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Associations of Amyloid, Tau, and Neurodegeneration Biomarker Profiles With Rates of Memory Decline Among Individuals Without Dementia

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IMPORTANCE A National Institute on Aging and Alzheimer's Association workgroup proposed a research framework for Alzheimer disease in which biomarker classification of research participants is labeled AT(N) for amyloid, tau, and neurodegeneration biomarkers.

OBJECTIVE To determine the associations between AT(N) biomarker profiles and memory decline in a population-based cohort of individuals without dementia age 60 years or older, and to determine whether biomarkers provide incremental prognostic value beyond more readily available clinical and genetic information.

DESIGN, SETTING, AND PARTICIPANTS Population-based cohort study of cognitive aging in Olmsted County, Minnesota, that included 480 nondemented Mayo Clinic Study of Aging participants who had a clinical evaluation and amyloid positron emission tomography (PET) (A), tau PET (T), and magnetic resonance imaging (MRI) cortical thickness (N) measures between April 16, 2015, and November 1, 2017, and at least 1 clinical evaluation follow-up by November 12, 2018.

EXPOSURES Age, sex, education, cardiovascular and metabolic conditions score, *APOE* genotype, and AT(N) biomarker profiles. Each of A, T, or (N) can be abnormal (+) or normal (−), resulting in 8 AT(N) profiles.

MAIN OUTCOMES AND MEASURES Primary outcome was a composite memory score measured longitudinally at 15-month intervals. Analyses measured the associations between predictor variables and the memory score, and whether AT(N) biomarker profiles significantly improved prediction of memory *z* score rates of change beyond a model with clinical and genetic variables only.

RESULTS Participants were followed up for a median of 4.8 years (interquartile range [IQR], 3.8-5.1) and 44% were women (211/480). Median (IQR) ages ranged from 67 years (65-73) in the A−T−(N)− group to 83 years (76-87) in the A+T+(N)+ group. Of the participants, 92% (441/480) were cognitively unimpaired but the A+T+(N)+ group had the largest proportion of mild cognitive impairment (30%). AT(N) biomarkers improved the prediction of memory performance over a clinical model from an R^2 of 0.26 to 0.31 ($P < .001$). Memory declined fastest in the A+T+(N)+, A+T+(N)−, and A+T−(N)+ groups compared with the other 5 AT(N) groups ($P = .002$). Estimated rates of decline in the 3 fastest declining groups were −0.13 (95% CI, −0.17 to −0.09), −0.10 (95% CI, −0.16 to −0.05), and −0.10 (95% CI, −0.13 to −0.06) *z* score units per year, respectively, for an 85-year-old *APOE* ε4 noncarrier.

CONCLUSIONS AND RELEVANCE Among older persons without baseline dementia followed for a median of 4.8 years, a prediction model that included amyloid PET, tau PET, and MRI cortical thickness resulted in a small but statistically significant improvement in predicting memory decline over a model with more readily available clinical and genetic variables. The clinical importance of this difference is uncertain.

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A work group commissioned by the National Institute on Aging and the Alzheimer's Association (NIA-AA) recently published a research framework for Alzheimer disease.[1] The framework used a scheme for biomarker classification of research participants that was labeled AT(N) for amyloid, tau, and neurodegeneration (or neuronal injury) biomarkers. A and T biomarkers are specific for the hallmark neuropathologic indicators of Alzheimer disease (amyloid plaques and tau neurofibrillary tangles),[2] while biomarkers of (N) (eg, atrophy on magnetic resonance imaging [MRI]) are not disease specific; this distinction was connoted by placing N in parentheses. With the application of cut points,[3] each of A, T, or (N) can be classified as abnormal (+) or normal (−), resulting in 8 different AT(N) biomarker profiles.

The NIA-AA Research Framework was created with the expectation that the biological information captured by AT(N) biomarker profiles would be clinically relevant; however, this was posed as a hypothesis to be tested. It was not known whether memory performance, which is demonstrably worse at older ages,[4] declines more quickly among those with abnormal AT(N) biomarker profiles. Therefore, the aim of this study was to determine the associations between the 8 AT(N) biomarker profiles and the rates of memory decline over several years in a population-based cohort of individuals without dementia aged 60 years and older, and to determine whether AT(N) biomarkers provided additional prognostic value beyond more readily available clinical and genetic information.

Key Points

Question Do rates of memory decline vary by the amyloid, tau, and neurodegeneration biomarker profiles described in the recent National Institute on Aging–Alzheimer's Association Research Framework?

Findings In this longitudinal cohort study that included 480 participants without dementia, the addition of amyloid positron emission tomography, tau positron emission tomography, and magnetic resonance imaging cortical thickness to a model that included clinical and genetic variables resulted in a small but statistically significant improvement in predictive accuracy for memory decline (R^2, 0.31 vs 0.26).

Meaning Amyloid, tau, and neurodegeneration biomarkers may provide incremental prognostic value in addition to more readily available clinical and genetic variables, but the clinical importance of this difference is uncertain.

Methods

Participants

This study was approved by the Mayo Clinic and the Olmsted Medical Center institutional review boards. All participants provided written informed consent at the time of enrollment.

All participants in this study were enrolled in the Mayo Clinic Study of Aging (MCSA), which is a population-based study of cognitive aging among a stratified random sample of a geographically defined population: Olmsted County, Minnesota.[5] Residents aged 30 to 89 years old were enumerated using the medical records-linkage system of the Rochester Epidemiology Project.[6] From this sampling frame, individuals were randomly selected by 10-year age and sex strata such that men and women were equally represented. Enumeration, stratified random sampling, and screening procedures were repeated to maintain a target of 2500 active participants who were evaluated approximately every 15 months.

A clinical diagnosis was determined independent of biomarkers for each participant by a consensus committee composed of physicians, neuropsychologists, and study coordinators.[5] Participants who did not meet established criteria for mild cognitive impairment (MCI)[7] or dementia[8] were deemed cognitively unimpaired.

Exposures

Clinical and genetic predictor variables were age, sex, education, *APOE* genotype, and a composite cardiovascular and metabolic conditions (CMC) score. A CMC score for each participant was computed as the sum of 7 conditions proposed by the US Department of Health and Human Services as indicators of vascular health. Using the Rochester Epidemiology Project database, *International Classification of Diseases, Ninth Revision,* and *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* codes were used to identify these 7 CMCs: hypertension, hyperlipidemia, cardiac arrhythmias, coronary artery disease, congestive heart failure, diabetes, and stroke.[9] The epidemiologic nature of the cohort is relevant to interpretation of results and, therefore, race/ethnicity of participants was assessed here by self-report of fixed categories.

MCSA participants without a medical contraindication were invited to participate in imaging studies. All participants included in this study had a study visit including a clinical evaluation incorporating cognitive testing, amyloid positron emission tomography (PET), tau PET, and magnetic resonance imaging (MRI) between April 16, 2015, and November 1, 2017, and at least 1 follow-up visit with a clinical evaluation by November 12, 2018. Because the prevalence of biomarker abnormalities is low at younger than age 60 years,[10] we included only participants aged 60 and older in this analysis. Tau PET was added to the MCSA imaging protocol in 2015 and a participant's first visit that included tau PET, amyloid PET, and MRI was labeled the index or baseline visit for this study.

Imaging predictor variables were AT(N) biomarker profiles. Amyloid PET imaging was performed with Pittsburgh Compound B[11] and tau PET with [^{18}F]flortaucipir.[12] Amyloid and tau PET standardized uptake value ratios (SUVRs) were formed by normalizing composite multiregion target regions of interest (ROIs) to the cerebellar crus gray matter.[3] The amyloid PET target meta-ROI included the prefrontal, orbitofrontal, parietal, temporal, anterior, and posterior cingulate and the precuneus.[3] The tau PET target meta-ROI used in the primary analysis included the amygdala, entorhinal cortex, fusiform, parahippocampal, and inferior temporal and middle temporal gyri.[3] MRI was performed at 3T. The MRI measure was a FreeSurfer (version 5.3)-derived cortical thickness meta-ROI (entorhinal cortex, fusiform,

inferior temporal, and middle temporal gyri).[3] The amyloid PET cut point denoting normal or abnormal was the SUVR value of 1.48 (centiloid 22[13]), beyond which rates of amyloid PET reliably increased.[3] The cut points for tau PET (SUVR, 1.25) and cortical thickness (2.68 mm) were those that most accurately discriminated between cognitively impaired individuals with abnormal amyloid PET and cognitively unimpaired young (aged 30-49 years) individuals with normal amyloid PET.[3] For tau PET, a more conservative cut point of an SUVR of 1.33, which most accurately discriminated between cognitively impaired individuals with abnormal amyloid PET and age-matched cognitively unimpaired individuals with normal amyloid PET,[3] was also evaluated in a post hoc sensitivity analysis.

Outcomes

The primary outcome was a numeric memory composite score.[14] Memory tests included the Wechsler Memory Scale-Revised Logical Memory-II (delayed recall), Wechsler Memory Scale-Revised Visual Reproduction-II (delayed recall), and Auditory Verbal Learning Test (delayed recall). Each test was *z* scored using the mean (SD) among cognitively unimpaired participants aged 50 and older who were newly enrolled in the MCSA between 2004 and 2012. A memory domain *z* score was calculated as the mean of these 3 component *z* scores and this domain score was itself *z* scored based on calculating a weighted mean and a weighted SD where the weights were based on the age and sex distribution of the Olmsted County population.[15] Therefore, approximately 68% of the population would have *z* scores in the range of −1 to +1.

Statistical Methods

We used linear mixed-effects models with a continuous memory *z* score as the outcome with terms for both memory effects at the index visit and longitudinal change from that time point. To address the question of incremental prognostic value of AT(N) biomarkers, we assessed the ability of 2 models to predict memory performance. The first model, termed the *clinical model*, included age at index date, sex, education, CMC score at index, and *APOE* ε4 status (carrier vs noncarrier). In the second model, the 8 AT(N) biomarker groups were added. Because the length of follow-up after the index AT(N) imaging visit was limited due to the recent introduction of tau PET to better estimate the within-person memory change over time, we included memory *z* score measurements obtained within 2 visits prior to the index visit along with all follow-up measurements. Because each participant contributed multiple observations to the model, a per-person intercept and slope were included as random effects to accommodate within-person correlation. Previous research[16] has shown that mean memory *z* scores in cognitively unimpaired individuals increased over the first few visits, a learning effect, by an amount of 0.23 between the first and second exposures to the test instruments, and there are further increases of 0.07 between the second and third exposures and 0.04 between the third and fourth exposures. To avoid confounding with this effect, we included these amounts as a fixed offset in the model (a term with known, prespecified coefficients). To be included in this study, all participants were required to have nonmissing data for the predictor and outcome variables used in the models. Therefore, the analyses did not have to account for missing data.

We tested whether AT(N) significantly predicted rates of memory decline relative to the clinical model using a 7-*df* likelihood ratio test. We followed this with a cluster analysis to determine which AT(N) groups were declining at different rates. To address the relative contribution of age vs AT(N) to the memory declines seen at older ages in the population, we presented AT(N) biomarker group prevalence weighted estimates of annual memory decline rates for the cohort and for a hypothetical subsample where AT(N) prevalence was constant. Further details on model specification can be found in the eMethods in the Supplement.

We also performed several post hoc sensitivity analyses in which we refit the AT(N) model: (1) excluding memory *z* score data collected prior to the index visit (ie, fitting the models with memory *z* score data from the index visit and subsequent visits only); (2) excluding participants with MCI to examine the relationships between AT(N) group and memory decline among the subset of cognitively unimpaired participants alone; (3) defining AT(N) using a more conservative cut point for the tau PET meta-ROI; (4) defining AT(N) using different tau PET reporter ROIs of entorhinal cortex alone and inferior temporal gyrus alone[17,18]; and (5) defining AT(N) using the tau PET meta-ROI with 2-compartment partial volume correction[19] (the main analysis was done without).

In addition, among 88 participants in our sample who had follow-up imaging at the next visit after the index visit, we examined the agreement between their AT(N) categorizations at baseline and at follow-up to assess stability of the AT(N) categorizations.

All analyses were done using the R language and environment for statistical computing version 3.4.2 (R Foundation for Statistical Computing) with mixed models fit using the nlme package version 3.1-131. All *P* values were two-sided. *P* values less than .05 were considered statistically significant.

Results

Demographics

The **Table** shows characteristics of the 480 participants in the study by AT(N) group. Median ages ranged from 67 years (interquartile range [IQR], 65-73) in the A−T−(N)− group to 83 years (IQR, 76-87) in the A+T+(N)+ group. Overall, 92% of participants were cognitively unimpaired but the A+T+(N)+ group had the largest proportion of MCI (30%). The proportion of *APOE* ε4 carriers was greater among the 4 A+ groups than the 4 A− groups (40% vs 21%, $P < .001$). Ninety-one percent of study participants had undergone cognitive testing before the index visit. Including up to 2 cognitive visits prior to the index visit, participants were followed up for a median of 4.8 years (IQR, 3.8-5.1), with median intervals varying from 4.1 to 5.0 years across AT(N) groups. Examples of some of the different AT(N) profiles are shown in **Figure 1**. Of the 480 participants, 473 (99%) self-reported their race as white.

Table. Characteristics of Study Participants by Amyloid, Tau, and Neurodegeneration (AT[N]) Biomarker Group[a]

Characteristic	Biomarker Group, No. (%)							
	A−T−(N)−	A−T+(N)−	A−T−(N)+	A−T+(N)+	A+T−(N)−	A+T+(N)−	A+T−(N)+	A+T+(N)+
Participants	140 (29)	33 (7)	81 (17)	22 (5)	54 (11)	24 (5)	69 (14)	57 (12)
Clinical diagnosis								
Cognitively unimpaired	139 (99)	32 (97)	72 (89)	20 (91)	52 (96)	24 (100)	62 (90)	40 (70)
Mild cognitive impairment	1 (1)	1 (3)	9 (11)	2 (9)	2 (4)	0 (0)	7 (10)	17 (30)
Age, y								
60-69	92 (66)	13 (39)	24 (30)	3 (14)	17 (31)	5 (21)	10 (14)	4 (7)
70-79	37 (26)	13 (39)	32 (40)	8 (36)	22 (41)	12 (50)	18 (26)	21 (37)
≥80	11 (8)	7 (21)	25 (31)	11 (50)	15 (28)	7 (29)	41 (59)	32 (56)
Median (IQR) [range], y	67 (65 to 73) [60 to 86]	75 (67 to 79) [60 to 89]	76 (69 to 82) [60 to 90]	80 (73 to 83) [63 to 94]	74 (69 to 80) [62 to 90]	78 (70 to 82) [65 to 94]	82 (77 to 86) [63 to 94]	83 (76 to 87) [63 to 92]
Sex								
Male	68 (49)	21 (64)	60 (74)	10 (45)	22 (41)	15 (62)	40 (58)	33 (58)
Female	72 (51)	12 (36)	21 (26)	12 (55)	32 (59)	9 (38)	29 (42)	24 (42)
Education, median (IQR), y	16 (13 to 16)	15 (13 to 16)	15 (12 to 17)	16 (13 to 16)	14 (12 to 17)	16 (14 to 16)	14 (12 to 16)	14 (12 to 16)
APOE ε4 carrier	32 (23)	5 (15)	19 (23)	1 (5)	23 (43)	13 (54)	28 (41)	18 (32)
MCSA cycle, median (IQR)[b]	3 (3 to 4)	4 (3 to 5)	4 (3 to 6)	5 (4 to 8)	4 (3 to 5)	4 (3 to 6)	6 (4 to 8)	6 (4 to 9)
Memory *z* score, median (IQR)[c]	0.7 (0.2 to 1.3)	0.1 (−0.8 to 0.5)	0.0 (−0.7 to 0.9)	0.4 (−0.6 to 1.0)	0.5 (−0.2 to 1.0)	0.6 (−0.2 to 1.2)	−0.2 (−1.1 to 0.4)	−0.4 (−2.0 to 0.6)
Amyloid PET, SUVR, median (IQR)	1.36 (1.32 to 1.41)	1.37 (1.34 to 1.42)	1.37 (1.32 to 1.42)	1.38 (1.34 to 1.42)	1.72 (1.55 to 2.00)	1.92 (1.62 to 2.16)	1.82 (1.54 to 2.15)	2.23 (1.61 to 2.56)
Tau PET, SUVR, median (IQR)	1.16 (1.11 to 1.20)	1.29 (1.27 to 1.31)	1.16 (1.10 to 1.20)	1.28 (1.26 to 1.31)	1.18 (1.13 to 1.21)	1.29 (1.26 to 1.37)	1.18 (1.14 to 1.22)	1.33 (1.29 to 1.42)
Cortical thickness, median (IQR), mm	2.78 (2.73 to 2.85)	2.77 (2.73 to 2.85)	2.60 (2.53 to 2.63)	2.59 (2.53 to 2.62)	2.74 (2.71 to 2.80)	2.75 (2.72 to 2.78)	2.60 (2.48 to 2.65)	2.56 (2.50 to 2.62)
Memory *z* score evaluations including the index AT(N) visit and follow-up visits								
2	49 (35)	15 (45)	38 (47)	7 (32)	26 (48)	4 (17)	35 (51)	21 (37)
3	91 (65)	18 (55)	43 (53)	15 (68)	28 (52)	20 (83)	34 (49)	36 (63)
Visit span, median (IQR) [range], y[d]	2.5 (1.3 to 2.6) [1.1 to 3.1]	2.4 (1.3 to 2.5) [1.2 to 2.9]	2.4 (1.3 to 2.5) [1.2 to 2.9]	2.4 (1.3 to 2.6) [1.2 to 2.9]	2.4 (1.3 to 2.5) [1.0 to 3.0]	2.5 (2.3 to 2.6) [1.3 to 3.0]	2.0 (1.2 to 2.5) [1.0 to 3.2]	2.5 (1.3 to 2.5) [1.0 to 2.7]
Individuals with memory *z* score evaluations prior to the AT(N) index visit	131 (94)	28 (85)	75 (93)	21 (95)	47 (87)	23 (96)	64 (93)	50 (88)
Total memory *z* score evaluations[e]								
2	6 (4)	2 (6)	3 (4)	1 (5)	5 (9)	0	4 (6)	6 (11)
3	6 (4)	3 (9)	7 (9)	0	5 (9)	1 (4)	4 (6)	2 (4)
4	59 (42)	14 (42)	34 (42)	7 (32)	20 (37)	5 (21)	30 (43)	16 (28)
5	69 (49)	14 (42)	37 (46)	14 (64)	24 (44)	18 (75)	31 (45)	33 (58)
Visit span, median (IQR) [range], y[f]	4.8 (3.8 to 5.0) [1.2 to 5.9]	4.5 (3.8 to 5.0) [1.2 to 5.5]	4.1 (3.8 to 5.0) [1.2 to 6.7]	4.9 (4.0 to 5.1) [1.3 to 5.7]	4.2 (3.8 to 5.0) [1.2 to 5.9]	5.0 (4.8 to 5.1) [2.9 to 5.5]	4.4 (3.7 to 5.1) [1.1 to 5.9]	4.9 (3.8 to 5.1) [1.0 to 5.5]
Annual change in memory *z* score[g]								
Median (IQR)	0.00 (−0.06 to 0.07)	−0.04 (−0.11 to 0.08)	0.00 (−0.15 to 0.08)	−0.03 (−0.10 to 0.01)	−0.02 (−0.11 to 0.07)	−0.07 (−0.15 to −0.01)	−0.07 (−0.24 to 0.05)	−0.08 (−0.18 to −0.01)
Annual change <0	71 (51)	18 (55)	41 (51)	14 (64)	31 (57)	18 (75)	48 (70)	43 (75)

Abbreviations: MCSA, Mayo Clinic Study of Aging; PET, positron emission tomography; SUVR, standardized uptake value ratio.

[a] Cut points are 1.48 SUVR (centiloid 22) for amyloid PET to 1.25 SUVR for tau PET and 2.68 mm for cortical thickness.

[b] Cycle 1 defined as the first assessment, cycle 2 as the second, and so on.

[c] Not adjusted for previous exposures to cognitive testing (ie, for potential learning effects).

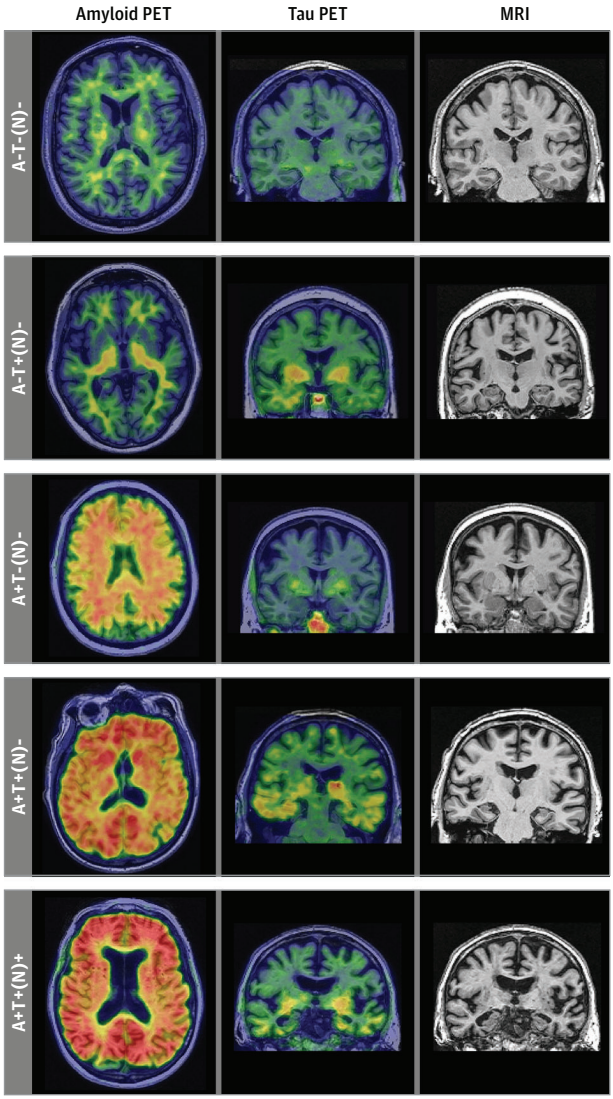
[d] Number of years between the memory *z* score evaluation at the index AT(N) visit to the memory *z* score evaluation at the last follow-up visit.

[e] Include measurements from the AT(N) index visit, up to 2 visits prior to the index visit, and up to 2 visits after the index visit. All of these measurements are included in the main models.

[f] Number of years between the first and last memory *z* score evaluations for all evaluations included in this study.

[g] Calculated by fitting a line within each participant across all available memory *z* score measurements including the AT(N) index visit, up to 2 visits prior to the index visit, and up to 2 visits after the index visit. Annual change in memory was adjusted for number of prior exposures to cognitive testing, which may differ across participants to account for potential learning effects in the cognitive tests.

Figure 1. Amyloid, Tau, and Neurodegeneration Biomarker (AT[N]) Examples



The amyloid positron emission tomography (PET) images show axial views and the tau PET and magnetic resonance imaing (MRI) images show coronal views. Amyloidosis characteristically appears diffusely throughout the cortex, whereas in the typical aging to Alzheimer disease continuum, both tauopathy and atrophy are most prominent in the medial-basal-lateral temporal lobes and thus are best displayed with coronal views. Five different participants are illustrated down the rows: A−T−(N)−, a 60-year old cognitively unimpaired man with nonspecific uptake of the amyloid PET ligand present in the white matter but no uptake present in the cortex; A−T+(N)−, an 81-year-old cognitively unimpaired woman; A+T−(N)−, a 70-year-old cognitively unimpaired woman; A+T+(N)−, a 75-year-old cognitively unimpaired man; and A+T+(N)+, an 84-year-old man with mild cognitive impairment.

Participants in this study were more often male than the 1442 participants not in this study (56% vs 49%, $P = .005$), but did not significantly differ on clinical diagnosis, age, education, proportion of *APOE* ε4 carriers, memory *z* score at index date, or annual change in memory *z* score (eTable 1 in the Supplement). Sixteen otherwise eligible individuals were excluded from this study for missing imaging or clinical data.

Primary Analysis: Predictors of Memory Performance

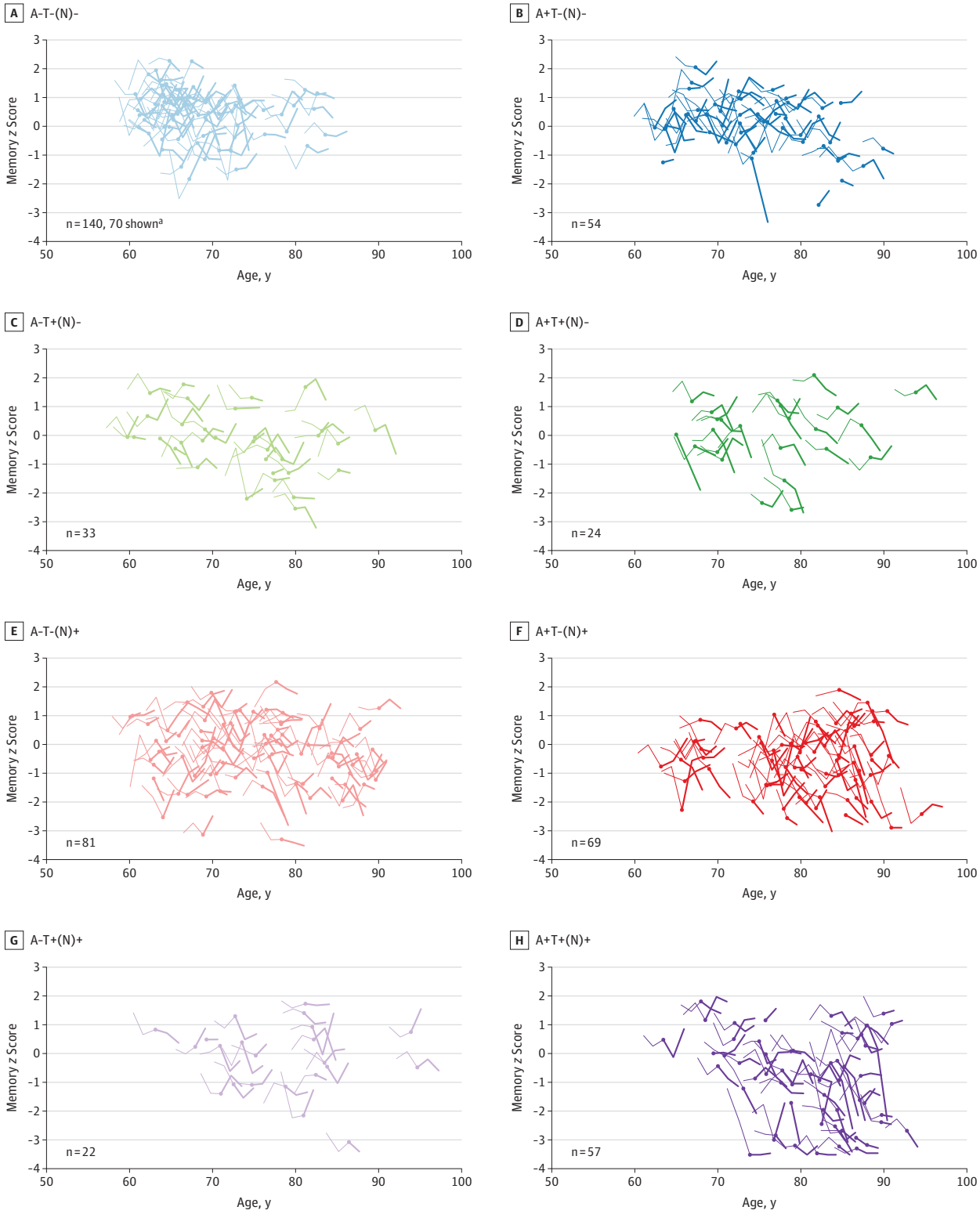
Plots of individual trajectories of memory *z* score by age within each AT(N) group (**Figure 2**) demonstrated substantial intraindividual variation in memory *z* scores over time and showed few participants older than age 80 were in the A−T−(N)− group and few younger than 70 were in the A+T+(N)+ group. In particular, only 11 participants (7%) aged 80 or older were A−T−(N)− and only 4 participants (2%) younger than 70 were A+T+(N)+ (eTable 2 in the Supplement).

In the clinical prediction model, age ($P < .001$) and *APOE* ε4 status ($P = .006$) were significantly associated with faster rates of memory decline, while sex (likelihood ratio test $P = .72$), education (likelihood ratio test $P = .99$), and CMC score (likelihood ratio test $P = .89$) were not (eTables 3 and 4 in the Supplement). **Figure 3** shows estimated rates of memory decline by age and *APOE* status. The estimated rate of memory decline in a 75-year-old individual who was an *APOE* ε4 noncarrier was −0.04 (95% CI, −0.05 to −0.02) *z* score units per year. An 85-year-old individual who was also an *APOE* ε4 noncarrier could be expected to have a decline of −0.08 (95% CI, −0.10 to −0.06) units per year, while a 75-year-old ε4 carrier could be expected to have a decline of −0.08 (95% CI, −0.10 to −0.05) units per year. eFigure 1 in the Supplement shows the estimated memory *z* score at index date (ie, cross-sectionally) for a female with 14 years of education, CMC score of 0, and who was an *APOE* ε4 noncarrier for 3 ages. A 10-year increase in age was significantly associated with a 0.4 (95% CI, 0.3-0.5; $P < .001$) lower memory *z* score at the index date and men had 0.5 (95% CI, 0.4-0.7; $P < .001$) lower memory *z* scores than women. A 4-year difference in education was significantly associated with a 0.6 (95% CI, 0.4-0.7; $P < .001$) higher memory *z* score at the index date, and *APOE* ε4 carriers had 0.3 (95% CI, 0.1-0.5; $P = .004$) lower memory *z* scores (eTable 4 in the Supplement).

The AT(N) model is summarized in eTable 5 in the Supplement. The AT(N) model offered a significant prediction improvement over the longitudinal clinical model (likelihood ratio test $P < .001$), with R^2 increasing from 0.26 (clinical model) to 0.31 (AT[N] model). AT(N) biomarkers were significantly associated with both rates of memory decline (likelihood ratio test $P < .001$) and memory *z* score at the index date (likelihood ratio test $P = .008$). The AT(N) association with memory decline was not significantly different by age (likelihood ratio test $P = .42$) or sex (likelihood ratio test $P = .47$) (eTable 3 in the Supplement).

The improvement in predicting rates of memory decline from adding AT(N) to the clinical model can be seen in Figure 3 where considerable variability in the rate of decline was present across the different AT(N) groups relative to the mean in the overall cohort. The A+T+(N)+, A+T+(N)−, and A+T−(N)+ groups had the fastest rates of memory decline compared with the other 5 groups ($P = .002$). At age 85 years, the estimated annual rates of decline in an *APOE* ε4 noncarrier were −0.13 (95% CI, −0.17 to −0.09), −0.10 (95% CI, −0.16 to −0.05), and −0.10 (95% CI, −0.13 to −0.06) for A+T+(N)+, A+T+(N)−, and A+T−(N)+, respectively, compared with a range of −0.02 to −0.06 for the other AT(N) groups.

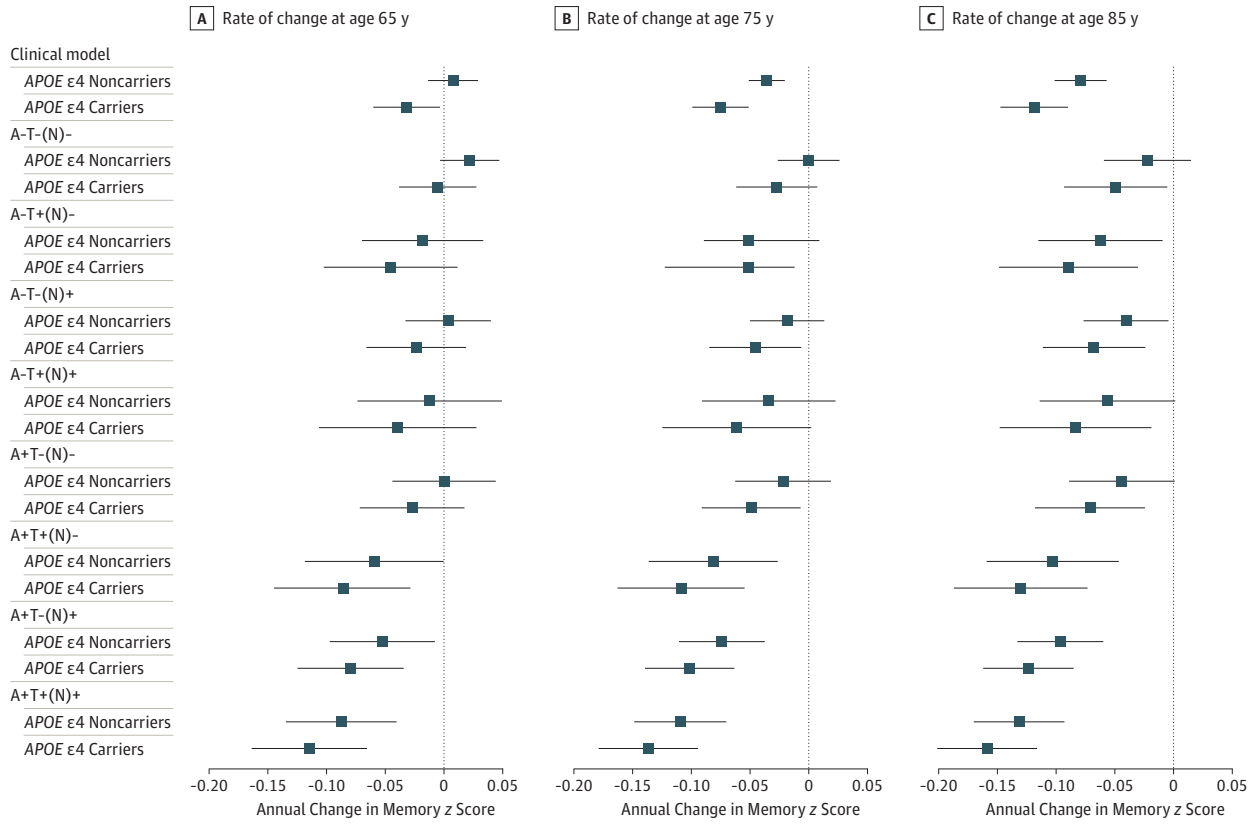
Figure 2. Plots of Individual Memory *z* Score Trajectories by Age and Amyloid, Tau, and Neurodegeneration Biomarker (AT[N]) Group



Each line represents 1 participant's trajectory, with the thinner portion of the line indicating memory *z* scores prior to the index (baseline) AT(N) imaging visit and the thicker portion of the line indicating memory *z* scores after the index AT(N) imaging visit. The *z* scores have been adjusted to account for the number of exposures to the cognitive battery by subtracting the estimated mean learning effect. The individual trajectories illustrate that there is substantial intraindividual variation in memory *z* scores over time.

[a] For the A–T–(N)– panel, a random subset of 50% of the data are shown to reduce overlap in the lines.

Figure 3. Estimated Rates of Annual Change in Memory *z* Score for 3 Exemplar Ages and *APOE* ε4 Carriers and Noncarriers



Rate estimates (95% CIs) are from 2 models: a clinical model in which rates depended on age and *APOE* status and an AT(N) model in which rates depended on age, *APOE* status, and AT(N) group. As illustrated in each age panel and for both *APOE* ε4 carriers and ε4 noncarriers, the rates of memory decline vary by AT(N), indicating better prediction of mean memory decline by age and *APOE* status (ie, the clinical model).

Secondary Analysis

Previous research has shown that prevalence of more abnormal AT(N) biomarker groups increased with age in the MCSA.[10] The consequences of the combination of increasing prevalence and faster declines in memory with age are graphically shown in **Figure 4**, which uses previous research[10] for the age-specific biomarker group prevalence estimates. The mean annual change in memory *z* score units in the population (blue line) was 0.02 (95% CI, −0.01 to 0.04) at age 60 and changed to −0.11 (95% CI, −0.14 to −0.08) by age 90. Forty-six percent of this increase in decline rate (−0.06) was partitioned to the increasing prevalence of abnormal AT(N) profiles while the remaining decline (−0.07) was partitioned to age, assuming a constant AT(N) prevalence.

Post Hoc Sensitivity Analyses

The estimated rates of memory decline by AT(N) group were similar across different variations of the models assessed in our sensitivity analyses (eFigure 2 in the Supplement).

Consistency of AT(N) Classification

Eighty-eight participants in our sample had a second AT(N) imaging visit at a median of 15 months (range, 12-19 months) after the index imaging visit (eTable 6 in the Supplement). Eighty-two percent (72/88) had no change in AT(N) classification from index to follow-up AT(N) imaging visit. AT(N) group classification was either stable or more abnormal in 80 of 88 individuals (91%) in the sample. A and T classifications were stable (98% and 97%, respectively) while (N) classification was slightly less stable (84%). Participants in the serial imaging subset (n = 88) more often had MCI (22% vs 5%; $P < .001$) and were slightly older (78 years [IQR, 69-83] vs 74 [67-81] years; $P = .05$) than participants in the study without serial imaging (n = 392), but they did not differ significantly on sex, education, proportion of *APOE* ε4 carriers, memory *z* score at the index date, or annual change in memory *z* score (eTable 1 in the Supplement).

Discussion

In this study, AT(N) biomarkers provided modest but statistically significant incremental information beyond more readily available clinical and genetic information in predicting memory decline. The variation in rate of memory decline between AT(N) groups was large at any age among both *APOE* ε4 carriers and noncarriers, indicating that the AT(N) biomarker groups provided more precise prediction

of memory decline rates beyond the variables in the clinical model (eTable 5 in the Supplement; Figure 3). To place the predictive utility of biomarkers in clinical context, the decline in rates of memory for A+T+(N)−, A+T−(N)+, A+T+(N)+ compared with A−T−(N)− were of similar magnitude to a 20-year increase in age and were twice that associated with *APOE* ε4 carriership, using estimates from the clinical model (eTables 4 and 5 in the Supplement; Figure 3).

In this study, the 3 groups with the fastest rates of memory decline all had abnormal amyloid (A+T+[N]−, A+T−[N]+, and A+T+[N]+). This illustrated a dominant association of memory decline with amyloidosis but only when present in combination with tauopathy, neurodegeneration, or both. However, biomarkers predicted not only which groups were likely to decline, but also which were not. *APOE* ε4 noncarriers who were A−T−(N)− exhibited minimal decline through age 85 (Figure 3).

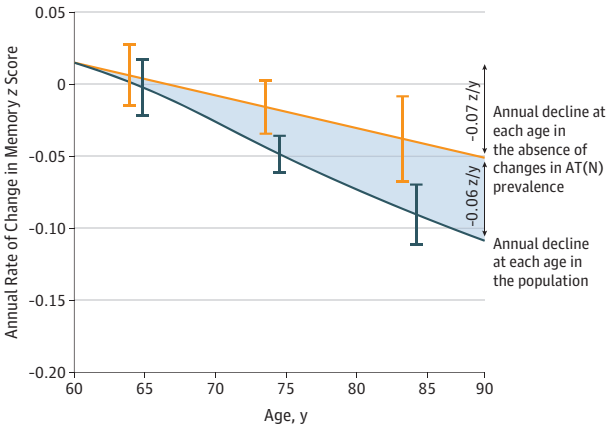
Many recent Alzheimer disease trials have focused on antiamyloid interventions and hence require enrollees to have an abnormal amyloid biomarker for inclusion.[20-22] However, the abnormal amyloid PET population consists of 4 subgroups. Both the A+T+(N)− and A+T+(N)+ groups were likely to decline cognitively over 2 to 3 years regardless of age or *APOE* genotype (Figure 3). The other 2 subgroups with abnormal amyloid (A+T−[N]− and A+T−[N]+), however, may present conceptual and practical challenges in clinical trials.

The A+T−(N)− group declined more slowly than the other A+ groups (eTable 5 in the Supplement; Figure 3) and therefore would give little signal on a memory composite in a 2- to 3-year clinical trial. Yet, this group constituted 26% of all participants with abnormal amyloid PET in this sample (Table).

Memory performance declined in the A+T−(N)+ group at all ages and in both *APOE* ε4 carriers and noncarriers (Figure 3); however, the biology underlying A+T−(N)+ is unclear at this point. A possible explanation is that these individuals have early Alzheimer disease (denoted by A+T−) plus neurodegeneration due to comorbid non-Alzheimer disease neuropathic changes.[1,23,24] Cognitive decline in Alzheimer disease may be driven by pathologic tau,[25] not amyloidosis (whose hypothesized pathogenic role is to facilitate the spread of pathological tau).[26] If so, it is not clear why the memory decline rate in A+T−(N)+ would be greater (eTable 5 in the Supplement) than that of A−T−(N)+. One possible explanation is an effect of subthreshold tau in A+T−(N)+ individuals, but this is speculative. Clearer understanding of the neuropathologic bases for the A+T−(N)+ group, as well as other AT(N) groups, awaits future biomarker-autopsy correlation studies.

In a secondary analysis, 46% of the mean rate of memory decline with age in the cohort was partitioned to the increasing prevalence of abnormal AT(N) groups with age (Figure 4). This observation is conceptually consistent with autopsy-based modeling.[27] Alzheimer disease is only one of several common diseases that are both associated with cognitive decline and increase in frequency with age.[24,28] These diseases (particularly α-synucleinopathy, cerebral microinfarctions, and TAR DNA-binding protein 43 proteinopathy) usually occur together rather than in isolation, particularly at older ages.[29,30]

Figure 4. Estimates of Annual Rate of Change in Memory *z* Score at Each Age



The solid blue line shows the expected annual rate of decline in memory *z* score at each age in the cohort. This reflects both aging alone and increasing fractions who will have a more abnormal amyloid, tau, and neurodegeneration biomarker (AT[N]) profile. The solid orange line shows the estimated portion of the rate of decline that is partitioned to aging alone, ie, if individuals of different ages but the same AT(N) profile were compared. The shaded blue region represents the portion of the rate that is partitioned to the change in AT(N) biomarker prevalence with age. Vertical bars show 95% confidence limits at 3 different ages for each line.

At present, specific biomarkers do not exist for these common non-Alzheimer age-related neuropathologies. Given the pathologic heterogeneity of the aging brain, the observation that AT(N) biomarker abnormalities were associated with 46% of mean memory decline rates by age was interesting because A and T biomarkers are related only to Alzheimer disease. The explanation could lie with the (N) biomarker group. (N) biomarkers (in this study, medial-basal-lateral temporal lobe atrophy) are nonspecific measures of damage to the brain from all etiologies. Thus, this (N) term captures, to some extent, the degenerative effects of Alzheimer disease plus the effects of non-Alzheimer pathologies.[24]

This study included several post hoc sensitivity analyses (eFigure 2 in the Supplement). While the primary analysis was in individuals without dementia (cognitively unimpaired plus MCI), most clinical trials would enroll either cognitively unimpaired individuals or individuals with MCI, not a mixed group. However, no substantive differences in findings were seen when only the cognitively unimpaired subset was examined vs the whole sample without dementia. This study also examined different tau PET implementations including choosing commonly used alternative target ROIs[17,31-34] as well as using partial volume correction[19] (the primary analysis was without). Results did not change notably, indicating robustness to different choices of imaging implementation.

AT(N) classification is the result of 3 independent biomarker test measurements. The potential for instability in AT(N) classification is high because measurement variance for the AT(N) group is compounded multiplicatively over the 3 independent tests. However, the AT(N) classification was found to be stable over short periods (eTable 6 in the Supplement).

Memory decline is a common clinical concern with advancing age.[35,36] This study illustrates the potential clinical utility of AT(N) biomarkers to improve prediction of short-term memory decline over commonly available clinical and genetic information, although the added predictive value of biomarkers, while significant, was small in magnitude.

Limitations

This study has several limitations. First, high inherent test-retest variance in memory *z* scores was evident in the individual trajectory plots in Figure 2. Within-person rates of memory decline were modeled as linear functions and used up to 2 cognitive test visits prior to the index AT(N) visit to stabilize the estimates of individual trajectories. A post hoc sensitivity analysis (eFigure 2 in the Supplement) demonstrated similar associations with and without including memory composite scores prior to the index AT(N) date, but with greater precision using the former approach. Memory decline is nonlinear over long periods but can be modeled as a linear function over the shorter periods[4] that were assessed in this study.

Second, new measures of interest will always be introduced into longitudinal natural history studies. Tau PET was introduced in 2015 and thus long-term follow-up in participants who have undergone tau PET imaging is not yet available. The neuropathologic processes that underlie age-related cognitive decline act over decades.[37] The length of follow-up from index visit (1-3 years) in this study was fairly short for processes of this nature and studies with longer follow-up times will be needed.

Third, a memory composite was used in this study because memory decline is often a harbinger of future global cognitive deterioration.[38,39] However, age-related cognitive decline is more complex than memory performance alone. It is possible that other composite measures might be more sensitive.[40]

Fourth, the NIA-AA research framework defines Alzheimer disease by β-amyloid plaques and pathologic tau deposits,[1] thus, the notion of cut points defining individuals who have abnormal amyloid and tau biomarkers is conceptually important. However, all biomarkers exist on a continuum and this continuous information is important for assessing disease severity and progression.

Fifth, this study is specific for the particular imaging biomarkers used and it is not yet known if these results will be replicated with biofluid biomarkers of AT(N).

Sixth, this cohort is from a population-based sample and so by design reflects the demographics of Olmsted County, Minnesota, which consists largely of a white population. Results may differ in populations where the prevalence of different neuropathologies underlying age-related cognitive decline or specific risk genes (eg, *APOE* ε4) differ.

Conclusions

Among older persons without baseline dementia followed for a median of 4.8 years, a prediction model that included amyloid PET, tau PET, and MRI cortical thickness resulted in a small but statistically significant improvement in predicting memory decline over a model with more readily available clinical and genetic variables. The clinical importance of this difference is uncertain.

ARTICLE INFORMATION

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Author Contributions: Dr Jack and Ms Wiste had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Jack, Lowe, Graff-Radford, Jones, Petersen.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Jack.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Wiste, Therneau, Weigand, Schwarz.
Obtained funding: Jack, Lowe, Vemuri, Roberts, Petersen.
Administrative, technical, or material support: Jack, Lowe, Schwarz, Gunter, Senjem, Graff-Radford, Jones, Roberts, Petersen.
Supervision: Jack, Lowe.

Conflict of Interest Disclosures: Dr Jack reported receiving grants from the National Institutes of Health (NIH) and Alexander Family Professorship of Alzheimer's Disease Research during the conduct of the study, consulting for Eli Lily, and serving on an independent data monitoring board for Roche outside the submitted work but receives no personal compensation from any commercial entity. Drs Therneau, Vemuri, Machulda, and Schwarz reported receiving grants from the NIH. Dr Knopman reported receiving personal fees from the Dominantly Inherited Alzheimer Network-Trials Unit data and safety monitoring board; serving as an investigator in clinical trials sponsored by Biogen, Lilly Pharmaceuticals, and the University of Southern California; and receiving research support from the NIH/National Institute on Aging (NIA) outside the submitted work. Dr Mielke reported receiving grants from the NIH/NIA during the conduct of the study and grants from Biogen, Lundbeck, and Roche and personal fees from Eli Lilly outside the submitted work. Dr Lowe reported consulting for Bayer Schering Pharma, Piramal Life Science, and Merck Research and receiving research support from GE Healthcare, Siemens Molecular Imaging, AVID Radiopharmaceuticals, and the NIH. Dr Senjem reported owning shares of the following medical-related stocks, unrelated to the current work, at the time of manuscript submission: Align Technology Inc, LHC Group Inc, Mesa Laboratories Inc, Natus Medical Inc, and Varex Imaging Corp. Within the past 3 years, he reported owning the following medical-related stocks, unrelated to the current work: CRISPR Therapeutics, Gilead Sciences Inc, Globus Medical Inc, Inovio Biomedical Corp, Ionis Pharmaceuticals, Johnson & Johnson, Medtronic Inc, and Parexel International Corp. Dr Graff-Radford reported receiving grants from the NIA during the conduct of the study. Dr Jones reported receiving grants from the NIH and State of Minnesota during the conduct of the study. Dr Petersen reported receiving personal fees from Hoffman-La Roche Inc, Merck Inc, Genentech Inc, Biogen Inc, GE Healthcare, and Eisai Inc and royalties from Oxford University Press for "Mild Cognitive Impairment: Aging to Alzheimer's Disease" outside the submitted work. No other disclosures were reported.

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