Association of Cerebral Amyloid-β Aggregation With Cognitive Functioning in Persons Without Dementia

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IMPORTANCE Cerebral amyloid-β aggregation is an early event in Alzheimer disease (AD). Understanding the association between amyloid aggregation and cognitive manifestation in persons without dementia is important for a better understanding of the course of AD and for the design of prevention trials.

OBJECTIVE To investigate whether amyloid-β aggregation is associated with cognitive functioning in persons without dementia.

DESIGN, SETTING, AND PARTICIPANTS This cross-sectional study included 2908 participants with normal cognition and 4133 with mild cognitive impairment (MCI) from 53 studies in the multicenter Amyloid Biomarker Study. Normal cognition was defined as having no cognitive concerns for which medical help was sought and scores within the normal range on cognitive tests. Mild cognitive impairment was diagnosed according to published criteria. Study inclusion began in 2013 and is ongoing. Data analysis was performed in January 2017.

MAIN OUTCOMES AND MEASURES Global cognitive performance as assessed by the Mini-Mental State Examination (MMSE) and episodic memory performance as assessed by a verbal word learning test. Amyloid aggregation was measured with positron emission tomography or cerebrospinal fluid biomarkers and dichotomized as negative (normal) or positive (abnormal) according to study-specific cutoffs. Generalized estimating equations were used to examine the association between amyloid aggregation and low cognitive scores (MMSE score ≤27 or memory *z* score≤−1.28) and to assess whether this association was moderated by age, sex, educational level, or apolipoprotein E genotype.

RESULTS Among 2908 persons with normal cognition (mean [SD] age, 67.4 [12.8] years), amyloid positivity was associated with low memory scores after age 70 years (mean difference in amyloid positive vs negative, 4% [95% CI, 0%-7%] at 72 years and 21% [95% CI, 10%-33%] at 90 years) but was not associated with low MMSE scores (mean difference, 3% [95% CI, −1% to 6%], *P* = .16). Among 4133 patients with MCI (mean [SD] age, 70.2 [8.5] years), amyloid positivity was associated with low memory (mean difference, 16% [95% CI, 12%-20%], *P* < .001) and low MMSE (mean difference, 14% [95% CI, 12%-17%], *P* < .001) scores, and this association decreased with age. Low cognitive scores had limited utility for screening of amyloid positivity in persons with normal cognition and those with MCI. In persons with normal cognition, the age-related increase in low memory score paralleled the age-related increase in amyloid positivity with an intervening period of 10 to 15 years.

CONCLUSIONS AND RELEVANCE Although low memory scores are an early marker of amyloid positivity, their value as a screening measure for early AD among persons without dementia is limited.

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Supplemental content

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Cerebral amyloid-β aggregation is an early pathologic event in Alzheimer disease (AD), starting 2 to 3 decades before dementia onset.[1,2] Approximately 25% of cognitively normal elderly individuals and 50% of patients with mild cognitive impairment (MCI) have biomarker evidence of amyloid pathology.[1,3] These persons are at increased risk for developing AD-type dementia,[1] but the extent to which amyloid-β aggregation is associated with cognition in persons without dementia is unclear. Understanding the association between amyloid pathology and cognitive functioning is important for a better understanding of the course of AD and for the design of AD-prevention trials.

Longitudinal cohort studies[4-6] have revealed an association between the presence of amyloid pathology and long-term cognitive decline. To assess the role of cognitive screening as a tool to enrich AD clinical trials, the cross-sectional association also needs to be established. However, findings from cross-sectional studies in cognitively normal individuals[4,7,8] and patients with MCI[7,9,10] have been inconsistent. This variability may be caused by differences among studies in demographic and genetic factors, disease stage and reserve capacity, and methodologic approaches. Effects are mainly observed in the episodic memory and global cognition domains and tend to be small,[11] indicating that large samples are needed to investigate the amyloid-cognition association.

We previously estimated the prevalence of amyloid positivity in persons without dementia and, in the present study, investigated the association between amyloid positivity and cognitive scores in this population by using individual participant data from 53 studies included in the multicenter Amyloid Biomarker Study.[1] We also examined whether age, cognitive status, sex, educational level, and apolipoprotein E (*APOE*) genotype modify the association between amyloid status and global cognition or episodic memory; estimated temporal associations among amyloid positivity, low memory scores, and AD-type dementia; and tested the usefulness of cognitive scores as a screening instrument for amyloid positivity.

Key Points

Question Is cerebral amyloid-β aggregation, a key characteristic of Alzheimer disease, associated with cognitive functioning in persons without dementia?

Findings In this cross-sectional, multicenter study of 7041 persons without dementia, amyloid-positive persons with normal cognition had low episodic memory scores almost twice as often as persons without amyloid aggregation after the age of 70 years. Low memory scores emerged 10 to 15 years after the onset of amyloid positivity.

Meaning Alzheimer disease manifests through low memory scores in elderly persons with normal cognition, but a low memory score has limited value as a screening tool for early Alzheimer disease.

Methods

Participants

Participants were recruited from studies that participated in the multicenter Amyloid Biomarker Study[1] on establishing the prevalence of amyloid pathology measured with a positron emission tomography (PET) or cerebrospinal fluid (CSF) biomarker. For details on study selection and data collection, see Jansen et al.[1] Study inclusion began in 2012 and is ongoing. At time of analysis (January 2017), we included participant-level data from 2908 participants with normal cognition and 4133 patients with MCI from 53 studies that had data available on the Mini-Mental State Examination (MMSE) and/or an episodic memory score. Participants with normal cognition had no cognitive concerns for which medical help was sought and scored within the normal range on cognitive tests. The diagnosis of MCI was made according to published criteria, including subjectively experienced and objectively verified decline in memory or another cognitive domain. Characteristics of the included studies are given in eTable 1 in the Supplement. All participants gave written informed consent to participate, and data were deidentified. Study protocols were approved by the local ethics committees of all centers participating in the Amyloid Biomarker Study.

Cognitive Tests

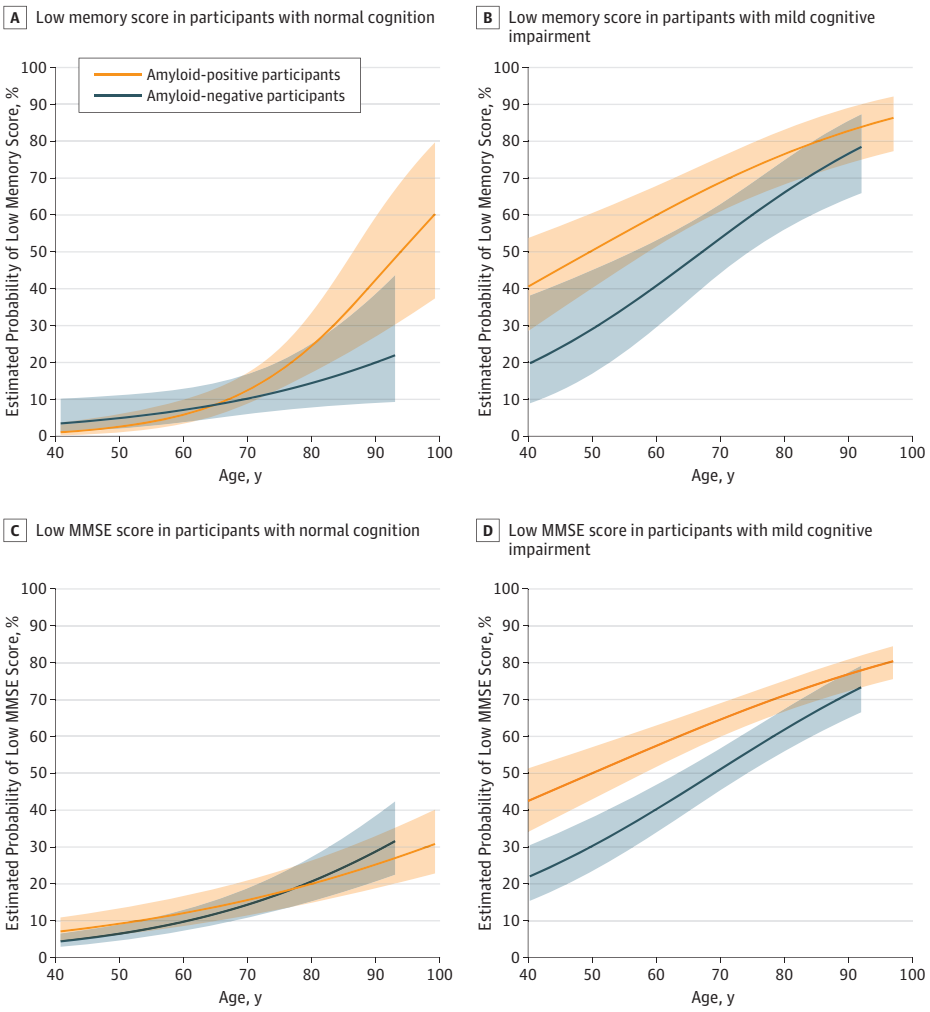
Global cognition was assessed with the MMSE.[12] The MMSE scores were available from 53 studies comprising a total of 2885 participants with normal cognition (38 studies) and 4133 patients with MCI (48 studies). A low MMSE score was defined as 27 or less.

Episodic memory was assessed with verbal word learning tests. Data were available from 31 studies including 2010 participants with normal cognition (21 studies) and 2615 patients with MCI (26 studies). Most studies provided raw scores (28 studies) that were transformed into *z* scores using the mean and SD of the center-specific group of cognitively unimpaired individuals or, in the absence of such a group, using published test-specific means. Three studies provided *z* scores that were calculated similarly. Episodic memory was assessed using 12 different verbal memory tests of immediate or delayed recall. When multiple memory test scores were provided for a participant, the delayed recall score was chosen. Tests of delayed recall were used for 2809 participants (21 studies) and tests of immediate recall for 1816 participants (10 studies). See eTable 2 in the Supplement for an overview of the memory tests used in each study. In our analyses, low episodic memory performance was defined as a *z* score of −1.28 or less, capturing performance in the 10th percentile or lower of the population mean.

Amyloid Assessment

In the sample selected for these analyses, amyloid pathology was assessed with amyloid-PET in 1224 participants with normal cognition (21 studies) and 956 patients with MCI (23 studies) and by amyloid-β1-42 level in CSF in 1684 participants with normal cognition (19 studies) and 3177 with MCI (29 studies). Measurement details have been described previously.[1] The PET and CSF biomarkers were dichotomized as negative (normal) or positive (abnormal) according to study-specific cutoffs or visual reads.

Figure 1. Frequencies of Low Memory and Low Mini-Mental State Examination (MMSE) Scores



A and B, Model with terms for age, amyloid status, and cognitive status and up to 3-way interactions among these terms (3-way interaction $P = .002$). C, and D, Model with terms for age, amyloid status, cognitive status, and interactions between amyloid status and age ($P = .03$) and between amyloid status and cognitive status ($P < .001$). Adjustment for sex and educational level did not change either model. Low score was defined as 10th percentile or lower of *z* scores for the memory score and 27 or lower for MMSE scores. Shading indicated 95% CIs.

Data Availability

Information on the level of education was available for 2558 participants (88.0%) with normal cognition (memory score: n = 1973; MMSE: n = 2536) and 3270 patients (79.1%) with MCI (memory score: n = 2456; MMSE: n = 3264). Information on *APOE*-ε4 carrier status (yes or no) was available for 2400 participants (82.5%) with normal cognition (memory score: n = 1764; MMSE: n = 2379) and 3292 patients (79.7%) with MCI (memory score: n = 2217; MMSE: n = 3286). The *APOE* genotype was available for 2347 participants (80.7%) with normal cognition (memory score: n = 1763; MMSE: n = 2326) and 3019 patients (73.0%) with MCI (memory score: n = 2215; MMSE: n = 3013).

Temporal Association Among Amyloid Positivity, Low Memory Scores, and AD-Type Dementia

To provide an estimation of the temporal associations among amyloid positivity, low memory scores, and AD-type dementia, we compared age-specific frequency estimates of low memory scores and amyloid positivity in participants with normal cognition with age-specific prevalence data of AD-type dementia in the general population (adopted from Jansen et al[1]).

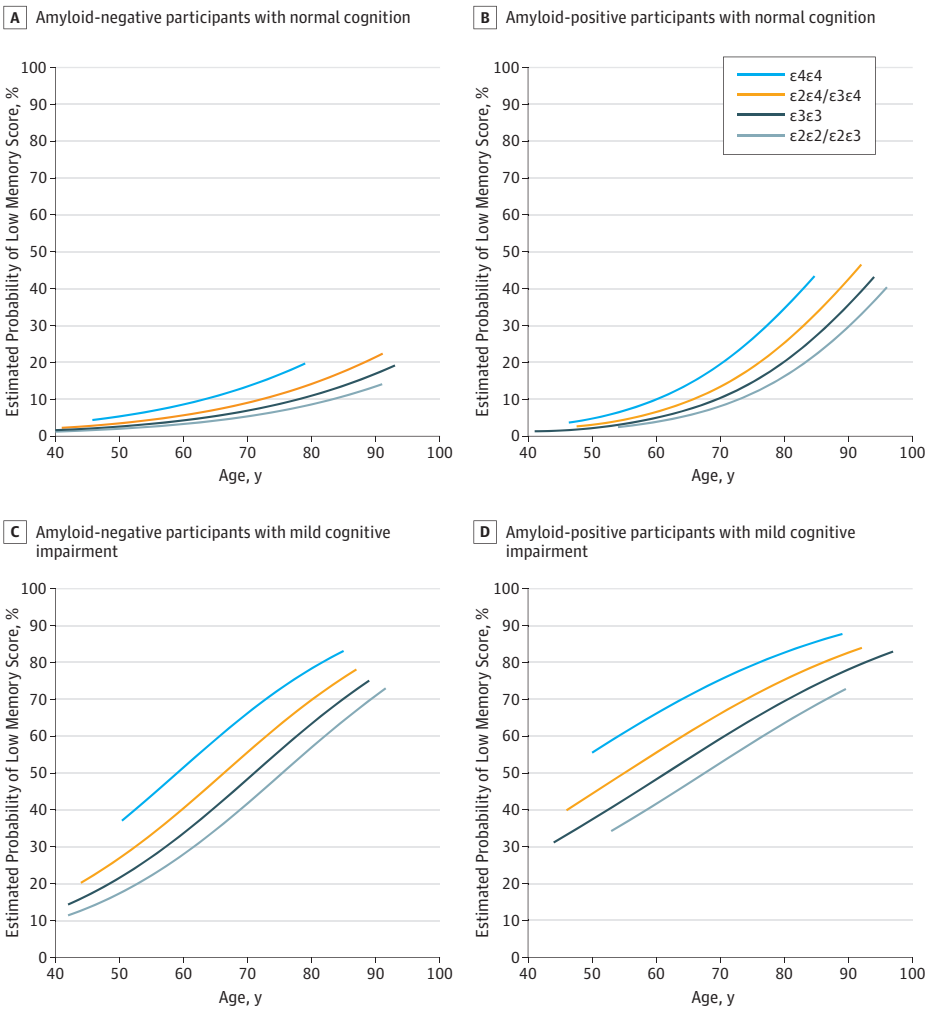
Cognitive Screening as an Indication of Amyloid Status

To investigate the screening potential of low cognitive scores, we calculated the odds of low cognitive performance for amyloid positivity and examined improvement in area under the receiver operating characteristic curve when cognitive scores were added to a model with age and *APOE*-ε4 carrier status.

Statistical Analysis

Differences in clinical and demographic characteristics between the amyloid-positive and amyloid-negative subgroups were analyzed using analyses of variance for continuous variables and χ^2 tests for categorical variables. Dichotomized MMSE and memory scores (low vs normal) were used as outcome variables in generalized estimating equations. Generalized estimating equations allow for the analysis of binary correlated

Figure 2. Frequency of Low Memory Score According to Apolipoprotein E (*APOE*) Genotype



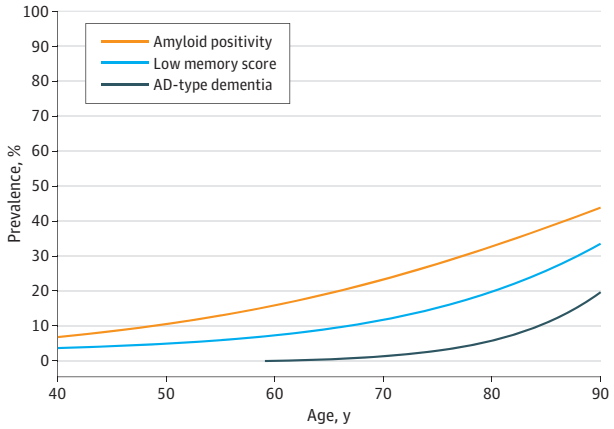
Model with terms for age, amyloid status, cognitive status, and up to 3-way interactions among these terms (3-way interaction $P = .007$), *APOE* genotype, and interactions among *APOE* genotype, amyloid status, and cognitive status ($P = .02$). Adjustment for sex and educational level did not change the model. Low score was defined as 10th percentile or lower of *z* scores.

data such that participant-level data from all studies could be modeled simultaneously while 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. Age was included as a continuous measure and was centered at the median. Educational level was dichotomized at the median (high [≥14 years] vs moderate to low [<14 years]). For each outcome measure, we performed the following 6 models. The first model included amyloid pathology (present or absent), cognitive status (normal cognition or MCI), age, interactions among these 3 variables as predictors, and sex and educational level as covariates. In the second, third, and fourth models, we added sex (model 2), educational level (model 3), and *APOE*-ε4 carrier status (model 4) with up to 3-way interactions of these variables with amyloid pathology, cognitive status, and age. In the fifth model, we entered all variables and included up to 3-way interactions among age, sex, educational level, *APOE*-ε4 carrier status, cognitive status, and amyloid pathology using a forward selection method. In the sixth model, we examined whether *APOE* genotype (coded as ε4ε4, ε2ε4/ε3ε4, ε3ε3, or ε2ε2/ε2ε3) modified the association among amyloid, age, and cognition while correcting for sex and educational level. Terms were retained in the equation in case of a significant Wald statistic ($P < .05$). For an overview of significant terms in each of the models tested, see eTable 3 in the Supplement. We report estimates corrected for age, sex, and educational level in the text. Models unadjusted for sex and educational level yielded similar results and were used to display estimates in **Figures 1**, **2**, **3** and **Table 1** and **Table 2**. Associations did not change after correcting for multiple comparisons with the Bonferroni method. Secondary analyses are described in eAppendix 1 and eFigure3 in the Supplement. Analyses were conducted with SPSS statistical software, version 22.0 (IBM Corp), with a significance level set at $P < .05$ for unpaired, 2-sided tests.

Results

A total of 2908 persons with normal cognition (mean [SD] age, 67.4 [12.8] years; 1628 of 2896 participants [56.2%] were female) and 4133 patients with MCI (mean [SD] age, 70.2 [8.5] years; 1911

Figure 3. Prevalence of Amyloid Positivity and Low Memory Score in Participants With Normal Cognition and of Alzheimer Disease (AD)–Type Dementia in the General Population



Prevalence estimates of amyloid positivity and low memory score were derived from separate models including age as a predictor. Prevalence estimates of AD-type dementia were derived from a meta-analysis of 14 studies.[1] Low score was defined as 10th percentile or lower of *z* scores.

female [46.2%]) participated in the study. Sample characteristics of the participants with normal cognition and MCI according to amyloid status are given in Table 1. The amyloid-positive and amyloid-negative groups differed on all variables except sex in participants with normal cognition and MCI and except MMSE score in participants with normal cognition.

Association Between Amyloid Status and Episodic Memory Score

Amyloid positivity was differentially associated with low memory scores across age and diagnostic groups (3-way interaction; β = −0.54 [95% CI, −0.097 to −0.011]). In participants with normal cognition, low memory scores were more frequent in amyloid-positive than in amyloid-negative participants but only after 70 years of age (mean difference for amyloid-positive vs amyloid-negative participants at 72 years of age, 4% [95% CI, 0%-7%], $P = .04$; at 90 years of age, 21% [95% CI, 10%-33%], $P < .001$). At 80 years of age, the frequency of low memory scores in amyloid-positive participants with normal cognition was almost double that of their amyloid-negative counterparts (25% vs 14%) (Figure 1A and Table 2). In patients with MCI, amyloid-positive participants more often had low memory scores than amyloid-negative participants (mean difference, 16% [95% CI, 12%-20%],

Table 1. Study Sample Characteristics by Cognitive Status and Amyloid Status[a]

Characteristic	Normal Cognition			MCI		
	Amyloid Negative (n = 2166)	Amyloid Positive (n = 742)	*P* Value	Amyloid Negative (n = 2000)	Amyloid Positive (n = 2133)	*P* Value
Age, mean (SD), y	65.6 (13.2)	72.9 (9.5)	<.001	68.6 (8.9)	71.7 (7.9)	<.001
Age groups, y						
<40	127 (5.9)	2 (0.3)		1 (0.1)	0	
40-49	91 (4.2)	10 (1.3)		29 (1.5)	8 (0.4)	
50-59	311 (14.4)	55 (7.4)		309 (15.5)	147 (6.9)	
60-69	714 (33.0)	180 (24.3)	NA	719 (36.0)	654 (30.7)	NA
70-79	714 (33.0)	322 (43.4)		736 (36.8)	1004 (47.1)	
80-89	195 (9.0)	160 (21.6)		200 (10.0)	308 (14.4)	
≥90	14 (0.6)	13 (1.8)		6 (0.3)	11 (0.5)	
Women	1231/2154 (57.1)	397/742 (53.5)	.08	898/2000 (45.0)	1013/2133 (47.5)	.11
Educational level						
Mean (SD), y	14.2 (3.7)	14.7 (3.7)	.001	11.8 (4.2)	12.7 (4.4)	<.001
High level (≥14 y)	1107/1906 (58.1)	430/652 (66.0)	<.001	536/1597 (33.6)	732/1673 (43.8)	<.001
MMSE score						
Mean (SD)	29.1 (1.2)	28.9 (1.3)	.001	27.2 (2.3)	26.4 (2.6)	<.001
MMSE score ≤27	208/2148 (9.7)	88/737 (11.9)	.08	938/1999 (46.9)	1312/2128 (61.7)	<.001
Memory *z* score						
Mean (SD)	0.04 (0.95)	−0.16 (1.07)	<.001	−1.27 (1.58)	−1.78 (1.47)	<.001
Memory *z* score ≤1.28	130/1480 (8.9)	76/530 (14.3)	<.001	594/1256 (47.3)	878/1359 (64.6)	<.001
APOE-ε4 positive	402/1746 (23.0)	324/654 (49.5)	<.001	421/1510 (27.9)	1134/1782 (63.5)	<.001
APOE genotype						
ε2ε2/ε2ε3	263/1713 (15.4)	26/634 (4.1)		172/1407 (12.2)	61/1612 (3.8)	
ε3ε3	1052/1713 (61.4)	293/634 (46.2)	NA	829/1407 (58.9)	513/1612 (31.8)	NA
ε2ε4/ε3ε4	376/1713 (21.9)	263/634 (41.5)		365/1407 (25.9)	753/1612 (46.7)	
ε4ε4	22/1713 (1.3)	52/634 (8.2)		41/1407 (2.9)	285/1612 (17.7)	

Abbreviations: *APOE*, apolipoprotein E; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; NA, not applicable.

[a] Data are presented as number/total number (percentage) of study participants unless otherwise indicated. Amyloid-negative and amyloid-positive subgroups were compared among participants with normal cognition and among patients with MCI with *t* tests or χ^2 tests.

Table 2. Estimated Frequencies of Low Cognitive Performance According to Amyloid Status and Age[a]

	Frequency, % (95% CI)											
	Memory						MMSE					
	Normal Cognition			MCI			Normal Cognition			MCI		
Age, y	Amyloid Negative	Amyloid Positive	*P* Value	Amyloid Negative	Amyloid Positive	*P* Value	Amyloid Negative	Amyloid Positive	*P* Value	Amyloid Negative	Amyloid Positive	*P* Value
50	4.9 (2.1-11.1)	2.7 (1.2-6.1)	.17	29.1 (17.0-45.1)	50.4 (40.1-60.6)	<.001	6.5 (4.7-9.0)	9.3 (6.3-13.4)	.09	30.2 (23.4-38.0)	50.0 (42.9-57.1)	<.001
55	5.9 (2.9-11.8)	4.0 (2.0-7.7)	.24	34.8 (22.8-49.0)	55.3 (45.9-64.2)	<.001	8.0 (5.9-10.8)	10.6 (7.4-15.0)	.11	35.0 (28.4-42.3)	53.7 (47.3-60.0)	<.001
60	7.1 (3.8-12.9)	5.9 (3.4-9.9)	.47	40.9 (29.6-53.2)	60.0 (51.5-68.0)	<.001	9.8 (7.3-13.0)	12.1 (8.6-16.7)	.15	40.2 (33.9-46.8)	57.4 (51.7-62.9)	<.001
65	8.5 (4.9-14.5)	8.6 (5.6-12.9)	.97	47.3 (37.0-57.8)	64.6 (56.6-71.9)	<.001	11.9 (9.0-15.6)	13.8 (10.0-18.7)	.24	45.6 (39.6-51.6)	61.0 (55.9-65.9)	<.001
70	10.2 (6.0-16.8)	12.4 (8.9-17.2)	.20	53.8 (44.3-63.0)	68.9 (61.1-75.8)	<.001	14.4 (10.9-18.8)	15.7 (11.5-21.0)	.43	51.0 (45.3-56.7)	64.5 (59.8-69.0)	<.001
75	12.2 (7.0-20.3)	17.7 (12.9-23.8)	.002	60.1 (50.7-68.9)	72.9 (65.0-79.7)	<.001	17.3 (13.0-22.7)	17.7 (13.1-23.5)	.80	56.5 (50.8-62.0)	67.9 (63.5-72.0)	<.001
80	14.4 (7.8-25.1)	24.5 (17.3-33.6)	<.001	66.2 (56.2-74.9)	76.6 (68.4-83.2)	<.001	20.7 (15.3-27.3)	20.0 (14.9-26.4)	.73	61.8 (55.9-67.3)	71.1 (66.7-75.1)	<.001
85	17.0 (8.5-21.3)	32.9 (22.0-46.1)	<.001	71.7 (60.7-80.7)	79.9 (71.4-86.4)	.004	24.5 (17.9-32.6)	22.6 (16.8-29.5)	.39	66.8 (60.6-72.5)	74.1 (69.6-78.0)	.001
90	20.0 (9.0-38.6)	42.6 (27.0-59.7)	<.001	76.7 (64.6-85.6)	82.9 (74.1-89.1)	.07	28.8 (20.7-38.5)	25.3 (18.9-33.0)	.22	71.5 (64.9-77.3)	76.8 (72.3-80.9)	.03

Abbreviations: MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination.

[a] Data are estimated probabilities uncorrected for sex, educational level, and apolipoprotein E ε4 carrier status. The model for memory included terms for age, amyloid status, cognitive status, and interactions among these terms (3-way interaction $P = .002$). The model for MMSE included terms for age, amyloid status, cognitive status, and interactions between amyloid status and age ($P = .02$), and between amyloid status and cognitive status ($P < .001$). Adjustment for sex and educational level did not change the models. Low score was defined as 10th percentile or lower of *z* scores for the low memory score and 27 or lower for low MMSE scores.

$P < .001$) (Figure 1B and Table 2), although this difference decreased with advancing age.

In participants with normal cognition and patients with MCI, sex, educational level, and *APOE*-ε4 carrier status were each associated with memory scores but did not moderate the association between amyloid status and memory scores (eFigure 1A in the Supplement). A low memory score was more frequent in men than in women (mean difference, 8% [95% CI, 3%-14%], $P = .004$), in participants with low rather than high educational level (mean difference, 8% [95% CI, 5%-11%], $P < .001$), and in *APOE*-ε4 carriers than in noncarriers (mean difference, 8% [95% CI, 4%-11%], $P < .001$).

Furthermore, *APOE* genotype was associated with low memory score independent of amyloid status, cognitive status, or age (Figure 2). Participants with the *APOE*-ε4ε4 genotype most often had a low memory score (mean difference vs ε2ε4/ε3ε4, 10% [95% CI, 4%-16%], $P < .001$; vs ε3ε3, 16% [95% CI, 9%-24%], $P < .001$; vs ε2ε2/ε2ε3, 21% [95% CI, 9%-24%], $P < .001$), followed by participants with the *APOE*-ε2ε4/ε3ε4 genotype (mean difference vs ε3ε3, 6% [95% CI, 3%-9%], $P < .001$; vs ε2ε2/ε2ε3, 11% [95% CI 4%-17%], $P = .001$) and the *APOE*-ε3ε3 and *APOE*-ε2ε2/ε2ε3 genotypes (mean difference, 5% [95% CI, −1% to 10%], $P = .09$).

Association Between Amyloid Status and MMSE Score

The association between amyloid positivity and a low score on the MMSE was dependent on age (β = 0.023 [95% CI, 0.009-0.037, $P = .001$ for interaction) and cognitive status (β = 0.348 [95% CI, 0.032-0.665], $P = .03$ for interaction; β = 0.006 [95% CI, −0.033 to 0.044], $P = .10$ for 3-way interaction). In participants with normal cognition, amyloid positivity was not associated with low MMSE scores at any age (mean difference, 3% [95% CI, −1% to 6%], $P = .16$) (Figure 1C and Table 2). In patients with MCI, the frequency of low MMSE scores was greater in amyloid-positive compared with amyloid-negative patients at all ages (mean difference, 14% [95% CI, 12%-17%], $P < .001$) (Figure 1D and Table 2).

When adjusting for sex, educational level, and *APOE*-ε4 carrier status, none of these factors modulated the association between amyloid status and MMSE score in participants with normal cognition or patients with MCI. *APOE*-ε4 carriership was more often associated with low MMSE scores regardless of cognitive status and age (mean difference, 4% [95% CI, 2%-7%], $P < .001$). Sex (β = −0.444 [95% CI, −0.681 to −0.207; $P<.001$ for interaction) and educational level (β = −0.554 [95% CI, −0.874 to −0.234], $P<.001$ for interaction) had an association with MMSE score that was dependent on cognitive status (eFigure 1B in the Supplement).

In addition, *APOE* genotype was associated with low MMSE score ($P = .002$) (eFigure 2 in the Supplement) independent of amyloid status, cognitive status, and age. Participants with the *APOE*-ε4ε4 genotype most often had a low MMSE score (mean difference vs ε2ε4/ε3ε4, 6% [95% CI, 0%-12%], $P = .06$; vs ε3ε3, 10% [95% CI, 3%-16%], $P = .005$; vs ε2ε2/ε2ε3, 10% [95% CI, 3%-16%], $P = .005$) followed by participants with the *APOE*-ε2ε4/ε3ε4 genotype (mean difference vs ε3ε3, 4% [95% CI, 1%-6%], $P = .008$; vs

ε2ε2/ε2ε3, 4% [95% CI, 1%-8%], P = .14) and the *APOE*-ε3ε3 and *APOE*-ε2ε2/ε2ε3 genotypes (mean difference, 0% [95% CI, −4% to 4%], P = .99).

Amyloid Positivity, Low Memory Scores, and AD-Type Dementia

In participants with normal cognition, the age-related increase in low memory scores paralleled the age-related increase in amyloid positivity with an intervening period of 10 to 15 years. Subsequently, the age-related increase in low memory score was paralleled by an age-related increase in prevalence of AD-type dementia 10 to 15 years later (Figure 3).

Cognitive Screening as an Indication of Amyloid Status

The odds ratio of low memory score for amyloid positivity varied depending on age from 1.06 to 1.80 for participants with normal cognition and from 1.47 to 2.81 for patients with MCI. The odds ratio of low MMSE score varied from 0.77 to 1.19 for participants with normal cognition and from 1.32 to 2.15 for patients with MCI (eTable 4 in the Supplement). The receiver operating characteristic curve analyses showed that low memory or MMSE scores did not add to the estimation of amyloid positivity above that of age and *APOE*-ε4 carrier status (eTable 5 in the Supplement).

Discussion

In this cross-sectional analysis of adults without dementia enrolled from multiple studies, amyloid pathology was associated with low memory scores among cognitively normal individuals older than 70 years and in patients with MCI until old age, whereas it was associated with low MMSE scores in patients with MCI only. However, a low cognitive score had limited value as a screening measure for early AD. The association between amyloid pathology and cognition existed independent of sex, educational level, and *APOE* genotype, but these factors contributed to individual estimates of cognitive level. We further observed 10- to 15-year intervals between the onset of amyloid positivity and emergence of low memory scores in persons with normal cognition and between the age-related increase in low memory scores and prevalence of AD-type dementia.

Of note, the proportion of low memory scores in amyloid-positive participants with normal cognition increased rapidly after the age of 70 years. Possible explanations for this age association are that more extensive amounts of amyloid deposition are needed before becoming clinically manifest, that other pathology is also present after this age, or that cognitive vulnerability to amyloid pathology may be higher at older age. This finding agrees with a recent population-based study[13] in cognitively normal individuals aged 50 to 69 years in which amyloid-PET levels were unrelated to cross-sectional and longitudinal measures of episodic memory. Previous contrasting findings from cross-sectional studies[4,7,8] that examined the amyloid-cognition association may therefore, in addition to the previously identified task complexity,[14] be explained by age of the individuals in the study sample.

We found no association of amyloid pathology with low MMSE score in participants with normal cognition. This result contrasts with a meta-analysis of biomarker and neuropathologic studies.[11] However, that meta-analysis also included global cognition tests that have a larger memory component than the MMSE.

In patients with MCI, amyloid-positive patients had (depending on age) low memory and MMSE scores 5% to 20% more often than amyloid-negative patients. Unlike in participants with normal cognition, frequencies of low cognitive scores in amyloid-positive and amyloid-negative patients were more similar at older ages in patients with MCI. This finding is in line with a study in persons with dementia,[15] suggesting that neuropathologic changes other than amyloid may contribute to cognitive impairment at more advanced age in patients with MCI but not in persons with normal cognition.

Sex and amyloid pathology independently predicted cognitive performance, suggesting that amyloid-related cognitive decline is equally prevalent in men and women, as has also been suggested in a large cross-sectional study[16] of cognitively normal individuals from the general population not included in our study. High educational level was also associated with fewer cognitive deficiencies independent of amyloid status. This finding is consistent with earlier studies[17,18] showing that cognitive reserve helps to preserve cognition in pathologic conditions and aging. Our study suggests that a high educational level does not counteract the effect of amyloid pathology on cognition but instead delays its expression, which agrees with earlier studies.[19,20]

Each *APOE*-ε4 allele increased the risk of low cognitive performance independent of amyloid status. Previous longitudinal studies examining the association among *APOE*-ε4, amyloid positivity, and cognition have had mixed results and identified mediating[8,21] or interactive effects.[22-24] Remarkably, our results indicate that the *APOE* genotype was also associated with cognitive performance in amyloid-negative participants. This finding may relate to subthreshold pathologic aggregation[25,26] or to the association of *APOE*-ε4 genotype with non–amyloid-dependent processes in the brain that are associated with cognitive functioning.[27]

This study has implications for understanding the individual contributions of amyloid pathology and various AD risk factors to cognitive decline and the time course of AD. Therefore, these findings are important for the design of secondary AD prevention trials. Because amyloid positivity has become a requirement for enrollment in many AD prevention trials, cognitive testing would be an inexpensive and noninvasive alternative to screen for amyloid positivity. Our study showed that a low cognitive score for screening of amyloid positivity had only limited utility. Cognitive screening efficiency may be improved by more sensitive neuropsychological tests or test norms based on cognitively normal persons without amyloid pathology. The latter is supported by our finding that amyloid pathology appeared to explain a substantial part of the so-called age-related memory decline (Figure 3). However, cognitive measures can serve as an additional source of enrichment to optimize clinical trial design as has already been implemented in a prevention study.[28]

Limitations

This study has several methodologic limitations. There were several sources of variance among the pooled studies, including differences in amyloid assessment methods, participant selection, and other aspects of study design. However, the association of these differences with amyloid positivity was modest,[1] and the association of amyloid status with cognitive performance was independent of biomarker modality. Furthermore, the type of memory test differed across studies but did not affect the association between amyloid and cognitive performance. Another potential limitation is that amyloid pathology might be associated with decline in other cognitive domains, such as executive functioning,[8,11] that were not assessed in this study. Furthermore, the power to detect an association between amyloid positivity and MMSE score in participants with normal cognition was limited by the restricted range of MMSE scores in this group. In addition, because our findings were based on research or memory clinic populations, results may not be generalizable to the overall population or other settings. Last, our findings are based on cross-sectional data, which might not accurately reflect individual trajectories of amyloid-related cognitive decline.

Conclusions

Although low memory scores are an early marker of amyloid positivity, their value as a screening measure for early AD among persons without dementia is limited.

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