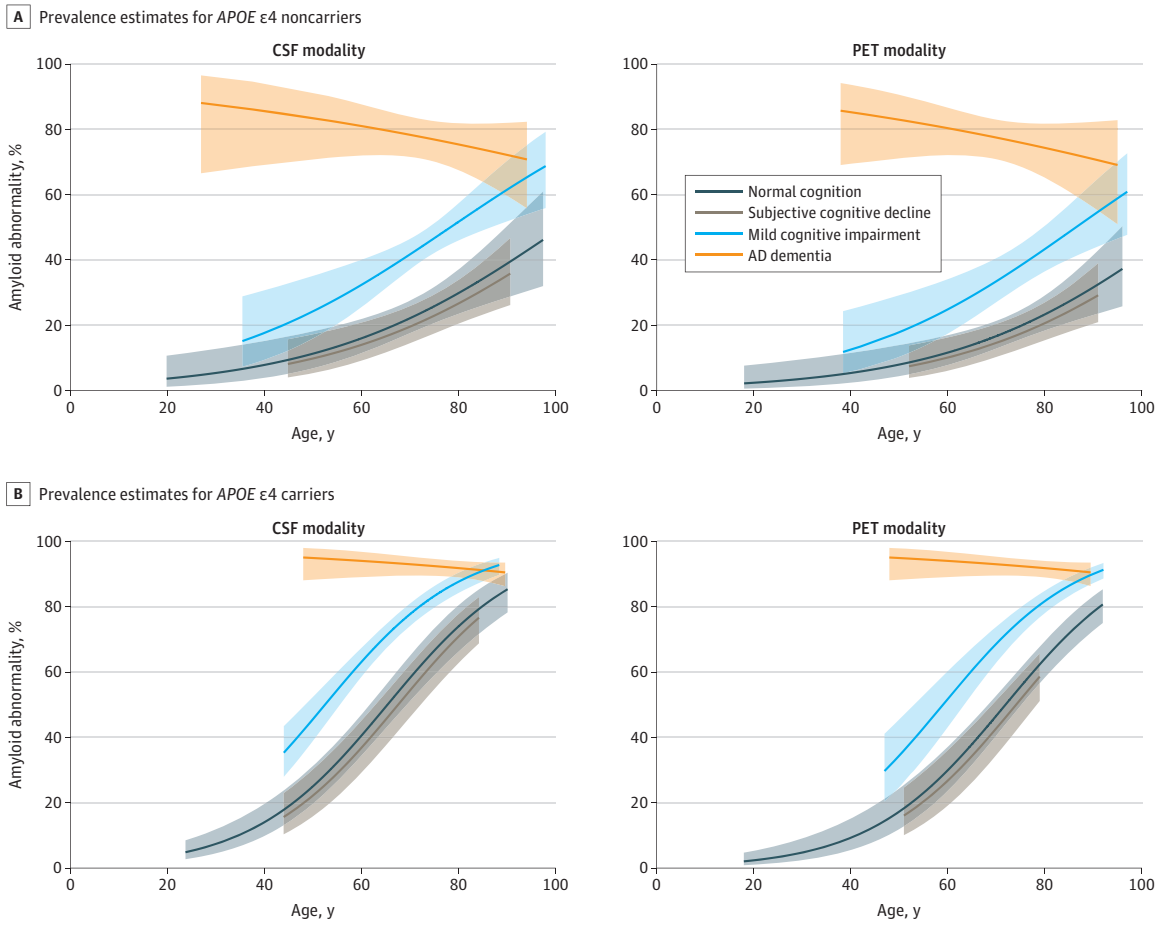
Age range, y	Cognitive status	No. with CSF measurement	Amyloid abnormality in CSF, No. (%)		No. with PET measurement	Amyloid abnormality on PET scans based on cohort-provided cutoff
			Based on cohort-provided cutoff	Based on adjusted cutoff		
50-54	Normal cognition	196	32 (16.3)	51 (26.0)	109	7 (6.4)
	Subjective cognitive decline	67	7 (10.4)	11 (16.4)	20	2 (10.0)
	Mild cognitive impairment	122	27 (22.1)	38 (31.1)	26	11 (42.3)
	Clinical AD dementia	49	40 (81.6)	43 (87.8)	47	41 (87.2)
55-59	Normal cognition	263	39 (14.8)	66 (25.1)	155	18 (11.6)
	Subjective cognitive decline	166	27 (16.3)	34 (20.5)	51	8 (15.7)
	Mild cognitive impairment	341	120 (35.2)	150 (44.0)	65	28 (43.1)
	Clinical AD dementia	89	77 (86.5)	81 (91.0)	166	153 (92.2)
60-64	Normal cognition	346	75 (21.7)	103 (29.8)	349	57 (16.3)
	Subjective cognitive decline	216	36 (16.7)	46 (21.3)	90	16 (17.8)
	Mild cognitive impairment	585	262 (44.8)	302 (51.6)	132	69 (52.3)
	Clinical AD dementia	145	122 (84.1)	129 (89.0)	183	157 (85.8)
65-69	Normal cognition	532	111 (20.9)	154 (28.9)	2692	555 (20.6)
	Subjective cognitive decline	236	50 (21.2)	61 (25.8)	118	25 (21.2)
	Mild cognitive impairment	804	403 (50.1)	461 (57.3)	221	110 (49.8)
	Clinical AD dementia	188	143 (76.1)	161 (85.6)	248	214 (86.3)
70-74	Normal cognition	510	143 (28.0)	166 (32.5)	1920	533 (27.8)
	Subjective cognitive decline	196	57 (29.1)	72 (36.7)	98	35 (35.7)
	Mild cognitive impairment	969	546 (56.3)	609 (62.8)	291	159 (54.6)
	Clinical AD dementia	187	163 (87.2)	171 (91.4)	235	207 (88.1)
75-79	Normal cognition	335	122 (36.4)	145 (43.3)	974	344 (35.3)
	Subjective cognitive decline	129	48 (37.2)	58 (45.0)	48	16 (33.3)
	Mild cognitive impairment	805	481 (59.8)	542 (67.3)	266	163 (61.3)
	Clinical AD dementia	166	133 (80.1)	141 (84.9)	235	199 (84.7)
80-84	Normal cognition	221	77 (34.8)	90 (40.7)	475	170 (35.8)
	Subjective cognitive decline	36	16 (44.4)	19 (52.8)	14	6 (42.9)
	Mild cognitive impairment	359	212 (59.1)	239 (66.6)	158	108 (68.4)
	Clinical AD dementia	91	78 (85.7)	81 (89.0)	124	104 (83.9)
85-89	Normal cognition	116	54 (46.6)	60 (51.7)	111	64 (57.7)
	Subjective cognitive decline	6	2 (33.3)	2 (33.3)	6	3 (50.0)
	Mild cognitive impairment	86	47 (54.7)	56 (65.1)	73	47 (64.4)
	Clinical AD dementia	33	26 (78.8)	27 (81.8)	48	33 (68.8)

Abbreviations: AD, Alzheimer disease; CSF, cerebrospinal fluid; PET, positron emission tomography.

[a] Percentage not shown when the number of participants who were stratified by age group, biomarker modality, and diagnosis was fewer than 5.

7%-28%; P = .002]; heterozygotes vs homozygotes, 10% [95% CI, 4%-17%; P = .002]) (eFigure 6 in the Supplement). *APOE* ε4 noncarriers no longer showed a steeper decrease in amyloid abnormality than *APOE* ε4 carriers, as previously observed (age × *APOE* P = .37). Sex was not associated with amyloid abnormality (AD dementia in female vs male, 86% vs 85%; P = .47). The association of educational level with amyloid abnormality depended on age (age × education P = .02). Higher educational level was associated with higher amyloid abnormality prevalence at age 60 years (mean difference, 7%; 95% CI, 1%-13%; P = .02), whereas at older ages, educational level was not associated with amyloid abnormality (mean difference, 4%; 95% CI, −1% to 9%; P = .11) (eFigure 5 in the Supplement). Among persons with clinical AD dementia, amyloid abnormality prevalence was higher in Australia at 98% than in Europe at 84%, Asia at 85%, and North America at 85% (mean difference, 13%-14%; 95% CI, 7%-24%; P = .002) (eFigure 7 in the Supplement). However, the number of participants with clinical AD dementia from Australia was relatively small (n = 107), with data from only 2 cohorts (1 population-based and 1 clinical) compared with 535 participants from 8 North American cohorts, 242 participants from 5 Asian cohorts, and 1376 participants from 28 European cohorts. The prevalence of amyloid abnormality was similar across mild (85%; 95% CI, 81%-88%), moderate (88%; 95% CI, 84%-91%), and severe (87%; 95% CI, 78%-92%) AD dementia cases; taking into account *APOE* ε4 carrier status, the prevalence rates for those with noncarrier status vs carrier status were 74% (95% CI, 68%-79%) vs 92% (95% CI, 89%-95%) for mild, 84% (95% CI, 73%-91%) vs 96% (95% CI, 92%-98%) for moderate, and 84% (95% CI, 64%-94%) vs 96% (95% CI, 88%-98%) for severe AD dementia (P = .17 vs P = .09) (eTable 12 and eFigure 8 in the Supplement).

Figure 2. Estimated Prevalence of Amyloid Abnormality According to Cognitive Status, Biomarker Modality, Age, and Apolipoprotein E (*APOE*) ε4 Carrier Status



Amyloid abnormality (based on adjusted cerebrospinal fluid [CSF] cutoffs and cohort-provided positron emission tomography [PET] cutoffs) in groups with normal cognition, subjective cognitive decline, and mild cognitive impairment was modeled using age (statistical significance: $P < .001$), cognitive status (statistical significance: $P < .001$), biomarker modality (statistical significance: $P = .01$), *APOE* ε4 carrier status (statistical significance: $P < .001$), and *APOE* ε4 carrier status by age (statistical significance: $P < .001$) as risk factors. Shaded areas indicate 95% CIs. Amyloid abnormality in the group with Alzheimer disease (AD) dementia was modeled using age (statistical significance: $P = .23$) and *APOE* ε4 carrier status (statistical significance: $P < .001$) as risk factors.

CSF- vs PET-Based Prevalence in Individuals With Both Measurements

In 21 cohorts with amyloid abnormality measured by both CSF and PET biomarkers in the same individuals (n = 1571 of 19 097 [8.2%]), 83% of the individuals (1304) had a concordant amyloid abnormality status (eTable 13 in the Supplement for comparison of individuals with concordant or discordant status). Amyloid abnormality prevalence using adjusted CSF cutoffs in persons with normal cognition (n = 477) was 34% (95% CI, 27%-42%) for CSF and 24% (95% CI, 17%-32%) for PET; in persons with subjective cognitive decline (n = 194), it was 31% (95% CI, 23%-40%) for CSF and 33% (95% CI, 26%-41%) for PET; in persons with mild cognitive impairment (n = 627), it was 53% (95% CI, 46%-59%) for CSF and 53% (95% CI, 45%-61%) for PET; and in persons with clinical AD dementia (n = 273), it was 67% (95% CI, 52%-80%) for CSF and 81% (95% CI, 68%-90%) for PET.

In a post hoc analysis, we compared amyloid abnormality estimates in cohorts with quantitatively vs visually rated PET scans but did not find a difference (mean difference quantitive vs visual in persons without dementia and those with dementia: 4% [95% CI, −6% to 13%; $P = .46$] vs 5% [95% CI, −2% to 12%]; $P = .14$).

Discussion

In this study, we estimated the prevalence of amyloid abnormality among 19 097 persons from 85 studies participating in the Amyloid Biomarker Study. Prevalence estimates based on cohort-provided PET and CSF cutoffs for participants with normal cognition, subjective cognitive decline, or mild cognitive impairment remained largely similar to the 2015 estimates, which included fewer cases.[6] The narrower CIs in the present study indicate more precise estimates especially in younger age groups. The CSF cutoff adjustment based on an unbiased gaussian mixture modeling approach identified 10% higher prevalence rates in persons without dementia, indicating that

preclinical and prodromal AD may be more prevalent than previously estimated.

The higher prevalence of amyloid abnormality in individuals with normal cognition, subjective cognitive decline, or mild cognitive impairment, which was measured using adjusted CSF cutoffs compared with PET imaging, is in line with previous findings in individuals without dementia.[18-21] This finding could mean that CSF assessment of amyloid abnormality is more sensitive than PET assessment. Because most PET studies applied a visual reading, which may be less sensitive than a quantitative reading,[22,23] we compared differences in amyloid abnormality between the 2 methods but did not find a difference. In the subsample with both biomarker modalities available, CSF estimates were higher than PET estimates in persons with normal cognition only. The question of whether CSF-based estimates are more sensitive than PET-based estimates for amyloid abnormality among people without dementia should be explored in studies that use both modalities and monitor the point at which PET abnormality follows CSF abnormality.

In clinical AD dementia, amyloid abnormality prevalence was lower with cohort-provided cutoffs for CSF than for PET estimates, whereas after CSF cutoff adjustment estimates were similar, suggesting again that uncorrected cutoffs might be too conservative. In a direct comparison of PET to CSF in persons with dementia, more than 90% of the results were concordant and the prevalence of amyloid abnormality in CSF was lower than on PET scans. Although both PET and CSF measurements in persons with dementia were available from relatively few cohorts, this result may reflect lower production of soluble amyloid forms in CSF as opposed to cumulative amyloid burden measured with PET in the dementia stage.[24-26]

The amyloid abnormality prevalence estimates in individuals without dementia are partly in line with the PET-based estimates from the population-based Mayo Clinic Study of Aging (MCSA), which was not included in the Amyloid Biomarker Study.[27] The PET-based estimates at age 85 years in individuals with normal cognition and subjective cognitive decline (38% and 41%, respectively, as shown in eTable 9 in the Supplement) were similar to that of the MCSA estimate (41%) at age 80 to 89 years. However, at age 50 to 59 years, the estimate was only 3% in the MCSA compared with 15% to 17% in the present study (as shown in eTable 9 in the Supplement). Also, the amyloid abnormality prevalence estimates in persons with mild cognitive impairment were much higher in this study than those in the MCSA: 34% vs 0% at age 50 to 59 years, and 65% vs 16% at age 80 to 89 years. These higher prevalence estimates may reflect the population-based design of the MCSA compared with the mostly research or clinical study settings of the present study.

Older age and *APOE* ε4 carrier status were associated with higher amyloid abnormality prevalence, in accordance with the 2015 results[6,7] and with previous studies.[28-30] The finding that the prevalence in *APOE* ε4 homozygous carriers started increasing first, followed by ε3ε4, ε2ε4, ε3ε3, and ε2ε3, fits largely with the previous findings.[6,7] In addition, we found approximately 10% higher prevalence of PET-based amyloid abnormality in ε3ε4 compared with ε2ε4, which is consistent with the protective effect of ε2.[31,32] In clinical AD dementia, amyloid abnormality prevalence was also higher in *APOE* ε4 homozygotes than *APOE* ε4 heterozygotes. The 2015 study observed that the prevalence of PET-based amyloid abnormality in those with dementia decreased with age, particularly for *APOE* ε4 noncarriers.[7] In the present study, however, this age-related decline was less prominent and no longer differed between *APOE* ε4 carriers and noncarriers.

Sex was not associated with amyloid abnormality in any disease stage, which is in line with previous studies and the MCSA.[6,7,33] Higher educational level was associated with a higher amyloid abnormality prevalence in persons without dementia, which is in accordance with previous findings.[6,7] This finding can be explained by delayed expression of amyloid-related cognitive decline because of higher cognitive reserve.[6,34,35]

No associations were found between geographical location and amyloid abnormality in persons without dementia, indicating no ethnicity-based difference in amyloid pathology prevalence. The higher prevalence in persons with clinical AD dementia in Australia should be interpreted cautiously and further investigated because relatively few cases originated from this region. Dementia severity was not associated with amyloid abnormality prevalence, which is in line with the notion that amyloid aggregation is an early marker that becomes abnormal years before dementia onset.[20,36]These estimates may guide health care planning, providing potential eligible patient population sizes for antiamyloid therapies, and recruitment strategies for clinical trials.

Strengths and Limitations

We combined data that were collected on persons across the AD spectrum within many cohorts in various settings and geographical locations. Studying individual participant-level data rather than aggregated data increased the statistical power to detect subgroup and interaction outcomes[37]; however, multiple cohorts also used different amyloid assessment methods, cutoff definitions, and study designs. The study showed that the potential bias introduced by these variations between cohorts might be reduced when using the same method to identify the cutoffs in CSF.[12,13,16] Nonetheless, we could only apply this method to a subset of cohorts that provided continuous data, and some cohorts did not show a multimodal distribution.

The use of cohort-specific cutoffs to define abnormal amyloid for cohorts for which no data-driven cutoff could be calculated may have led to an underestimation of amyloid abnormality in these cohorts. We expect this potential underestimation to be limited given that the sample sizes for most of these Amyloid Biomarker Study cohorts included were small. Another limitation is the cross-sectional design of the study, which might underestimate amyloid abnormality as opposed to lifetime risk estimates. Furthermore, generalizability of the findings to the general population might be limited. In addition, persons with AD dementia were clinically diagnosed, and it remains unknown whether these diagnoses were correct on histopathological examination.

Conclusions

This study found that the prevalence of amyloid abnormality based on data-driven CSF cutoffs among persons with normal cognition, subjective cognitive decline, or mild cognitive impairment appeared to be 10% higher compared with cohort-provided CSF and PET cutoffs. The CSF- and PET-based estimates were similar for those with clinical AD dementia. Older age, *APOE* ε4 gene dose, and higher educational level were associated with higher prevalence of amyloid abnormality. These updated estimates suggest that preclinical and prodromal AD are more prevalent than previously estimated. The findings may be useful in health care planning, providing potential eligible patient population sizes for antiamyloid therapies, and in recruitment strategies for clinical trials.

ARTICLE INFORMATION

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Correction: This article was corrected on March 14, 2022, to fix the affiliations for Agneta Nordberg, MD, PhD and the Figure 1 caption.

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