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Prevalence of Amyloid PET Positivity in Dementia Syndromes:

A Meta-analysis

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Abstract

IMPORTANCE—Amyloid-β positron emission tomography (PET) imaging allows in vivo detection of fibrillar plaques, a core neuropathological feature of Alzheimer disease (AD). Its diagnostic utility is still unclear because amyloid plaques also occur in patients with non–AD dementia.

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OBJECTIVE—To use individual participant data meta-analysis to estimate the prevalence of amyloid positivity on PET in a wide variety of dementia syndromes.

DATA SOURCES—The MEDLINE and Web of Science databases were searched from January 2004 to April 2015 for amyloid PET studies.

STUDY SELECTION—Case reports and studies on neurological or psychiatric diseases other than dementia were excluded. Corresponding authors of eligible cohorts were invited to provide individual participant data.

DATA EXTRACTION AND SYNTHESIS—Data were provided for 1359 participants with clinically diagnosed AD and 538 participants with non–AD dementia. The reference groups were 1849 healthy control participants (based on amyloid PET) and an independent sample of 1369 AD participants (based on autopsy).

MAIN OUTCOMES AND MEASURES—Estimated prevalence of positive amyloid PET scans according to diagnosis, age, and apolipoprotein E (APOE) ε4 status, using the generalized estimating equations method.

RESULTS—The likelihood of amyloid positivity was associated with age and APOE ε4 status. In AD dementia, the prevalence of amyloid positivity decreased from age 50 to 90 years in APOE ε4 noncarriers(86%[95%CI,73%–94%]at 50 years to 68% [95% CI,57%–77%] at 90 years; n = 377) and to a lesser degree in APOE ε4 carriers (97% [95% CI, 92%–99%] at 50 years to 90% [95% CI, 83%–94%] at 90 years; n = 593; $P < .01$). Similar associations of age and APOE ε4 with amyloid positivity were observed in participants with AD dementia at autopsy. In most non–AD dementias, amyloid positivity increased with both age (from 60 to 80 years) and APOE ε4 carriership.

		Amyloid Positivity, % (95% CI)	
	Total Participants	Age 60 y	Age 80 y
Dementia with Lewy bodies			
emsp;APOE ε4 carrier	16	63 (48–80)	83 (67–92)
emsp;APOE ε4 noncarrier	18	29 (15–50)	54 (30–77)
Frontotemporal dementia			
emsp;APOE ε4 carrier	48	19 (12–28)	43 (35–50)
emsp;APOE ε4 noncarrier	160	5 (3–8)	14 (11–18)
Vascular dementia			
emsp;APOE ε4 carrier	30	25 (9–52)	64 (49–77)
emsp;APOE ε4 noncarrier	77	7 (3–18)	29 (17–43)

CONCLUSIONS AND RELEVANCE—Among participants with dementia, the prevalence of amyloid positivity was associated with clinical diagnosis, age, and APOE genotype. These findings indicate the potential clinical utility of amyloid imaging for differential diagnosis in

early-onset dementia and to support the clinical diagnosis of participants with AD dementia and noncarrier APOE ε4 status who are older than 70 years.

More than 35 million people worldwide experience dementia, with Alzheimer disease (AD) hallmark pathologies amyloid-β plaques and neurofibrillary tangles as the most common cause.[1] Accurately determining the cause of dementia during life is essential to developing and implementing disease-specific therapies. However, a diagnosis based on clinical criteria alone has limited capacity to determine the histopathological cause of dementia. For example, the clinical diagnosis of probable AD shows only modest sensitivity (71%–81%) and specificity (approximately 70%) against postmortem examination,[2,3] which potentially confounds clinical trials in AD.[4,5] Development of amyloid-β–specific positron emission tomography (PET) tracers[6–9] now enable human in vivo detection of fibrillar amyloid-β in neuritic plaques. Incorporating amyloid imaging into the diagnostic workup can lead to change in diagnosis,[10–12] increased diagnostic confidence,[11] and altered patient management.[10,12] Approval by the US Food and Drug Administration (FDA) for [^{18}F]florbetapir (in 2012), [^{18}F]flutemetamol (in 2013), and [^{18}F]florbetaben (in 2014) supports potential application of amyloid imaging in clinical practice.[13]

However, the clinical utility of amyloid imaging is potentially limited by a proportion of patients with non–AD dementia and cerebral amyloid-β plaques.[14,15] To correctly interpret the clinical significance of amyloid PET results, clinicians need to understand the prevalence of amyloid positivity across different types of dementia and how this is associated with demographic, genetic, and cognitive factors. Most amyloid PET studies to date come from single centers with modest sample sizes.[16] Therefore, we conducted an individual participant meta-analysis to estimate the prevalence of amyloid positivity in a large sample encompassing a variety of dementia syndromes and to evaluate relationships between amyloid PET positivity and age, sex, education, global cognition, and the AD risk-allele apolipoprotein E (APOE) ε4. We also compared the prevalence of amyloid positivity between participants with dementia and participants who were cognitively healthy, and tested associations of amyloid prevalence with age and APOE genotype in an independent autopsy sample of participants with AD.

Methods

Study Selection

Informed consent was obtained from all participants or their assigned surrogate decision makers, and the institutional review boards for human research of the participating centers approved all studies. The MEDLINE and Web of Science databases were searched from January 2004 (when the first human amyloid PET study was published with carbon 11–labeled Pittsburgh Compound B [{^{11}C}PIB][6]) to April 7, 2015, on amyloid PET studies in patients with dementia. The search terms used were *PET* and *amyloid* or *abeta* or PET tracer (ie, *PIB*, *Pittsburgh*, *florbetapir*, *AV-45*, *florbetaben*, or *flutemetamol*). Due to its affinity to both amyloid and tau pathology, 2-(1-{6-[(2-fluorine 18–labeled fluoroethyl)methylamino]-2-napthyl}ethylidene) malononitrile ([^{18}F]FDDNP) was not included.[17] The search resulted in 3250 studies. Titles and abstracts were reviewed and 227 relevant full-text articles were retrieved to assess their eligibility. Studies were excluded if

they presented case reports, included duplicate participants, or involved neurological or psychiatric diseases other than dementia. The search identified 40 unique cohorts. We asked 37 study contact persons to provide participant-level data on amyloid status, age, sex, education, APOE ε4 status,[18] Mini-Mental State Examination(MMSE)score, and Clinical Dementia Rating (CDR) scale score (3 cohorts published their studies after our inclusion stop in April 2014). Eight contact persons declined or did not respond, leaving participant-level data from 29 cohorts for analysis (Figure 1). Seven cohorts provided additional unpublished participant-level data, acquired using peer-reviewed clinical and PET procedures (eTable 1A in the Supplement). Only 1 cohort provided data that were not yet published in a peer-reviewed journal (n = 37, participants with dementia only). Following the same procedure, we selected 1849 healthy control participants from 23 cohorts (eFigure 1 in the Supplement), defined as participants who performed cognitive testing within normal limits and without any major neurological or psychiatric disorder.[19] The quality of primary reports from each cohort was systematically assessed by examining the setting, generalizability, selection, measurements, reference, bias, participant flow, descriptives, outcome, and dichotomization using combined STROBE[20] and QUADAS[21] guidelines (eTable 2A and eTable 2B in the Supplement). All cohorts reported their studies following the STROBE and QUADAS guidelines, although bias could not be assessed in 17 of 29 dementia cohorts and 13 of 23 control cohorts.

Data Collection and Operationalization

Information on study procedures, extracted from the publications or provided by the study contact person, was used to create a common set of variables.

Participants—Participants met diagnostic criteria for AD (including the atypical variants posterior cortical atrophy and logopenic-variant primary progressive aphasia), frontotemporal dementia (including behavioral, semantic, and progressive nonfluent variants), dementia with Lewy bodies (DLB), vascular dementia, and corticobasal syndrome. All diagnoses were made clinically without using amyloid PET or cerebrospinal fluid biomarker information. Detailed characteristics for each study are in eTable 1 in the Supplement. For an indirect comparison between in vivo and postmortem prevalence of amyloid positivity, the National Alzheimer's Coordinating Center (NACC) database[22] provided autopsy data of participants who were clinically diagnosed with probable AD dementia at their last visit. Participants who met the Consortium to Establish a Registry for Alzheimer's Disease criteria[23] for definite, probable, or possible AD (indicating presence of moderate to frequent neuritic plaques) were considered amyloid positive.

PET Procedures—The PET scans were dichotomized (amyloid positive or negative) using quantitative thresholds or visual reads according to the method used at the study site. Detailed PET procedures for all participating cohorts are presented in eTable 1 in the Supplement.

APOE Genotype and Clinical Measures—Information on APOE genotype was available for 1370 participants (72.2%). The MMSE[24] (measure of global cognition) was available for 1817 participants with dementia (95.8%) and the CDR scale[25] (indicator of

disease severity based on caregiver information) was available for 1329 participants with dementia (70.0%). Participants with missing data for any of those variables did not differ in amyloid positivity compared with participants with complete data sets.

Statistical Analysis

We conducted a meta-analysis with individual participant data. Baseline characteristics were compared using analysis of variance and Fisher exact tests where appropriate. Generalized estimating equations (GEE, using SPSS software [IBM], version 21.0) were used to estimate probabilities for amyloid positivity on PET and odds ratios. Generalized estimating equations was the method of choice for the study as it allows analysis of binary-correlated data, such that participant-level data from all cohorts can be modeled while simultaneously accounting for participants within studies. A logit link function for binary outcome with an exchangeable correlation structure was assumed to account for within-study correlation. Analyses were conducted using the total study population, unless specified otherwise.

The main analyses were performed with diagnosis, age, sex, and APOE genotype as independent variables. Age was entered as a continuous measure centered at the median. We tested 2-way and 3-way interactions between variables, and these terms were retained in the model if they appeared significant by the Wald statistical test (indicated in Table footnotes and Figure legends). The GEE method derived unstandardized βs, and standard errors (SE) of the main effect were reported. Estimated probabilities and 95% CIs from the GEE analysis were used in Tables and Figures. These GEE probabilities were compared with the observed probabilities to determine the goodness-of-fit between actual data and the smoothed GEE estimates. The relationship between amyloid positivity on PET and MMSE scores was examined using general linear mixed models including education as an additional covariate.

The degree of heterogeneity across cohorts was assessed in several ways. In the total sample, the random intercept variance related to a study was estimated in a random effect analysis with age, APOE ε4 carriership, and interactions by the “xtmelogit” function from STATA (StataCorp), version 12.0. This variance was expressed as an intraclass correlation coefficient. For each diagnostic group, we assessed heterogeneity within 10-year strata using the I^2 statistic[26] generated by a random-effects meta-analysis in STATA. An I^2 statistic value greater than 50% indicates substantial heterogeneity.[26] Across the age range, study variability was visualized by plotting prevalence estimates for each AD and frontotemporal dementia cohort that contained at least 5 participants.

Significance level was set at a 2-sided *P* value less than .05. All reported *P* values were not corrected for multiple comparisons. Secondary analyses using Bonferroni correction were also conducted, and results for which interpretation changed are noted. R (R Foundation for Statistical Computing), version 3.1.2, and GraphPad Prism (GraphPad Software), version 6.0 were used for the Figures.

Results

The study included 1897 participants with a clinical diagnosis of dementia (AD, 1359 participants; frontotemporal dementia, 288 participants; DLB, 51 participants; vascular dementia, 138 participants; corticobasal syndrome, 61 participants) and 1849 healthy control participants with PET data (Table 1). From the NACC database, 1369 participants with AD dementia and autopsy data were included (eTable 2 in the Supplement). Amyloid positivity refers to positive (abnormal) amyloid PET scans or presence of moderate-to-frequent plaques on neuropathological examination.

Prevalence of Amyloid Positivity According to Diagnosis, Age, and APOE

In AD dementia, the mean prevalence of amyloid positivity was 88% (95% CI, 85% to 90%, Figure 2A). The prevalence decreased with age from 93% (95% CI, 90% to 95%) at age 50 to 79% (95% CI, 73% to 85%) at age 90 (β for change in GEE estimated prevalence of amyloid positivity per year, −0.032 [95% CI, −.050 to −.014], $P < .001$). This association differed according to APOE ε4 status (Figure 2C and Figure 2D). In APOE ε4 carriers, the prevalence remained at least 90% regardless of age, whereas the prevalence in noncarriers declined from 86% (95% CI, 73% to 94%) at age 50 years to 68% (95% CI, 57% to 77%) at age 90 years (β, −0.034 [95% CI, −.058 to −.010], $P < .01$). Similar associations were found for age and APOE ε4 with amyloid positivity as assessed using neuropathological criteria in an independent cohort of AD dementia participants with autopsy data (Figure 2B). The mean prevalence estimate for the autopsy data was 85% (95% CI, 82% to 87%), with stable estimates across age in APOE ε4 carriers and a decreasing prevalence with increasing age in noncarriers.

Mean amyloid positivity in non–AD dementias was highest in DLB (51% [95% CI, 33% to 69%]), followed by vascular dementia (30% [95% CI, 21% to 42%]) and frontotemporal dementia (12% [95% CI, 8% to 18%]). In these dementias, amyloid positivity increased with age (β, 0.042 [95% CI, .012 to .071], $P < .01$), Figure 2A and Table 2). The rate of increase was independent of APOE genotype but APOE ε4 carriers had higher overall mean prevalence estimates than noncarriers (18% [95% CI, 8% to 28%]) (Figure 2C and Figure 2D). In participants with corticobasal syndrome, the overall prevalence of amyloid positivity was 38% (95% CI, 23% to 54%), which decreased with age (β, −0.073 [95% CI, −.130 to −.016], $P < .05$), independent of APOE ε4 status. This analysis was no longer statistically significant after Bonferroni correction ($P = .15$). Repeating all analyses above using only participant data from published cohorts (28 of 29 cohorts) yielded essentially the same results (eTable 3 in the Supplement).

The prevalence of amyloid positivity was not significantly associated with sex in both AD (women, 89% [95% CI, 86% to 91%]; men, 86% [95% CI, 83% to 89%], β for change in GEE estimated prevalence of amyloid positivity for men vs women, −0.287 [95% CI, −.620 to .046], $P = .09$) and non–AD dementias (women, 26% [95% CI, 19% to 34%); men, 21% [95% CI, 15% to 29%], β, −0.134 [95% CI, −.447 to .299], $P = .54$). Years of education was also not associated with the prevalence of amyloid positivity in AD (β for change in GEE estimated prevalence of amyloid positivity per year of education, 0.016 [95% CI, −0.31 to .063], $P = .51$) and non–AD dementias (β, 0.025 [95% CI, −.038 to .088], $P = .44$).

For comparison with the GEE estimated probabilities for amyloid positivity on PET, the observed probabilities are provided in Table 3. Estimates of overall amyloid positivity in different subtypes of AD and frontotemporal dementia are provided in eTable 4 in the Supplement.

Amyloid Positivity Prevalence Relative to Controls

The mean prevalence of amyloid positivity was higher in the total group of participants with AD (β for difference in GEE estimate compared with the control group, 3.215 [95% CI, 3.013 to 3.417], $P < .001$), DLB (β, 1.231 [95% CI, .663 to 1.799], $P < .001$), and corticobasal syndrome (β, 0.787 [95% CI, .250 to 1.324], $P < .001$), similar in those with vascular dementia (β, 0.090 [95% CI, −.294 to .475], $P = .65$), and lower in those with frontotemporal dementia (β, −0.691 [95% CI, −1.065 to −.318], $P < .001$) compared with cognitively normal participants (Figure 2A and Figure 2D).

Amyloid Positivity as Discriminator Between Clinical Dementia Syndromes

Figure 3 displays the odds ratios for discrimination of AD from non–AD participants using amyloid PET. Odds ratios decreased in all non–AD dementias with increasing age, except for corticobasal syndrome participants.

Association of Amyloid Positivity With Global Cognition

Amyloid positivity was associated with lower MMSE scores in both AD dementia (amyloid positive, 21.2 [95% CI, 20.2 to 22.2]; amyloid negative, 22.2 [95% CI, 20.9 to 23.4]; $P < .05$) and non–AD dementia (amyloid positive, 20.6 [95% CI, 19.2 to 21.9]; amyloid negative, 23.2 [95% CI, 22.2 to 24.3]; $P < .001$). Among non–AD dementias, the association between MMSE scores and amyloid status was significant for DLB (amyloid positive, 19.6 [95% CI, 17.3 to 21.9]; amyloid negative, 25.3 [95% CI, 22.9 to 27.8]; $P < .001$), and vascular dementia (amyloid positive, 19.5 [95% CI, 15.9 to 23.1]; amyloid negative, 22.3 [95% CI, 18.9 to 25.7]; $P < .05$; no longer significant after Bonferroni correction [$P = .07$]), but not for frontotemporal dementia (amyloid positive, 22.4 [95% CI, 20.3 to 24.4]; amyloid negative, 23.9 [95% CI, 23.0 to 24.8]; $P = .17$) and CBS (amyloid positive, 21.6 [95% CI, 18.5 to 24.7]; amyloid negative, 23.0 [95% CI, 20.8 to 25.2]; $P = .48$).

PET Tracers and Procedures

In most participants, [^{11}C]PIB was used (n = 1330), followed by [^{18}F]florbetapir (n = 328), [^{18}F]flutemetamol (n = 120), and [^{18}F]florbetaben (n = 119). On post hoc analyses, there were no significant differences in prevalence of amyloid positivity between [^{11}C]PIB and [^{18}F]florbetapir (eTable 6 in the Supplement, [^{18}F]flutemetamol and [^{18}F]florbetaben were excluded from this analysis due to their sample size). The method of assessment (visual reads [n = 1123] or quantitative thresholds [n = 774]) and type of data acquisition (static [n = 1318] or dynamic [n = 579]) were not associated with the prevalence of amyloid positivity either.

Assessment of Study-Related Heterogeneity

In the total study population, the intraclass correlation coefficient for study-related random intercept variance was 0.046, indicating minor heterogeneity across cohorts. Within age and diagnostic groups, heterogeneity was not substantial according to the I^2 statistic, except for the vascular dementia group with participants older than 80 years (eTable 7 in the Supplement). Upon visual inspection, variability in prevalence estimates as a function of age in cohorts with at least 5 participants was limited (eFigure 3 in the Supplement).

Discussion

The main findings of this individual participant meta-analysis were that the prevalence of amyloid on PET decreased with age in participants diagnosed with AD (greatest in APOE ε4 noncarriers) and increased with age in most non–AD dementias. The convergence of amyloid positivity across dementias with increasing age suggests that amyloid imaging might have the potential to be most helpful for differential diagnosis in early-onset dementia, particularly if the goal is to rule-in AD dementia. However, the high concordance between PET and pathology suggests that amyloid imaging might have the potential to be used to rule-out AD dementia regardless of age. Furthermore, amyloid in non–AD dementia may be clinically important as amyloid positivity was associated with worse global cognition. Data from this study may inform research into the clinical application of amyloid PET and highlight the necessity of biomarker-based participant selection for clinical trials.

A negative amyloid PET scan was observed in 12% of clinically diagnosed AD dementia participants and was most common in older APOE ε4 noncarriers. The latter finding is consistent with 2 recent phase 3 trials with humanized anti– amyloid-β monoclonal antibodies.[4,5] The “AD phenocopy” was most prevalent in older and APOE ε4 negative participants and may best be explained by a mix of age-related pathologies (eg, hippocampal sclerosis, argyrophilic grain disease, or tangle-predominant dementia[27–29]) that preferentially target the limbic system, resulting in a memory-predominant presentation that may be mistaken for AD, as well as false-negative PET scans. False-negative PET scans may reflect insensitivity to detect advanced amyloid pathology, possibly caused by distinct conformations of amyloid plaques, amyloid deposition in reference regions, or severe neurodegeneration. This is likely only a partial explanation because, with a few exceptions,[30,31] PET and neuropathological assessments correspond well,[32] and the independent samples of AD dementia participants with autopsy or PET showed similar prevalence estimates. Alternatively, elderly people may develop AD dementia in the presence of a lower amyloid burden (potentially not captured by PET) due to age-related diminished resilience (cognitive reserve theory[33]) or the cumulative effect of comorbid pathologies (double-hit hypothesis[34]). Future studies with antemortem amyloid PET and postmortem neuropathological examination are needed to identify which proportion of amyloid negative PET scans can be attributed to clinical misclassification or to false-negative PET findings in patients with clinical AD dementia.

In participants with frontotemporal dementia, vascular dementia, and DLB, the prevalence of amyloid positivity increased with age. A proportion of these participants may have been clinically misdiagnosed, with AD as the pathological substrate for their dementia.[2] Another

explanation is that amyloid is present as secondary pathology whereas the clinical syndrome is driven by non–AD pathologies.[15,35,36] The finding that the prevalence of amyloid positivity increases with presence of the 2 major risk factors for sporadic AD, aging and APOE ε4 genotype, supports the latter interpretation. The advent of novel tau PET tracers[37–39] could provide further clues when 2 pathologies manifest simultaneously, because prominent neocortical tau pathology is typically absent in patients with DLB, vascular dementia, and some frontotemporal dementia subtypes.

In corticobasal syndrome the prevalence of amyloid positivity decreased with age. Corticobasal syndrome is a clinically and pathologically heterogeneous entity including motor, behavioral, and cognitive features.[40] Corticobasal syndrome is mostly associated with underlying 4-repeat tauopathy (corticobasal degeneration or progressive supra-nuclear palsy), but up to 25% of patients have AD as the primary pathology at autopsy.[41,42] This study suggests that AD may be the causative pathology in young corticobasal syndrome patients, whereas a primary tauopathy becomes more likely with increasing age.

This study underscores that clinical diagnosis, age, and APOE status are crucial factors when ordering and interpreting clinical amyloid PET scans. The likelihood of detecting incidental amyloid pathology increased with advancing age in both controls and non–AD dementia patients. In line with recently proposed appropriate use criteria,[43] this suggests that amyloid imaging might be particularly helpful for differential diagnosis in early-onset dementia. In contrast, the convergence between AD and non–AD dementia participants with age warrants careful interpretation of positive amyloid PET scans in older patients. Also, amyloid imaging does not seem justified in APOE ε4 carriers to confirm their clinical diagnosis of AD dementia, as the prevalence of amyloid positivity remained around 90% regardless of age. In noncarriers, however, an amyloid PET scan may be informative in patients older than 70 years as the prevalence declined to 78% and further decreased to 68% at age 90. Although not recommended for routine diagnostic assessment,[44] knowledge of APOE status may be helpful when considering amyloid assessment in clinical practice.

There are a number of limitations that need to be considered in interpreting this study. First is its limited generalizability as participants were highly educated (mean, 14.3 years of education [SD, 3.6]) and relatively small proportions of AD (15.9%) and non–AD (10.9%) dementia participants were older than 80 years (this age range represents the largest segment in the community). This meta-analysis reflects a collection of studies conducted in research memory clinics or focused epidemiological studies with limits on age and medical comorbidities. Furthermore, data on race/ethnicity would have been informative because previous studies have reported differences in the prevalence of APOE ε4 and its association with cognitive decline between white patients and black patients.[45–47]

Second, we pooled data from a large number of cohorts, which may have introduced bias due to differences in study designs. However, there was limited evidence for heterogeneity across cohorts (eFigure 3 and eTable 7 in the Supplement). Third, due to the absence of histopathological data in participants with amyloid PET, it remains unknown whether the clinical diagnoses were correct and what type of pathologies underlie non–AD diagnoses, particularly in amyloid positive participants. Fourth, differences in acquisition methods did

not allow for harmonized PET data analysis across cohorts, so that we adopted the methodology as specified by the different study sites. This lack of standardization was addressed by adjusting all analyses for study effects. Also, post hoc analyses showed no significant differences for assessment methods or acquisition modus (eTable 6 in the Supplement).

Fifth, 70% of participants underwent [^{11}C]PIB imaging, although, from 2012 to 2014, the FDA approved three ^{18}F-labeled PET tracers for clinical use.[13] Although the number of ^{18}F-labeled amyloid PET scans was relatively small, comparable prevalence estimates between [^{11}C]PIB and [^{18}F]florbetapir suggests that present findings are coherent across tracers.[48] Sixth, although by design this is, to our knowledge, the largest amyloid PET study in patients with dementia, sample sizes in some non–AD dementia groups were relatively small and resulted in wide CIs. In particular, the prevalence estimates at the lower and higher age extremes in models that include both age and APOE genotype in non–AD dementias should be interpreted with caution.

Conclusions

Among participants with dementia, the prevalence of amyloid positivity was associated with clinical diagnosis, age, and APOE genotype. These findings indicate the potential clinical utility of amyloid imaging for differential diagnosis in early-onset dementia and to support the clinical diagnosis of patients with AD dementia and noncarrier APOE ε4 status who are older than 70 years.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix

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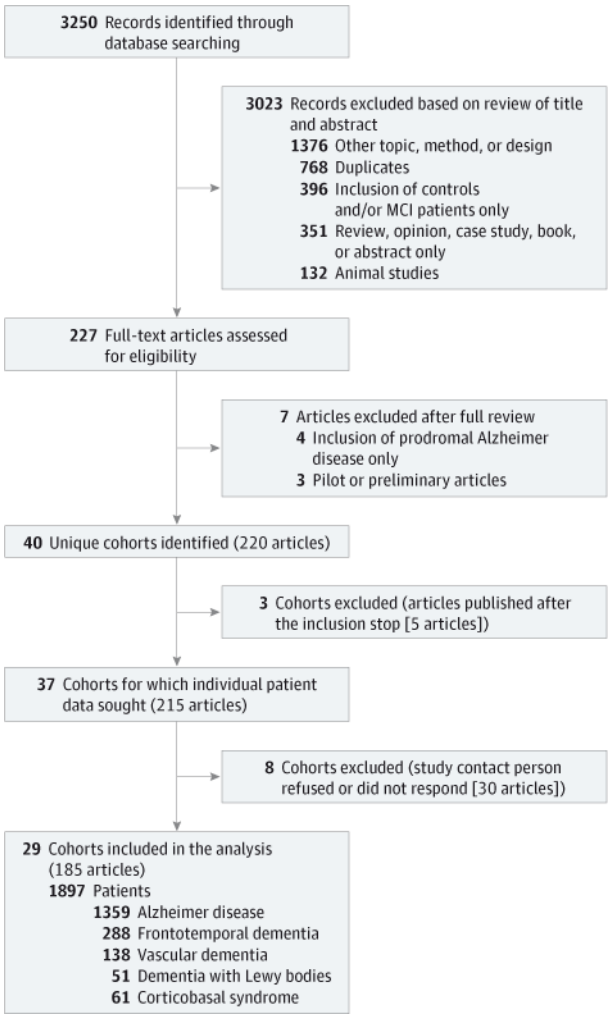

Figure 1. Flow Diagram of Participant Selection for Dementia Syndromes

MCI indicates mild cognitive impairment. MEDLINE and Web of Science databases were searched from January 2004 to April 2015.

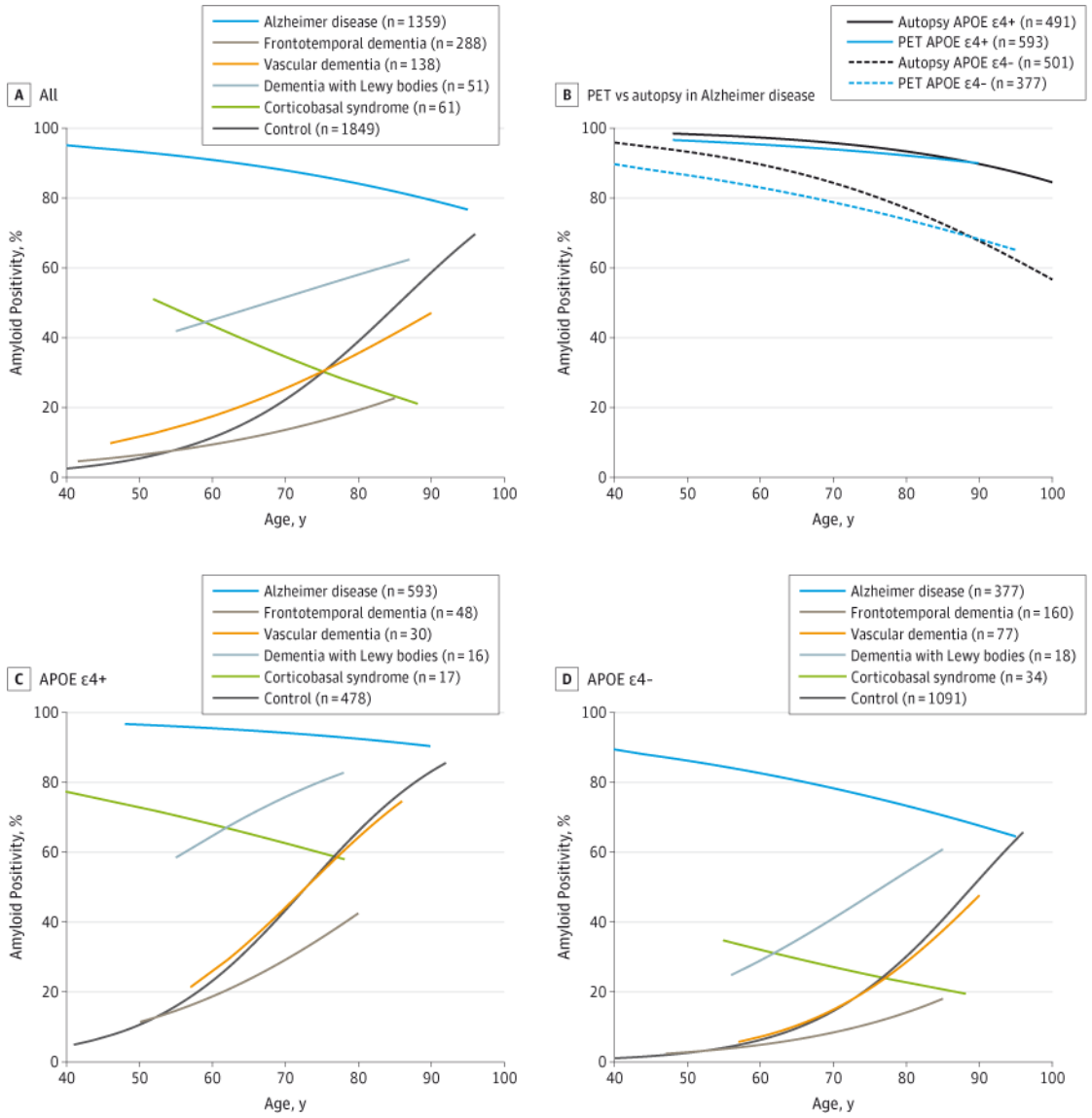

Figure 2. Prevalence of Amyloid Positivity on PET According to Age for the Different Dementia Diagnostic Groups

PET indicates positron emission tomography. The curves were plotted using the point estimates generated by generalized estimating equations and are within the age limits of the diagnostic groups. The models were adjusted for study effects. The 95% CIs are presented in Table 2 and eFigure 3 in the Supplement.

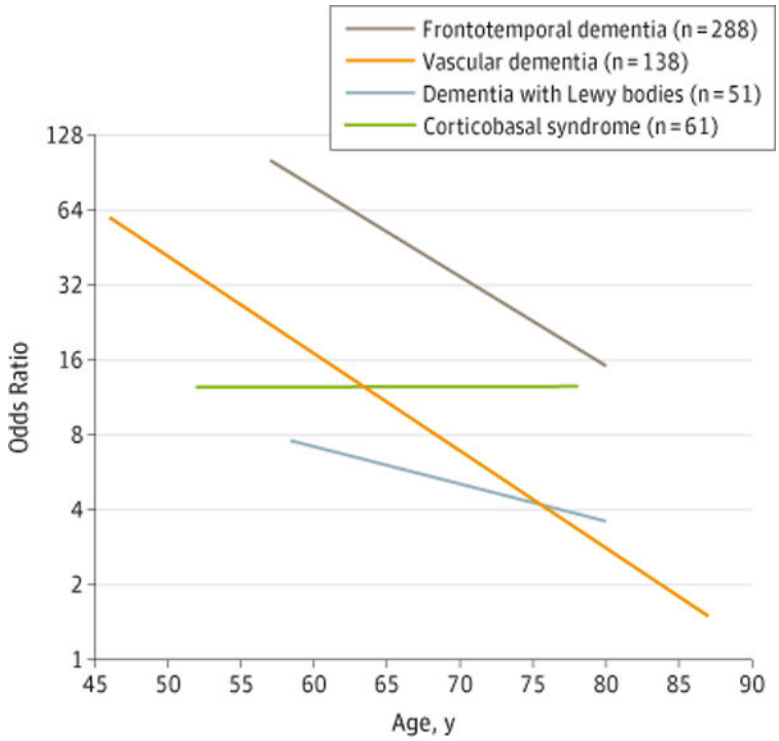

Figure 3. Relative Odds of Non–Alzheimer Dementias vs Alzheimer Dementia

AD indicates Alzheimer disease. The curves were plotted using the point estimates generated by generalized estimating equations and represent odds ratios of amyloid positivity for the different non–AD dementia syndromes (with patients with AD dementia as the reference group) as a function of age. The models include amyloid status on PET (positive or negative), age (as a continuous variable), and an interaction between amyloid status and age. The curves are within the age limits of the diagnostic groups.

Table 1

Participant Characteristics in Each Dementia Diagnostic Group[a]

	Alzheimer Disease (n = 1359)	Frontotemporal Dementia (n = 288)	Vascular Dementia (n = 138)	Dementia With Lewy Bodies (n = 51)	Corticobasal Syndrome (n = 61)	Control (n = 1849)
Age, mean (SD), y	69.4 (9.3)	65.9 (8.2)[b]	74.5 (8.5)[b]	69.1 (7.6)	66.6 (7.5)	68.1 (14.0)
Age, median (range), y	69 (38–95)	66 (41–85)	75 (46–90)	68 (55–87)	68 (40–88)	68 (40–88)
Age groups, No. (%), y						
<55	58 (4.3)	25 (8.7)	2 (1.4)		2 (3.3)	209 (11.3)
55–59	164 (12.1)	37 (12.8)	4 (2.9)	4 (7.8)	6 (9.8)	128 (6.9)
60–64	201 (14.8)	62 (21.5)	12 (8.7)	12 (23.5)	16 (26.2)	173 (9.4)
65–69	249 (18.3)	63 (21.9)	20 (14.5)	12 (23.5)	11 (18.0)	352 (19.0)
70–74	259 (19.1)	62 (21.5)	25 (18.1)	11 (21.6)	20 (32.8)	334 (18.1)
75–79	212 (15.6)	29 (10.1)	32 (23.2)	7 (13.7)	5 (8.2)	305 (16.5)
80–84	147 (10.8)	9 (3.1)	27 (19.6)	3 (5.9)		193 (10.4)
≥85	69 (5.1)	1 (0.3)	16 (11.6)	2 (3.9)	1 (1.6)	155 (8.4)
Men, No. (%)	721 (53.1)	148 (51.4)	85 (61.6)	19 (37.3)	29 (47.5)	756 (41.4)
Education, mean (SD), y	13.8 (3.6)	13.6 (3.5)	10.1 (4.2)[b]	13.7 (3.1)	13.7 (3.6)	15.1 (3.3)
MMSE score, mean (SD)[c]	21.8 (4.7)[b]	23.8 (5.5)	19.4 (5.8)[b]	22.9 (5.4)	22.5 (6.3)	29.1 (1.2)
Global CDR, mean (SD) [d]	0.9 (0.4)	0.8 (0.6)	1.2 (0.7)[b]	1.1 (0.7)[b]	0.9 (0.6)	0
APOE ε4 carrier/noncarrier (% carrier)[e]	593/377 (61.1)[b]	48/160 (23.1)	30/77 (28.0)	16/18 (47.1)[b]	17/34 (33.3)	478/1091 (30.5)

Abbreviations: APOE, apolipoprotein E; CDR, Clinical Dementia Rating; MMSE, Mini-Mental State Examination.

[a] Participant characteristics were compared between diagnostic groups using analysis of variance and Fisher exact tests, with post hoc Bonferroni tests for all possible pairs.

[b] Pairwise comparisons were statistically significant for the group indicated.

[c] Range: 0 to 30, lower scores indicate worse global cognition.

[d] Range: 0 to 3, higher scores indicate more advanced disease severity.

[e] APOE datamissing in 27.8%of dementia participants and 15.9%of control participants.

Table 2

Prevalence Estimates According to Age, Diagnosis, and APOE ε4 Status

	Age, years											
	50		60		70		80		90		All	
	No. of Participants[a]	Prevalence Estimates (95% CI)[b]	No. of Participants[a]	Prevalence Estimates (95% CI)[b]	No. of Participants[a]	Prevalence Estimates (95%CI)[b]	No. of Participants[a]	Prevalence Estimates (95% CI)[b]	No. of Participants[a]	Prevalence Estimates (95%CI)[b]	No. of Participants[a]	Prevalence Estimates (95% CI)[b]
Alzheimer disease	58	93 (90–95)	365	91 (89–93)	508	88 (86–90)	359	84 (81–87)	69	79 (73–85)	1359	88 (85–90)
APOE ε4+	19	97 (92–99)	151	96 (93–98)	242	94 (92–96)	160	93 (89–95)	21	90 (83–94)	593	95 (90–96)
APOE ε4−	22	86 (73–94)	116	83 (73–90)	106	78 (71–84)	100	73 (67–79)	33	68 (57–77)	377	77 (70–85)
Frontotemporal dementia	25	6 (3–14)	99	9 (6–15)	125	14 (10–19)	38	19 (11–32)	1		288	12 (8–18)
APOE ε4+	5	11 (6–22)	18	19 (12–28)	22	30 (24–38)	3	43 (35–50)	0		48	19 (16–33)
APOE ε4−	10	3 (1–6)	51	5 (3–8)	74	8 (6–11)	25	14 (11–18)	1		160	9 (5–11)
Vascular dementia	2		16	18 (9–33)	45	26 (18–35)	59	36 (27–46)	16	50 (19–81)	138	30 (21–42)
APOE ε4+	0		4	25 (9–52)	8	44 (35–54)	16	64 (49–77)	2		30	47 (38–66)
APOE ε4−	0		9	7 (3–18)	23	15 (11–20)	35	29 (17–43)	10	49 (17–80)	77	26 (14–37)
Dementia with Lewy bodies	0		16	45 (26–66)	23	51 (37–64)	10	58 (34–78)	2		51	51 (33–69)
APOE ε4+	0		4	63 (48–80)	9	75 (65–83)	3	83 (67–92)	0		16	69 (58–85)
APOE ε4−	0		8	29 (15–50)	4	38 (28–49)	5	54 (30–77)	1		18	44 (23–60)
Corticobasal Syndrome	2		22	44 (28–60)	31	35 (23–49)	5	28 (13–51)	1		61	38 (23–54)
APOE ε4+	2		5	67 (49–82)	9	63 (57–68)	1		0		17	53 (48–77)
APOE ε4−	0		17	32 (18–51)	14	27 (23–31)	2		1		34	35 (19–42)
Control	209	6 (4–7)	301	11 (10–14)	686	22 (20–24)	498	39 (36–42)	155	59 (53–64)	1849	24 (22–27)
APOE ε4+	54	11 (7–16)	82	24 (19–29)	205	43 (39–48)	102	66 (58–73)	35	83 (74–90)	478	41 (36–47)
APOE ε4−	109	3 (1–5)	163	7 (4–10)	367	15 (11–19)	340	30 (24–37)	112	53 (41–64)	1091	19 (15–24)

Abbreviations: APOE, apolipoprotein E.

[a] For the number of participants in each age group: 50 includes participants 54 years and younger; 60, 55–64 years; 70, 65–74 years; 80, 75–84 years; 90, 85 years and older. All includes the entire age range.

[b] The prevalence estimates and 95% CIs were derived from generalized estimating equation models. Data were adjusted for study effects. No estimates were provided if the 5-year range around the indicated age included fewer than 3 participants.

Table 3

Observed Probabilities of Amyloid Positivity on PET Across Diagnostic and Age Groups[a]

	No. of Amyloid Positive/No. of Total Group (%)					
	Alzheimer Disease	**Frontotemporal Dementia**	**Vascular Dementia**	**Dementia With Lewy Bodies**	**Corticobasal Syndrome**	**Control**
Age groups, y[b]						
All	1193/1359 (87.8)	35/288 (12.2)	42/138 (30.4)	26/51 (51.0)	23/61 (37.7)	448/1849 (24.2)
50	51/58 (87.9)	0/25 (0)	1/2 (50.0)		1/2 (50.0)	2/209 (1.0)
60	333/365 (91.2)	10/99 (10.1)	1/16 (6.3)	6/16 (37.5)	11/22 (50.0)	35/301 (11.6)
70	453/508 (89.2)	22/125 (17.6)	9/45 (20.0)	14/23 (60.9)	8/31 (25.8)	163/686 (23.8)
80	303/359 (84.4)	3/38 (7.9)	25/59 (42.4)	6/10 (60.0)	3/5 (60.0)	172/498 (34.5)
90	53/69 (76.8)	0/1 (0)	6/16 (37.5)	0/2 (0)	0/1 (0)	76/155 (49.0)

Abbreviations: PET, positron emission tomography.

[a] Observed probabilities (percentages) of amyloid positivity on PET were calculated by No. amyloid positive/No. total group.

[b] Age groups: 50 includes participants 54 years and younger; 60, 55–64 years; 70, 65–74 years; 80, 75–84 years; 90, 85 years and older. All includes the entire age range.