Age-specific and sex-specific prevalence of cerebral β-amyloidosis, tauopathy, and neurodegeneration in cognitively unimpaired individuals aged 50–95 years: a cross-sectional study

Clifford R Jack Jr, Heather J Wiste, Stephen D Weigand, Terry M Therneau, David S Knopman, Val Lowe, Prashanthi Vemuri, Michelle M Mielke, Rosebud O Roberts, Mary M Machulda, Matthew L Senjem, Jeffrey L Gunter, Walter A Rocca, Ronald C Petersen

Summary

Background A new classification for biomarkers in Alzheimer's disease and cognitive ageing research is based on grouping the markers into three categories: amyloid deposition (A), tauopathy (T), and neurodegeneration or neuronal injury (N). Dichotomising these biomarkers as normal or abnormal results in eight possible profiles. We determined the clinical characteristics and prevalence of each ATN profile in cognitively unimpaired individuals aged 50 years and older.

Methods All participants were in the Mayo Clinic Study of Aging, a population-based study that uses a medical records linkage system to enumerate all individuals aged 50–89 years in Olmsted County, MN, USA. Potential participants are randomly selected, stratified by age and sex, and invited to participate in cognitive assessments; individuals without medical contraindications are invited to participate in brain imaging studies. Participants who were judged clinically as having no cognitive impairment and underwent multimodality imaging between Oct 11, 2006, and Oct 5, 2016, were included in the current study. Participants were classified as having normal (A–) or abnormal (A+) amyloid using amyloid PET, normal (T–) or abnormal (T+) tau using tau PET, and normal (N–) or abnormal (N+) neurodegeneration or neuronal injury using cortical thickness assessed by MRI. We used the cutoff points of standard uptake value ratio (SUVR) 1·42 (centiloid 19) for amyloid PET, 1·23 SUVR for tau PET, and 2·67 mm for MRI cortical thickness. Age-specific and sex-specific prevalences of the eight groups were determined using multinomial models combining data from 435 individuals with amyloid PET, tau PET, and MRI assessments, and 1113 individuals who underwent amyloid PET and MRI, but not tau PET imaging.

Findings The numbers of participants in each profile group were 165 A–T–N–, 35 A–T+N–, 63 A–T–N+, 19 A–T+N+, 44 A+T–N–, 25 A+T+N–, 35 A+T–N+, and 49 A+T+N+. Age differed by ATN group ($p<0·0001$), ranging from a median 58 years (IQR 55–64) in A–T–N– and 57 years (54–64) in A–T+N– to a median 80 years (75–84) in A+T–N+ and 79 years (73–87) in A+T+N+. The number of *APOE* ε4 carriers differed by ATN group ($p=0·04$), with carriers roughly twice as frequent in each A+ group versus the corresponding A– group. White matter hyperintensity volume ($p<0·0001$) and cognitive performance ($p<0·0001$) also differed by ATN group. Tau PET and neurodegeneration biomarkers were discordant in most individuals who would be categorised as stage 2 or 3 preclinical Alzheimer's disease (A+T+N–, A+T–N+, and A+T+N+; 86% at age 65 years and 51% at age 80 years) or with suspected non-Alzheimer's pathophysiology (A–T+N–, A–T–N+, and A–T+N+; 92% at age 65 years and 78% at age 80 years). From age 50 years, A–T–N– prevalence declined and A+T+N+ and A–T+N+ prevalence increased. In both men and women, A–T–N– was the most prevalent until age late 70s. After about age 80 years, A+T+N+ was most prevalent. By age 85 years, more than 90% of men and women had one or more biomarker abnormalities.

Interpretation Biomarkers of fibrillar tau deposition can be included with those of β-amyloidosis and neurodegeneration or neuronal injury to more fully characterise the heterogeneous pathological profiles in the population. Both amyloid-dependent and amyloid-independent pathological profiles can be identified in the cognitively unimpaired population. The prevalence of each ATN group changed substantially with age, with progression towards more biomarker abnormalities among individuals who remained cognitively unimpaired.

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See Comment page 411

Department of Radiology (Prof C R Jack Jr MD, P Vemuri PhD), **Department of Health Sciences Research** (H J Wiste BA, S D Weigand MS, Prof T M Therneau PhD, Prof M M Mielke PhD, Prof R O Roberts MB ChB, Prof W A Rocca MD, Prof R C Petersen MD), **Department of Neurology** (Prof D S Knopman MD, Prof M M Mielke, Prof R O Roberts, Prof W A Rocca, Prof R C Petersen), **Department of Nuclear Medicine** (Prof V Lowe MD), **Department of Psychiatry and Psychology** (M M Machulda PhD), **and Department of Information Technology** (M L Senjem MS, J L Gunter PhD), **Mayo Clinic, Rochester, MN, USA**

Correspondence to:
Prof Clifford Jack Jr, Mayo Clinic, Rochester, MN 55905, USA
jack.clifford@mayo.edu

Introduction

Use of biomarkers as an aid to the diagnosis of Alzheimer's disease gained acceptance with the publication of the National Institute on Aging–Alzheimer's Association (NIA-AA) recommendations[1–4] and the International Working Group (IWG) criteria[5,6] for Alzheimer's disease. In the NIA-AA recommendations, biomarkers were divided into two classes: biomarkers of

Research in context

Evidence before this study

We searched PubMed with the terms "preclinical AD", "tau PET", and "amyloid PET" for English-language articles published from Jan 1, 2006, to Sept 1, 2016. Cognitively unimpaired cohorts have been studied using the National Institute on Aging–Alzheimer's Association (NIA-AA) staging recommendations plus the suspected non-Alzheimer's pathophysiology (SNAP) construct with the terms amyloid abnormal (A+), amyloid normal (A–), neurodegeration abnormal (N+), or neurodegeration normal (N–), resulting in four different biomarker categories: A–N–, A+N–, A–N+ (SNAP), or A+N+. Proportions of these four groups were roughly similar in many cohorts. The proportion of *APOE* ε4 carriers was greater in the A+N– and A+N+ groups than in A–N– or SNAP. Clinical and psychometric outcomes were uniformly worst in individuals classified as A+N+. These findings were largely the same whether biomarker categorisation was done using imaging or CSF. The NIA-AA staging plus SNAP construct has been useful because it has provided a common framework for different research groups to communicate their own findings.

Added value of this study

In retrospect, a weakness of the NIA-AA staging plus SNAP construct is the grouping of CSF phosphorylated tau into the same neurodegeneration or neuronal injury category with total tau, MRI, and ^{18}F-fluorodeoxyglucose (^{18}F-FDG)-PET. The ATN construct remedies this weakness and enables researchers to investigate multidomain biomarker associations for which the effects of tauopathy (defined by tau PET or CSF phosphorylated tau) and neurodegeneration or neuronal damage (defined by CSF total tau, MRI, or ^{18}F-FDG PET) are segregated at an individual level. We described clinical characteristics and age-specific and sex-specific prevalence of amyloid, tau, and neurodegeneration or neuronal injury in individuals aged 50 years and older using the ATN construct. To our knowledge, this is the first study to do so. We showed that tau and neurodegeneration were often discordant: among individuals who would have been classified as NIA-AA stage 2 or 3 preclinical Alzheimer's disease (ie, A+T+N–, A+T–N+, and A+T+N+), tau PET and neurodegeneration biomarkers were discordant in 86% of those aged 65 years and 51% of those aged 80 years; among the individuals who would have been labelled SNAP (ie, A–T+N–, A–T–N+, A–T+N+) tau PET and neurodegeneration biomarkers were discordant in 92% of those aged 65 years and 78% of those aged 80 years.

Implications of all the available evidence

The ATN classification scheme is a useful approach to characterise abnormalities in the biomarkers of amyloid, tau, and neurodegeneration or neuronal injury to understand the underlying heterogeneous pathological profiles in the population. Marked age variation in biomarker prevalence requires careful interpretation of biomarker results from studies across cohorts of different ages. Future research will determine the within-individual biomarker changes to assess amyloid-dependent (ie, Alzheimer's disease) and amyloid-independent (ie, SNAP) pathological pathways and sequences of biomarker abnormality.

amyloid (A) and biomarkers of tau-related neurodegeneration or neuronal injury (N),[1–4] for which biomarkers were used to classify individuals as amyloid abnormal (A+), amyloid normal (A–), neurodegeration abnormal (N+), or neurodegeration normal (N–). When the NIA-AA recommendations for preclinical Alzheimer's disease staging were applied to a cohort of 450 cognitively unimpaired individuals aged older than 70 years, roughly a third were categorised as stages 1–3 preclinical Alzheimer's disease, 40% were amyloid normal and neurodegeneration normal (A–N–), and a quarter were amyloid normal and neurodegeneration abnormal (A–N+).[7] We labelled the A–N+ group as suspected non-Alzheimer's pathophysiology (SNAP) on the assumption that this was a pathologically heterogeneous group with various non-Alzheimer's pathologies.[7] To reflect NIA-AA staging while accounting for the SNAP and A–N– groups, many research groups have adopted a two-class biomarker construct in which individuals are assigned to one of four biomarker categories: A–N–, A+N–, A–N+ (SNAP), or A+N+.[8–13] This approach has been useful because it has provided a common framework for different research groups to communicate findings in their own cohorts.[8–13]

However, a weakness of the NIA-AA staging method plus SNAP construct was the grouping of CSF phosphorylated tau, MRI, and ^{18}F-fluorodeoxyglucose (^{18}F-FDG)-PET into one neurodegeneration or neuronal injury category.[1–4,7] In individuals with Alzheimer's disease, it is reasonable to assume that neurodegeneration in areas sensitive to Alzheimer's disease is most often related to tauopathy; however, neurodegeneration, even when defined on the basis of its pattern in Alzheimer's disease, also occurs in disorders other than Alzheimer's disease. A solution to this problem is to separate biomarkers that are specific for deposits of fibrillar tau and its associated pathophysiology from those that are non-specific measures of neurodegeneration or neuronal injury.[14–19] This refinement enables identification of tauopathies and neurodegeneration or neuronal injuries that are associated, and not associated, with each other, leading to a more precise understanding of the biological underpinnings of brain ageing. To this end, an international group has proposed a new descriptive classification construct[20] for biomarkers used in Alzheimer's disease and cognitive ageing research. The construct is called ATN[20] and is based on grouping biomarkers into three categories: fibrillary β-amyloid

deposition or associated pathophysiology (A);[19] paired helical filament tau or associated pathophysiology (T);[14–19] and neurodegeneration or neuronal injury (N). One possible implementation of ATN is to dichotomise each biomarker category as either normal (–) or abnormal (+), which results in eight different biomarker group combinations. We use the terms normal and abnormal in this paper, rather than negative and positive as in previous reports, as we can know whether a scan is normal or abnormal but not whether a normal appearing scan is truly negative (ie, that no plaques or tangles would be present if the person were to come to autopsy).

The goal of this study was to apply the ATN categorisation to cognitively unimpaired individuals aged 50 years and older in the population-based Mayo Clinic Study of Aging (MCSA)[21] to estimate the age-specific and sex-specific prevalence of each ATN group, and to describe the clinical and demographic characteristics of individuals in each group. We used amyloid PET to define A, tau PET to define T, and cortical thickness to define N.

Methods

Study design and participants

We did a cross-sectional study of participants enrolled in the MCSA, a population-based study of cognitive ageing among residents of Olmsted County (MN, USA).[21] The Rochester Epidemiology Project[22] medical records linkage system was used to enumerate all Olmsted County residents aged 50–89 years. Potential participants were randomly selected from this enumeration, stratified by age and sex, with equal numbers of men and women in each age category. The random selection was achieved by randomly ordering the population enumeration in lists based on age-stratification and sex-stratification; potential participants were selected from those ordered lists by taking the first individual on each list who had not already been selected until the target enrolment in each strata was achieved. All individuals without a medical contraindication were invited to participate in imaging studies. Since 2004, the MCSA has enrolled individuals without dementia aged 70–89 years; in 2012, the study started to enrol individuals aged 50 years and older.[7,8,21] Before May 28, 2015, imaging included amyloid PET, ^{18}F-FDG PET, and MRI. From May 28, 2015, individuals who participated in imaging underwent each of amyloid PET, tau PET, and MRI.[23]

Individuals from the MCSA were included in our cross-sectional study if they were judged clinically to have no cognitive impairment and had undergone amyloid PET, tau PET (in a subset), and MRI between Oct 11, 2006, and Oct 5, 2016. We analysed data from the first visit with amyloid PET, tau PET, and MRI, or the most recent amyloid PET and MRI visit if no tau PET was available, to estimate the age-specific and sex-specific prevalence of each ATN group and to describe the clinical and demographic characteristics of the eight ATN biomarker groups.

The MCSA and related studies were approved by the Mayo Clinic and Olmsted Medical Center institutional review boards and written informed consent was obtained from all participants before they joined the study.

Procedures

Amyloid PET imaging was done with ^{11}C-Pittsburgh Compound B, synthesised on site with precursor purchased from ABX Biochemical Compounds (Radeberg, Germany). Tau PET was done with AV1451, synthesised on site with precursor supplied by Avid Radiopharmaceuticals (Philadelphia, PA, USA).[17] Late-uptake amyloid PET images were acquired 40–60 min, and tau PET 80–100 min, after injection. Methods of amyloid PET data analysis have been described previously.[7,23] We expressed amyloid PET values both as standard uptake value ratio (SUVR) units and as centiloid units.[24] A tau PET composite reporter region of interest (ROI) was formed from a voxel-number-weighted average of the median uptake in the entorhinal, amygdala, parahippocampal, fusiform, inferior temporal, and middle temporal ROIs normalised to the cerebellar crus grey median.[23] PET data were not partial-volume corrected.

MRI was done with one of three 3-Tesla systems from the same vendor (General Electric, Waukesha, WI, USA). The primary MRI measure was a FreeSurfer (version 5.3)-derived temporal lobe cortical thickness composite reporter ROI of the entorhinal, inferior temporal, middle temporal, and fusiform ROIs.[23] These were consistently among the top-performing ROIs across our previous ROI selection studies discriminating between A– cognitively unimpaired and A+ cognitively impaired individuals.[25,26] As an alternative measure of neurodegeneration we used the sum of right and left hippocampal volumes from FreeSurfer, adjusted for total intracranial volume as described previously.[27] The MRI acquisition also included a fluid-attenuated inversion recovery (FLAIR) sequence from which white matter hyperintensity volume was measured using an algorithm that we had developed previously.[28]

We had previously examined several different methods for selecting cutoff points to define abnormality with amyloid PET, tau PET, and MRI thickness.[23] The optimum amyloid PET cutoff point of SUVR 1·42 (centiloid 19) was based on the threshold value beyond which the rate of change in amyloid PET reliably increases. We determined cutoff points for tau PET and MRI thickness by maximising the accuracy (ie, maximising sensitivity plus specificity) in discriminating between A+ individuals with mild cognitive impairment or dementia versus MCSA cognitively unimpaired individuals aged 30–49 years. Based on this method, the cutoff point for tau PET was 1·23 SUVR and for MRI cortical thickness was 2·67 mm.

Each participant was classified into one of the eight ATN states using the predefined cutoff points, and we determined age-specific and sex-specific prevalences of

the eight ATN biomarker groups. As a secondary analysis, abnormal N was defined as hippocampal volume adjusted for total intracranial volume of less than –1·15 mL (HVa). This cutoff point was derived in the same manner and using the same samples described previously.[23]

Statistical analysis

The MCSA sampled similar numbers of individuals within 5-year age and sex strata from age 50 to 90 years. As a result, individuals in the older age strata were over-represented relative to the population. Therefore, to summarise the overall clinical and demographic characteristics of the eight ATN groups (appendix), we weighted our sample to reflect the actual age and sex distributions of the Olmsted County cognitively unimpaired population. Census bureau estimates for 2010 along with mild cognitive impairment and dementia-prevalence estimates from the MCSA were used to create the weights, and the survey package in R was used to correct SEs to account for strata weights (appendix).

See Online for appendix

We estimated the prevalence of each of the eight ATN groups by partitioning the full eight-group model into two components: a multinomial model with the four-level AN group as the response and age and sex as covariates (n=1548); and a logistic model with T+ as the response and AN, age, and sex as covariates (n=435). In this framework, the individuals without tau imaging can stabilise the overall prevalence estimates of the ATN groups by contributing information to the first part of the model. Inference from the model was based on posterior simulations using the maximum likelihood estimate and the variance covariance matrix. These simulations allowed us to obtain point estimates and 95% CIs for functions of the model variables such as prevalence estimates, differences in prevalence estimates, and the age at which a prevalence curve peaks (appendix).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all the data in the study. The corresponding author had final responsibility for the decision to submit for publication.

	A–T–N– n=165 (38%)	A–T+N– n=35 (8%)	A–T–N+ n=63 (14%)	A–T+N+ n=19 (4%)	A+T–N– n=44 (10%)	A+T+N– n=25 (6%)	A+T–N+ n=35 (8%)	A+T+N+ n=49 (11%)
Age (years)								
Median (IQR)	65 (58 to 69)	68 (62 to 78)	75 (67 to 81)	79 (73 to 82)	71 (66 to 78)	77 (70 to 82)	82 (77 to 85)	82 (76 to 87)
Range	51 to 84	53 to 90	53 to 90	63 to 95	53 to 88	65 to 94	66 to 91	64 to 94
Sex								
Male	83 (50%)	19 (54%)	45 (71%)	9 (47%)	16 (36%)	15 (60%)	22 (63%)	27 (55%)
Female	82 (50%)	16 (46%)	18 (29%)	10 (53%)	28 (64%)	10 (40%)	13 (37%)	22 (45%)
Education (years)	16 (13 to 16)	16 (14 to 17)	15 (13 to 16)	16 (13 to 16)	14 (13 to 17)	14 (14 to 17)	14 (12 to 16)	14 (12 to 16)
APOE ε4 carriers	30 (19%)	5 (15%)	13 (22%)	1 (5%)	20 (49%)	13 (52%)	14 (41%)	16 (33%)
WMH volume (mL)	5·3 (3·4 to 9·7)	6·8 (3·7 to 10·4)	11·9 (5·6 to 17·3)	15·0 (8·2 to 20·7)	9·6 (5·2 to 15·5)	8·9 (6·4 to 16·0)	19·1 (9·7 to 33·1)	18·9 (11·1 to 31·7)
Cognitive *Z* scores								
Memory	0·5 (–0·2 to 1·0)	–0·1 (–0·5 to 0·7)	–0·2 (–0·8 to 0·6)	0·2 (–0·8 to 0·9)	0·1 (–0·5 to 0·5)	0·1 (–0·8 to 0·8)	–0·6 (–1·1 to –0·1)	–0·5 (–1·1 to 0·3)
Attention	0·4 (–0·1 to 0·9)	0·6 (0·0 to 0·9)	–0·2 (–0·8 to 0·3)	0·2 (–0·2 to 0·8)	0·1 (–0·5 to 0·6)	–0·2 (–0·7 to 0·3)	–0·3 (–0·8 to 0·2)	–0·5 (–1·4 to 0·0)
Language	0·3 (–0·3 to 0·9)	0·5 (–0·2 to 1·1)	–0·2 (–0·7 to 0·3)	0·0 (–0·4 to 0·4)	0·2 (–0·2 to 0·8)	0·0 (–0·6 to 0·4)	–0·6 (–1·0 to 0·0)	–0·3 (–0·8 to 0·1)
Visuospatial	0·3 (–0·3 to 0·9)	0·3 (–0·2 to 0·8)	–0·2 (–0·7 to 0·4)	0·1 (–0·4 to 0·5)	0·1 (–0·8 to 0·5)	0·2 (–0·6 to 0·7)	–0·4 (–0·8 to 0·0)	–0·1 (–1·3 to 0·4)
Amyloid PET								
SUVR	1·31 (1·26 to 1·35)	1·33 (1·30 to 1·37)	1·33 (1·28 to 1·37)	1·35 (1·31 to 1·37)	1·57 (1·47 to 1·77)	1·62 (1·55 to 2·10)	1·58 (1·50 to 1·77)	2·22 (1·54 to 2·44)
Centiloid	9 (5 to 12)	11 (8 to 14)	11 (7 to 14)	13 (9 to 14)	31 (23 to 48)	35 (29 to 76)	32 (25 to 48)	86 (28 to 105)
Tau PET (SUVR)	1·15 (1·11 to 1·19)	1·28 (1·25 to 1·30)	1·17 (1·10 to 1·20)	1·28 (1·25 to 1·30)	1·16 (1·13 to 1·20)	1·27 (1·25 to 1·34)	1·16 (1·12 to 1·20)	1·30 (1·26 to 1·36)
Cortical thickness (mm)	2·79 (2·73 to 2·85)	2·78 (2·75 to 2·87)	2·59 (2·53 to 2·62)	2·59 (2·52 to 2·62)	2·76 (2·72 to 2·82)	2·76 (2·72 to 2·78)	2·59 (2·47 to 2·63)	2·56 (2·51 to 2·62)

Data are median (IQR) or number (%), unless stated otherwise. ATN=amyloid, tau, and neurodegeneration or neuronal injury. A–=amyloid normal using amyloid PET. A+=amyloid abnormal using amyloid PET. T–=tau normal using tau PET. T+=tau abnormal using tau PET. N–=neurodegeneration or neuronal injury normal using cortical thickness. N+=neurodegeneration or neuronal injury abnormal using cortical thickness. WMH=white matter hyperintensities. SUVR=standard uptake value ratio.

Table 1: **Characteristics of 435 participants by ATN biomarker classification**

Results

Table 1 shows unweighted data in our ATN sample (n=435). Summaries by ATN group weighted to the cognitively unimpaired Olmsted County population by age and sex are in figure 1. Age differed among ATN groups (p<0·0001) with individuals with worse biomarker profiles tending to be older (table 1, figure 1). The group with the greatest estimated proportion of men was A–T–N+ (57%, 95% CI 37–77) and the group with the greatest proportion of women was A+T–N– (78%, 64–93); however, overall the sex distribution was not different among the ATN groups (p=0·21). *APOE* ε4 varied by ATN group (p=0·04) and was roughly twice as frequent among A+ individuals compared with A– individuals. White matter hyperintensity volume differed between ATN groups (figure 1, p<0·0001) even after adjustment for age (p=0·01; appendix), and was higher in N+ than N– groups (p=0·05; not shown), although the magnitude of the differences was small. There were small, but significant, differences in cognition by group for all domains (figure 1, p<0·0001) even after adjustment for age (appendix, p≤0·03).

The appendix shows demographic features of the full sample of 1548 cognitively unimpaired MCSA individuals with amyloid PET and MRI (but not necessarily tau PET) who were used to constrain or stabilise ATN-prevalence estimates among the subset of 435 who had amyloid PET, MRI, and tau PET.

For both men and women, A–T–N– prevalence declined from age 50 years onwards, while that of A–T+N+ increased gradually with age starting at 60 years, and that of A+T+N+ increased more markedly with age beginning in the late 60s (figure 2). The remaining ATN groups reached individual peaks in prevalence. Comparisons of

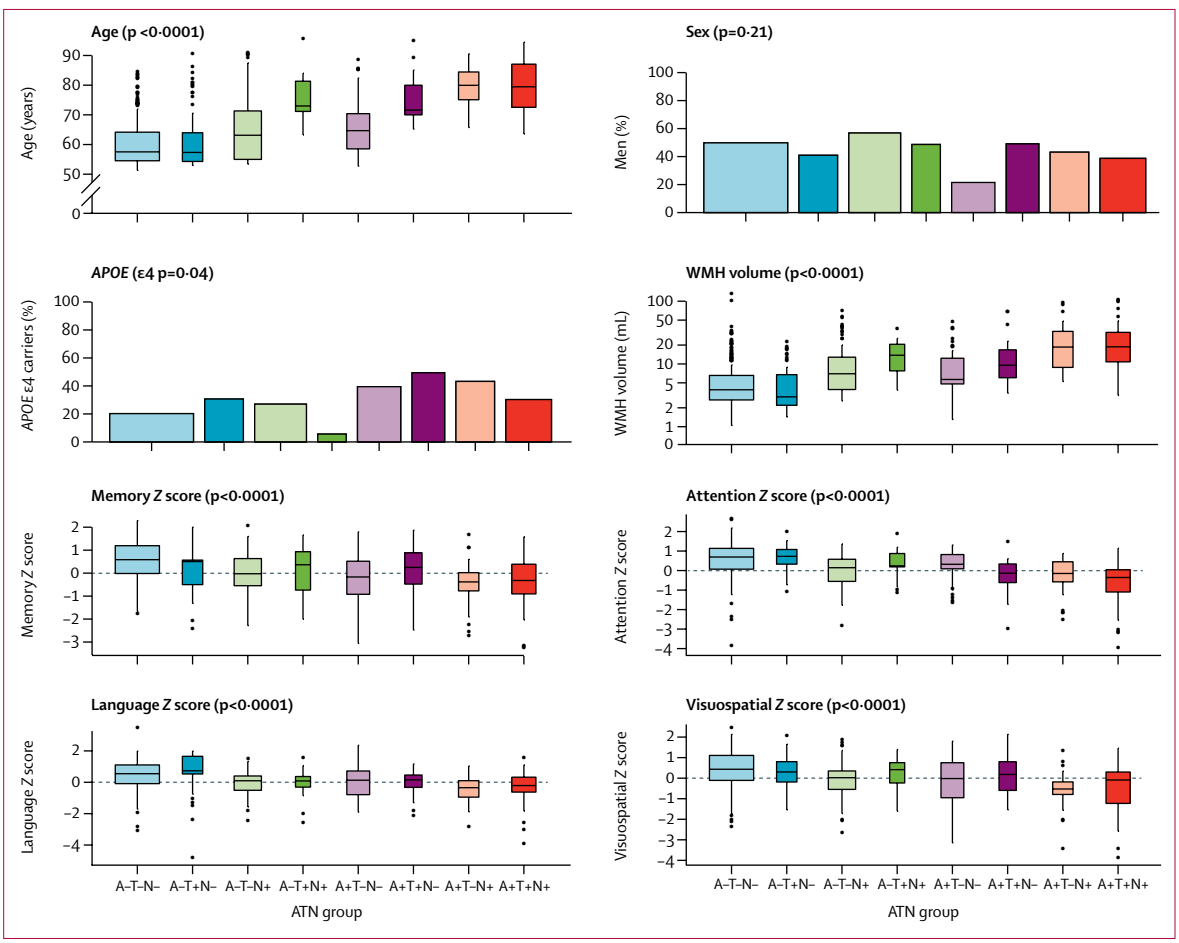

***Figure 1*: ATN group characteristics**

Box plots of continuous variables and bar charts summarising percentages of categorical variables from table 1 by ATN biomarker group. The box plots and estimated percentages reflect weighting of the sample to match the age distribution and sex distribution of the sample population (Olmsted County [MN, USA] residents who were clinically normal). Box and bar widths reflect sample sizes. p values test for any difference in each variable among the eight groups. The box plot whiskers extend to the lowest and highest data points within 1·5 times the IQR from the lower and upper quartiles. The dots represent individual points that fall outside this range. ATN=amyloid, tau, and neurodegeneration or neuronal injury. A–=amyloid normal using amyloid PET. A+=amyloid abnormal using amyloid PET. T–=tau normal using tau PET. T+=tau abnormal using tau PET. N–=neurodegeneration or neuronal injury normal using cortical thickness. N+=neurodegeneration or neuronal injury abnormal using cortical thickness. WMH=white matter hyperintensities.

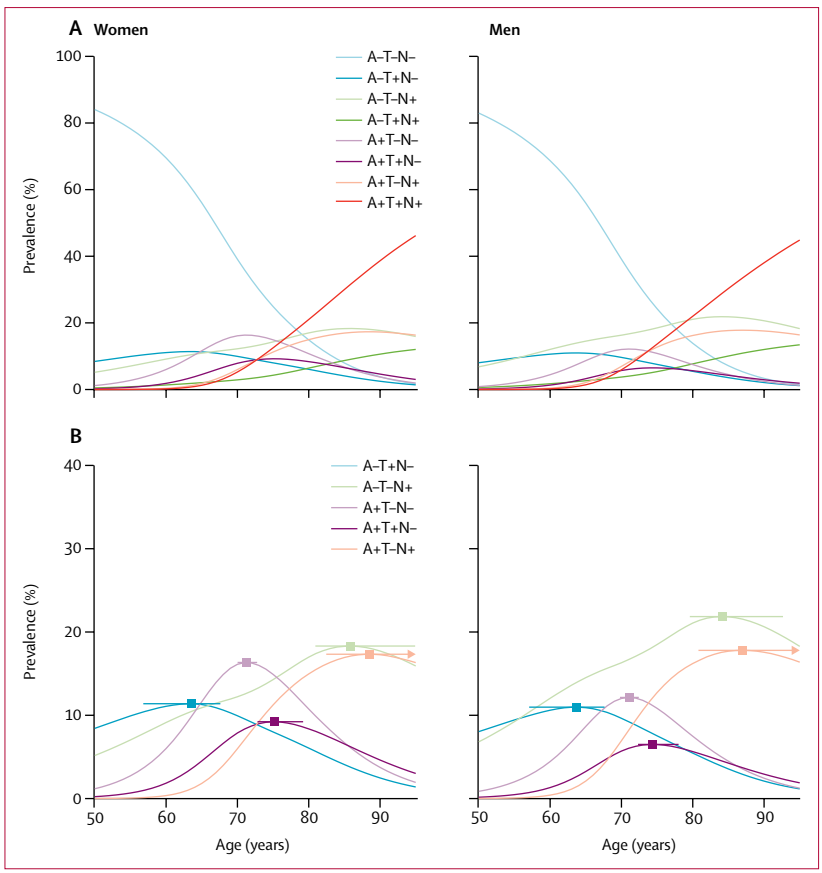

***Figure 2*: Estimated prevalence of the ATN biomarker groups by age and sex**
Estimated prevalence curves by age and sex for all ATN groups (A) and the same curves (except for A–T–N–, A–T+N+, and A+T+N+) on an enlarged scale with the estimated peak for each curve shown with a square and 95% CI (B). Arrows represent CIs that extended past the x-axis limits of the figure (ie, where the upper limit was 100). ATN=amyloid, tau, and neurodegeneration or neuronal injury. A–=amyloid normal using amyloid PET. A+=amyloid abnormal using amyloid PET. T–=tau normal using tau PET. T+=tau abnormal using tau PET. N–=neurodegeneration or neuronal injury normal using cortical thickness. N+=neurodegeneration or neuronal injury abnormal using cortical thickness.

	Women, peak age (years)	Men, peak age (years)	Differences in peak age (years)
A–T+N–	64 (57 to 68)	64 (57 to 68)	0 (–1 to 2)
A+T–N–	71 (70 to 73)	71 (70 to 72)	0 (–1 to 0)
A+T+N–	75 (73 to 79)	74 (72 to 78)	–1 (–2 to 0)
A–T–N+	86 (81 to 95)	84 (80 to 93)	–2 (–4 to 0)
A+T–N+	88 (82 to 100)	87 (81 to 100)	–2 (–4 to 1)

Data are peak age (95% CI), or differences in peaks by sex. ATN=amyloid, tau, and neurodegeneration or neuronal injury. A–=amyloid normal using amyloid PET. A+=amyloid abnormal using amyloid PET. T–=tau normal using tau PET. T+=tau abnormal using tau PET. N–=neurodegeneration or neuronal injury normal using cortical thickness. N+=neurodegeneration or neuronal injury abnormal using cortical thickness. Peak ages are not shown for A–T–N– because the prevalence declined over the entire age range, or for A–T+N+ or A+T+N+ because the prevalence of these groups increased over the entire age range.

***Table 2*: Age at which the percentage of each ATN prevalence curve reaches its peak for women and men**

the curves for men versus women (appendix) revealed a slightly greater prevalence of A–T–N+ in men from age 65 to 75 years but no other clear sex differences.

We averaged the sex-specific prevalence estimates to make direct age-specific prevalence comparisons between ATN groups (appendix). The dominant trends were that A–T–N– was the most prevalent group from age 50 years to the late 70s, and that A+T+N+ was the most prevalent group from age early 80s onwards.

The ages at which the prevalence curves peaked differed substantially among ATN groups but were similar for men and women within each group (table 2, figure 2). A–T+N– was the first group to peak (age 64 years), followed by A+T–N– and A+T+N– (ages 71 and 74–75 years, respectively). The N– groups all peaked by age 75 years or younger, whereas the N+ groups did so at or above age 84 years. Differences in peak age between some ATN groups were substantial (appendix), particularly between N– and N+ groups. For example, the A+T–N+ and A–T–N+ groups peaked 25 years (95% CI 15–42) and 22 years (14–34) later than the A–T+N– group.

Figure 3 illustrates that abnormalities in A, T, and N mostly did not overlap at young ages. At older ages, the presence of more than one abnormal biomarker was common and there was substantial discordance among the three. Tau and neurodegeneration were discordant in 86% of individuals categorised as NIA-AA preclinical Alzheimer's disease stage 2 or 3 (ie, individuals classified as A+T+N– or A+T–N+ as a proportion of those classified as A+T+N–, A+T–N+, or A+T+N+) at age 65 years and in 51% at age 80 years (figure 3). Tau PET and neurodegeneration biomarkers were also discordant in most individuals categorised as SNAP (ie, individuals classified as A–T+N– or A–T–N+ as a proportion of those classified as A–T+N–, A–T–N+, or A–T+N+; 92% at age 65 years and 78% at age 80 years; figure 3). ATN prevalence by age was also calculated using HVa instead of cortical thickness as the N measure (appendix). Although agreement between measures of HVa and thickness was moderate (κ=0·45), overall the ATN prevalence trends by age were similar when either measure was used. One difference was a higher prevalence of N+ in men than in women when using HVa, which was evident when comparing the A–T–N+ curves (figure 2, appendix).

Discussion

Our main findings were that A–T–N– prevalence declined from age 50 years onwards whereas the prevalence of A–T+N+ and A+T+N+ increased continuously with age for both men and women. A–T–N– was the most prevalent group from age 50 years to the late 70s. From age late 70s onwards, A+T+N+ was the most prevalent group. The other N– groups (A–T+N–, A+T–N–, and A+T+N–) all reached peak prevalence by age 75 years or younger whereas the other N+ groups (A–T–N+ and A+T–N+) reached a peak prevalence at or above age 84 years.

Cross-sectional prevalence curves are the first step in understanding the complex and interdependent evolution of amyloid, tau, and neurodegeneration in ageing individuals. Because our sample came from a geographically stable population, secular changes are likely to be minimised, and thus we interpreted differences in ATN prevalence curves across the 50–90 years age range as being largely due to transitions between biomarker groups as people age. The declining prevalence of A–T–N– with age is logical, since individuals can only transition out of A–T–N–, while the increasing prevalence of A+T+N+ with age makes sense because this is an absorbing biomarker state—ie, people can transition out of all states except A+T+N+. The increasing prevalence of A–T+N+ might reflect an absorbing state for those on a non-Alzheimer's disease pathway.

For the other five ATN groups, the prevalence increased to a peak with age, then declined. The age at which the prevalence curves peaked differed, but peak ages can be grouped into two clusters. The N– groups with evidence of either abnormal amyloid or tau deposition all peaked by age 75 years or younger, whereas the N+ groups peaked at or above age 84 years. From age 75–85 years, the prevalence of the three N– groups fell whereas the prevalence of the two N+ groups rose. This finding is consistent with the idea that neurodegeneration or neuronal injury is a downstream consequence of antecedent proteinopathies. The fact that A–T–N+ was more frequent than some N– groups in middle age is consistent with the idea that this group is on a separate, non-Alzheimer's disease trajectory where neurodegeneration is not driven by Alzheimer's disease proteinopathy.

Overall the effect of sex on the prevalence of all ATN groups was small when using cortical thickness as a measure, but more pronounced when using HVa. *APOE* ε4 was more frequent among the A+ than the A– groups. Among individuals who were A–, we noted no clear evidence of elevation in *APOE* ε4 frequency among A–T+N–, A–T–N+, or A–T+N+ relative to A–T–N–. Similarly, among individuals who were A+, we showed no evidence of elevation in *APOE* ε4 frequency among A+T+N–, A+T–N+, or A+T+N+ relative to A+T–N–. One interpretation of this finding is that the primary effect of *APOE* ε4 is to increase amyloidosis, not to enhance tau deposition, neurodegeneration, or both through non-amyloid-related mechanisms.

Abnormal biomarker profiles were associated with worse cognition across different domains after adjusting for age. White matter hyperintensity volume was higher in N+ than in N– groups (p=0·05). This finding supports the position that ischaemic brain injury is, among other conditions,[29] a likely contributor to N+.

SNAP was first described as A–N+ where N+ was based on ^{18}F-FDG PET and MRI findings.[7] In the 2011 NIA-AA criteria, the definition of N+ also included abnormal CSF phosphorylated and total tau.[1–4] In our data, 15% of individuals were classified as SNAP defined by MRI and amyloid PET at age 65 years, and 26% at age 80 years. Of these individuals, 13% at age 65 and 27% at age 80 also had abnormal tau PET (ie, A–T+N+). Thus, tau and neurodegeneration were concordant only in a few A–N+ (SNAP) individuals for whom N+ was defined by cortical thickness.[30,31] Mormino and colleagues[32] and Wisse and colleagues[33] have reported that tau was not elevated in SNAP relative to A–N– individuals who were classified by amyloid PET and hippocampal volume or ^{18}F-FDG PET using the NIA-AA staging plus SNAP construct. Similarly, we noted that the proportions of T+ participants

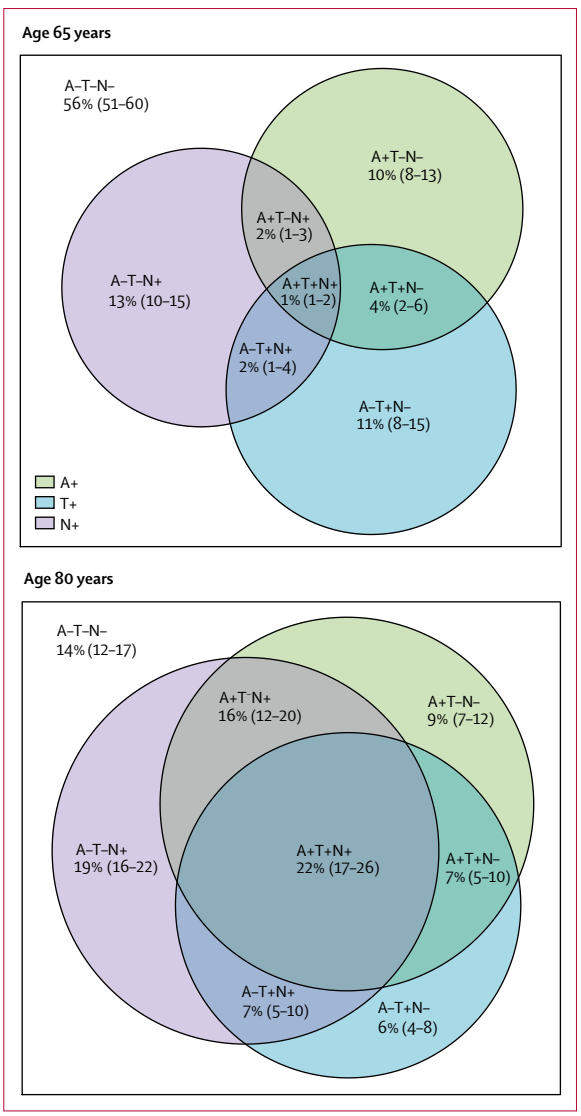

***Figure 3*: Estimated prevalence of each ATN group at ages 65 and 80 years.** Data are estimates (95% CIs) averaged over men and women. Since estimates were for a given age among clinically normal individuals, weighting to the population was not necessary. ATN=amyloid, tau, and neurodegeneration or neuronal injury. A–=amyloid normal using amyloid PET. A+=amyloid abnormal using amyloid PET. T–=tau normal using tau PET. T+=tau abnormal using tau PET. N–=neurodegeneration or neuronal injury normal using cortical thickness. N+=neurodegeneration or neuronal injury abnormal using cortical thickness.

were similar among the A–N– and A–N+ groups (16% *vs* 13% at age 65 years and 30% *vs* 27% at age 80 years). However, by classifying A, T, and N separately, we showed that tau PET is frequently abnormal in SNAP where N+ is defined by cortical thickness. Tau PET had not yet been studied in humans when SNAP was first described in 2012.[7] If the A–T+N– profile is included in the SNAP category where T+ is defined by tau PET, which we believe should be the case, then the proportion of SNAP with evidence of tauopathy is 50% at age 65 and 41% at age 80 years.

We postulate that the A–T–N+ profile corresponds to neurodegeneration due to a heterogeneous group of non-Alzheimer's disease pathologies that increase in prevalence with age including cerebrovascular disease, Lewy body disease, TDP 43, argyrophilic grains, and hippocampal sclerosis.[34] A logical assumption is that the A–T+N– profile corresponds to primary age-related tauopathy.[35] The A–T+N+ profile might correspond to a combination of primary age-related tauopathy and other non-Alzheimer's disease pathologies. However, imaging–autopsy correlation studies will be needed to confirm these hypotheses.

The four A+ profiles represent preclinical Alzheimer's disease according to the 2011 NIA-AA guidelines. Tau and neurodegeneration were discordant in 86% of individuals categorised as NIA-AA preclinical Alzheimer's disease stage 2 or 3 at age 65 years and in 51% at age 80 years. A model of Alzheimer's disease pathogenesis proposes that amyloidosis promotes increased local tau deposition and its spread, which in turn is responsible for neurodegeneration.[36] The ATN biomarker counterpart would be a sequence of A+T–N– to A+T+N– to A+T+N+. The median ages of these three groups and the ages at which the prevalence curves peak increase incrementally; this evidence lends support to the hypothesis that A+T–N– to A+T+N– to A+T+N+ is the biomarker sequence of preclinical Alzheimer's disease. However, longitudinal data will be necessary to confirm this sequence. The A+T–N+ profile, which does not fit into the sequence of preclinical Alzheimer's disease we propose, perhaps indicates individuals in whom two different types of pathology are evident by biomarkers: a non-Alzheimer's disease degenerative process resulting in N+, plus early Alzheimer's disease resulting in the A+T– profile.

For our primary analyses, we used cortical thickness rather than commonly used hippocampal volume as our measure of neurodegeneration to avoid necessitating an adjustment for head size. Brain volumes scale with head size,[37] and correcting for this is not straightforward since head size is related to sex, yet sex-specific effects on atrophy probably exist. A solution is to use cortical thickness, which does not scale closely with head size and consequently does not require an adjustment.[37] Overall, the ATN prevalence curves by age were similar when either HVa or cortical thickness was used as the N measure. These findings suggest that the prevalence of ATN groups we report should be robust to different definitions of N. However, with only moderate agreement between abnormal HVa and thickness, there might be differences in which individuals are labelled N+ by the two biomarkers. We are uncertain whether the more pronounced sex differences when using HVa as the N measure represent an artifact of head size adjustment or a true biological effect.

Our use of the ATN scheme reflected several methodological factors and decisions. Both clinical-imaging correlation[14–18] and autoradiographic[38,39] evidence point to AV1451 as a useful measure of the 3R/4R paired helical filament tau deposits that are characteristic of Alzheimer's disease and primary age-related tauopathy.[35] Binding in primary tauopathies (except those that produce 3R/4R fibrillar tau deposits) is however less certain. In our study, we used a single-reporter tau PET meta-ROI that included medial, basal, and lateral temporal lobe areas.[23] Our rationale was that tau PET uptake in these areas is consistently associated with characteristics of Alzheimer's disease such as the presence of amyloid on PET, worse cognitive performance across the clinical spectrum, and abnormal CSF phosphorylated tau.[14–18] This set of ROIs captures a broad dynamic range across the normal to pathological ageing to Alzheimer's disease dementia spectrum; it therefore seems to represent a reasonable tau PET summary measure.[23]

The ATN framework requires definition of abnormality in each biomarker. We have previously examined different methods for selecting cutoff points to define abnormality on amyloid PET, tau PET, and cortical thickness.[23] We regard plaques, tangles, and synapse loss to be pathological. Although all of these processes increase in frequency and severity with age,[34] our cutoff points were not age-adjusted. We believe that, although not age-norming the cutoff points results in a greater proportion of older individuals being labelled abnormal, the fact that an entity is frequent does not disqualify it from being pathological. Age-norming of cognitive tests is common practice, but biomarkers in other fields are typically not age-normed. For example, the cutoff points used to define diabetes or hypertension do not change with age. Loss of synapses and dendritic spines and associated cognitive or functional loss seem to be a nearly universal feature of ageing in human beings and a range of animal species.[40,41] Whether these losses should be considered pathological or not is an unresolved question.

The methods of selecting reporter meta-ROIs and cutoff points used in ATN classification centred around Alzheimer's disease. However, although temporal lobe atrophy is characteristic of Alzheimer's disease, it is not diagnostic for this condition. Many non-Alzheimer's disease disorders (eg, argyrophillic grains and hippocampal sclerosis) might produce atrophy in these brain areas. However, until specific biomarkers of the common non-Alzheimer's disease entities are developed, the only available biomarker evidence of their presence are non-specific indicators of neurodegeneration or neuronal injury.

Our study had limitations. For example, because eight possible ATN combinations exist, participant numbers in some groups were small. Dichotomising each biomarker simplifies what is an underlying continuous process. Measurement imprecision inevitably results in some classification errors, particularly for values close to cutoff points. With three different biomarker classes per individual, the likelihood of classification error is compounded compared with the use of only one biomarker. We did not examine individuals in the population who had become clinically impaired; this awaits greater enrolment of impaired individuals in the MCSA. While the most rational explanation for the changing prevalence of ATN groups with age is within-individual ATN group transitions, our data are cross-sectional. Our study raises questions for which no answers exist currently; for example, what are the longitudinal clinical or cognitive outcomes and the pathological underpinnings of these ATN groups? Answers to such questions require longitudinal clinical follow-up in many well characterised individuals with eventual autopsy correlation. To our knowledge, such data do not currently exist for individuals characterised by ATN profiles, and data addressing these issues await maturation of ours and others' research cohorts.

Contributors

CRJ Jr conceptualised the study, analysed and interpreted the data, and drafted and revised the manuscript. HJW and SDW conceptualised the study, analysed and interpreted the data, drafted and revised the manuscript, and did the statistical analysis. TMT analysed and interpreted the data, drafted and revised the manuscript, and did the statistical analysis. DSK, PV, MMMi, ROR, MMMa, and WAR drafted and revised the manuscript. VL collected the data and drafted and revised the manuscript. MLS, JLG, and RCP analysed and interpreted the data and drafted and revised the manuscript.

Declaration of interests

CRJ Jr reports grants from the US National Institutes of Health (NIH), and other finances from Eli Lilly. DSK reports personal fees from the data safety monitoring board of the DIAN study, and personal fees from the data safety monitoring board of Lundbeck Alzheimer's disease trial. VL reports personal fees from Bayer Pharmaceuticals, grants from GE Health Care, grants from Siemens Molecular Imaging, grants from AVID Radiopharmaceuticals, personal fees from Piramal Imaging, and personal fees from Merck Research. MLS reports stock or options ownership from Celgene Corporation, Inovio Pharmaceuticals, Medtronic, Parexel International Corporation, and Gilead Sciences. RCP reports grants from the NIH during the study, and personal fees from Hoffman-La Roche, Merck, Genentech, Biogen, and Eli Lilly. The other authors declare no competing interests.

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