Received: 4 September 2025 | Revised: 23 December 2025 | Accepted: 8 January 2026

DOI: 10.1002/trc2.70223

Alzheimer's & Dementia
Translational Research & Clinical Interventions

RESEARCH ARTICLE

Mapping sex differences in brain and cognition in relation to *APOE ε4* and amyloid burden: A longitudinal normative modelling study

Sivaniya Subramaniapillai[1] | **Serena Verdi**[2,3] | **Sarah Keuss**[2] | **Kirsty Lu**[2] | **Sarah-Naomi James**[2,4] | **William Coath**[2] | **David M. Cash**[2,5] | **Frederik Barkhof**[2,3,6] | **Marcus Richards**[4] | **Andre Marquand**[7] | **Jon Schott**[2,5] | **James H. Cole**[2,3] | **Ann-Marie de Lange**[8,9,10]

[1]Department of Ambulatory Care, Center for Primary Care and Public Health (Unisanté), University of Lausanne, Lausanne, Switzerland

[2]Queen Square Institute of Neurology, University College London, London, UK

[3]Department of Computer Science, Hawkes Institute, University College London, London, UK

[4]Department of Population Science, MRC Unit for Lifelong Health and Ageing at UCL, University College London, London, UK

[5]UK Dementia Research Institute, London, UK

[6]Department of Radiology & Nuclear Medicine, Amsterdam UMC, Vrije Universiteit, Amsterdam, the Netherlands

[7]Donders Institute for Brain, Cognition and Behaviour, Radboud University Medical Centre, Nijmegen, the Netherlands

[8]School of Biological and Behavioural Sciences, Queen Mary University of London, London, UK

[9]Department of Psychology, University of Oslo, Oslo, Norway

[10]Department of Psychiatry, University of Oxford, Oxford, UK

Correspondence
Sivaniya Subramaniapillai, Department of Ambulatory Care, Center for Primary Care and Public Health (Unisanté), University of Lausanne, Lausanne, Switzerland.
Email: sivaniya.subramaniapillai@unil.ch

Ann-Marie de Lange, School of Biological and Behavioural Sciences, Queen Mary University of London, London, UK.
Email: ann-marie.delange@psych.ox.ac.uk

Sivaniya Subramaniapillai and Serena Verdi are co-first authors

James H. Cole and Ann-Marie de Lange are co-senior authors

Funding information
Wolfson Foundation; Medical Research Council; Weston Brain Institute; Brain Research UK; Selfridges Group Foundation;

Abstract

INTRODUCTION: Sex differences in Alzheimer's disease (AD) risk are increasingly recognized, with females exhibiting higher global prevalence rates. Yet, it remains unclear how genetic and biomarker indicators of AD risk, such as apolipoprotein E (*APOE*) ε4 and amyloid burden, relate to sex differences in brain and cognitive health during the preclinical stage.

METHODS: Using established normative models trained on ≈ 58,000 healthy participants, we computed regional *Z* scores from T1-weighted magnetic resonance imaging scans in 372 cognitively normal participants from the Insight 46 cohort. Scans were acquired at two timepoints, ≈ 3 years apart, beginning at age 70. Regions with *Z* scores < −1.96 were classified as brain-structure outliers and summarized as total outlier count (tOC). We used linear mixed effects models to examine how sex, age, and AD risk (*APOE* ε4 status and amyloid burden) predict tOC and cognitive outcomes (Preclinical Alzheimer Cognitive Composite [PACC] scores). We examined cross-sectional

Medical Research Council Dementias Platform UK; British Heart Foundation; UCL Centre of Research Excellence (funded by British Heart Foundation); NIHR Biomedical Research Centre at UCLH; Natural Sciences and Engineering Research Council of Canada; Swiss National Science Foundation; Alzheimer's Society; Alzheimer's Research UK; UK Dementia Research Institute; Alzheimer's Association

associations and longitudinal changes in tOC and PACC scores, and tested whether the effects of *APOE* ε4 status and amyloid burden on brain and cognitive measures differed by sex.

RESULTS: Cross-sectional analyses showed that males had greater tOC than females at younger ages. At timepoint 1, spatial maps showed more outlier regions in males, though high outlier proportions were limited to occipital areas. By timepoint 2, sex differences became more spatially distinct, with males and females showing deviations in different regions. Longitudinally, older males exhibited steeper increases in tOC over time compared to females. Greater tOC and amyloid burden were both associated with poorer cognitive outcomes, with a trend toward stronger associations in female *APOE* ε4 carriers. We found no evidence that AD risk influenced age-related changes in tOC or cognition over time.

DISCUSSION: These findings highlight normative modelling's utility in revealing the complex interplay among sex, age, and AD risk in shaping brain structure and cognition in later life.

KEYWORDS
amyloid burden, apolipoprotein E ε4 status, brain health, cognition, normative modelling, sex differences

Highlights

- Normative models detect sex- and Alzheimer's disease risk-related brain changes in older adults.
- Sex-specific brain outlier patterns emerge in distinct regions over time.
- Younger males show more brain outliers (greater cortical thinning) than females.
- Older males exhibit faster accumulation of brain-structure outliers.
- More outliers and amyloid predict worse cognition, stronger in female apolipoprotein E ε4 carriers.

1 | BACKGROUND

Sex differences in Alzheimer's disease (AD) risk and prevalence are well documented.[1] Females carrying the apolipoprotein E (*APOE*) ε4 genetic variant are at greater risk of developing AD at younger ages[2] and show higher amyloid beta (Aβ) burden.[3,4] Yet it remains unclear how these factors relate to brain structure in cognitively unimpaired older adults, and whether their effects differ by sex. This is critical to understand, as AD-related brain changes often emerge long before clinical symptoms.

Alongside *APOE* ε4 and tau, Aβ accumulation increases dementia likelihood.[5,6] Aβ forms extracellular plaques contributing to AD pathology and cognitive deficits.[7] However, sex differences in cognitive performance may mask early pathology in females.[8] Women tend to perform better on verbal memory tests, and females with mild cognitive impairment maintain this advantage despite having greater AD pathology.[9–11] However, a longitudinal study of clinically normal older adults found that females with higher amyloid burden decline faster than males with comparable pathology,[12] highlighting the need to examine sex differences in long-term brain and cognitive trajectories.

Most prior research on sex differences in AD has relied on cross-sectional cohorts, focusing on specific brain regions implicated early in AD. However, the heterogeneity in AD pathology requires characterizing structural changes both regionally and globally, using metrics that capture individual differences beyond group averages. Normative modelling offers a framework for characterizing how brain regions are expected to appear across healthy aging based on age and sex.[13] By training a model to predict cortical thickness or brain volume, we can identify individuals deviating from normative expectations. Beyond regional deviations, the total outlier count (tOC) provides a global measure of the cumulative number of brain regions exhibiting negative deviation. While normative models have been applied in dementia,[13,14] no study has explored sex differences and the role of AD risk factors in brain aging among cognitively normal individuals in population-based longitudinal cohorts.

In this study, we used normative modelling to examine how sex, age, *APOE* ε4 status, and amyloid burden predict brain outliers and cognitive outcomes. We included 372 cognitively normal adults aged 69 to 75 from Insight 46, assessed across two timepoints. This cohort of individuals from the United Kingdom were born within the same year in 1946, allowing precise control of age effects. While prior studies in this cohort have examined regional cortical thickness and volume differences between the sexes,[15] the tOC provides a novel approach capturing overall burden of heterogeneous structural deviations across the brain through a single metric, which we then used to examine associations with risk factors and cognition. We examined cognitive outcomes using the Preclinical Alzheimer Cognitive Composite (PACC).[16]

Linear mixed models were used to examine: (1) the effects of age and sex on tOC and PACC scores; (2) the interaction between sex and AD risk (*APOE* ε4 status and amyloid Centiloid [CL]) on tOC; (3) whether the effects of tOC and amyloid burden on PACC scores vary by sex and *APOE* ε4 status; and (4) the effects of age, sex, and AD risk on longitudinal changes in tOC/PACC. We used statistically significant results to guide the creation of outlier brain maps to visualize the percentage of outliers within each group and highlight regional differences.

RESEARCH IN CONTEXT

1. **Systematic review**: The authors reviewed the literature using traditional (e.g., PubMed) sources. Prior studies on sex differences in Alzheimer's disease (AD) risk, brain structure, and cognition are mostly cross-sectional, and often restricted to selected brain regions. No studies have used normative modelling in longitudinal cohorts to track sex differences and AD risk during the preclinical stage.
2. **Interpretation**: Our findings point to subtle but distinct brain and cognitive patterns across sex and AD risk groups, offering insight into early variation that may precede disease-related decline.
3. **Future directions**: Our study highlights normative modelling as a sensitive method for detecting subtle, regional variation across risk groups. Future studies with larger samples and longer follow-up periods are needed to better understand when and how sex differences in brain pathology and cognitive decline emerge.

2 | METHODS

2.1 | Participants

The Medical Research Council (MRC) National Survey of Health and Development (NSHD) birth cohort has followed 5362 British individuals since their birth in 1946. A subgroup from this cohort participated in the neuroscience substudy, Insight 46,[17–19] undergoing clinical and cognitive assessments, as well as simultaneous T1-weighted MRI and [^{18}F]florbetapir positron emission tomography (PET) imaging using a 3T Siemens Biograph mMR combined PET/MRI scanner. Participants were randomly selected from those aged 60 to 64. Assessments began in 2015 when participants were ≈ 70 years, with timepoint 2 occurring 2 to 4.5 years later. See Table 1 for participant demographics and Section S1, Figure S1 in supporting information for a flowchart detailing participant selection.

2.2 | Data availability

Data are available from the MRC NSHD Data Sharing Committee (https://skylark.ucl.ac.uk/NSHD/doku.php?id = home). The code used for normative modelling is available through the PCNtoolkit version 0.20 (https://pcntoolkit.readthedocs.io/en/latest/). The reference normative models were created using PCNtoolkit (github.com/amarquand/PCNtoolkit).

2.3 | *APOE* genotyping

APOE ε4 status was determined by examining two single-nucleotide polymorphisms (rs7412, rs429358) using TaqMan technology.[17] Individuals were "carriers" if they had ε2/ε4, ε3/ε4, or ε4/ε4, and "non-carriers" if they had ε2/ε2, ε2/ε3, or ε3/ε3. Individuals with ε4/ε4 were not analyzed separately due to the small number of participants across timepoints.

2.4 | Estimation of amyloid PET CL

The standardized uptake value ratios (SUVRs) from [^{18}F]florbetapir PET scans were previously processed using a whole cerebellum reference region with partial volume correction and transformed to the CL scale.[20] Amyloid positivity was defined using a bi-modal Gaussian mixture modelling–derived cutpoint of 12 CL values, equivalent to the 99th percentile of the lower component.

2.5 | Estimation of cortical thickness and subcortical brain volumes

T1-weighted MRI data were corrected for gradient non-linearity and quality checked at timepoint 1 and across both timepoints. Data passing quality control were processed cross-sectionally using FreeSurfer 7.1.0, and then using the longitudinal stream.[21] Cortical thickness

TABLE 1 Sample demographics for Insight 46.

	Timepoint 1 (n = 372)			Timepoint 2 (n = 321)		
	Males	**Females**	**Comparison (test: *p*, effect size)**	**Males**	**Females**	**Comparison (test: *p*, effect size)**
N (%)	195 (52%)	177 (48%)		159 (50%)	162 (50%)	
Age (years)	70.60 (0.69)	70.62 (0.65)	t-test: $p = 0.77$, $d = 0.03$	72.94 (0.68)	72.98 (0.62)	t-test: $p = 0.53$, $d = 0.07$
Age Range	69.25 - 71.78	69.27 - 71.85		71.90 - 74.67	71.92 - 74.55	
***APOE4* status (n, %)**			X^2: $p = 0.86$, $V = 0.01$			X^2: $p = 0.76$, $V = 0.02$
ε4 carrier*	67 (35%)	59 (33%)		49 (31%)	47 (29%)	
ε4 non-carrier	126 (65%)	118 (67%)		108 (69%)	115 (71%)	
APOE4 status unavailable	2	0		2	0	
Mean tOC	4.36 (4.11)	3.45 (3.81)	WT: $p = 0.01$, $r = 0.15$	3.62 (4.97)§	3.41 (3.78)	WT: $p = 0.61$, $r = 0.03$
Range	0 - 20	0 - 25		0 - 24	0 -18	
Median	4	2		2	2	
IQR	5	4		3	4	
Left hemisphere cortical thickness (mm)	2.40 (0.07)	2.41 (0.07)	t-test: $p = 0.32$, $d = 0.10$	2.38 (0.07)	2.40 (0.07)	t-test: $p = 0.02$, $d = 0.27$
Right hemisphere cortical thickness (mm)	2.40 (0.07)	2.41 (0.07)	t-test: $p = 0.24$, $d = 0.12$	2.38 (0.07)	2.39 (0.07)	t-test: $p = 0.03$, $d = 0.24$
Amyloid PET Positive	51 (27%) 6 NA	47 (27%) 3 NA	X^2: $p = 1.00$, $V = 0$	45 (29%) 2 NA	52 (32%) 1 NA	X^2: $p = 0.56$, $V = 0.03$
Amyloid PET Centiloid	11.57 (24.40) N = 189	10.59 (24.15) N = 174	WT: $p = 0.69$, $r = 0.02$	13.24 (27.31) N = 157	15.12 (29.57) N = 161	WT: $p = 0.53$, $r = 0.04$
Range	−13.61 - 97.93	−16.14 - 125.49		−16.63 - 115.72	−14.18 - 133.40	
Median	1.42	1.46		0.73	2.25	
IQR	19.67	18.29		25.40	27.12	
Education			X^2: $p = 0.005$, $V = 0.20$			X^2: $p = 0.003$, $V = 0.23$
No qualifications	18	20		15	18	
Vocational only	14	15		10	14	
O Level or equivalent	36	48		28	47	
A level or equivalent	65	67		54	59	
Higher	62	27		52	24	

(Continues)

TABLE 1 (Continued)

	Timepoint 1 (n = 372)			Timepoint 2 (n = 321)		
	Males	Females	Comparison (test: *p*, effect size)	Males	Females	Comparison (test: *p*, effect size)
MMSE	29.17 (0.94)	29.37 (0.83)	WT: $p = 0.03$, $r = 0.12$	28.99 (1.02)	29.30 (0.90)	WT: $p = 0.002$, $r = 0.19$
Range	26-30	26 - 30		24 - 30	26 - 30	
Median	29	30		29	30	
IQR	1	1		2	1	

Note: Mean and standard deviation (SD) for key demographic variables. *At timepoint 1, there were 11 participants with the ε4/ε4 genotype (6 females, 5 males), and 8 at timepoint 2 (4 females, 4 males). § The participants present at timepoint 1 but not at timepoint 2 did not exhibit substantially higher tOC counts. For more details on this subsample and longitudinal analyses using participants with data from both timepoints, see SI Section 5. *P*-values and effect sizes were calculated for each group comparison: Cohen's *d* for t-tests, Cramér's *V* for chi-squared tests (X^2), and rank-biserial *r* for Wilcoxon rank-sum tests (WT); only absolute values are reported to reflect magnitude. This table excludes the 41 participants used in the normative modelling calibration step.
Abbreviations: *APOE*, apolipoprotein E; MMSE, Mini-Mental State Examination; NA, Not Available.

segmentations were visually inspected, and values for 148 Destrieux atlas regions and 20 subcortical volumes were extracted.[22]

2.6 | Neuroanatomical normative modelling

A hierarchical Bayesian regression model previously trained on 58,836 scans (82 sites, ages 2–100) was used to model regional brain structure.[23,24] Sex and age are included in the normative models to ensure that deviation scores reflect differences relative to what is typical for each sex and age.[25] Using these variables as predictors in subsequent mixed-effects models then determines whether males and females in our sample differ in the magnitude of deviation from their respective sex- and age-specific norms.

This recalibrated model was then applied to the remaining Insight 46 participants, generating regional mean cortical thickness and subcortical volume *Z* scores, which reflect how much an individual's brain measure differs from what is expected, based on the normative range of the reference dataset. *Z* scores ≤ −1.96 (lowest 2.5% of the normal distribution per region) were categorized as outliers, focusing on lower thresholds reflecting potentially neurodegeneration-related thinning or volume loss. The tOC across all 168 regions was calculated by summing the number of outliers per participant.

2.7 | PACC scores

PACC scores, previously used in multiple studies,[7,26] was assessed at each timepoint. This score is derived from neuropsychological tests measuring episodic memory (Wechsler Memory Scale-Revised Logical Memory Test,[27] Face-Name Associative Memory Exam 12[28]), processing speed (Wechsler Adult Intelligence Scale-Revised Digit Symbol Substitution Test[29]), and global cognition (Mini-Mental State Examination[30]). Each of the four test components is converted into *Z* scores and then averaged, with higher scores indicating better cognitive performance.[31]

2.8 | Statistical analyses

Statistical analyses used R version 4.3. For models with tOC measures as the outcome, we ran negative binomial generalized linear mixed models (i.e., glmmTMB type 2 family) to fit the count data, which exhibited a non-Gaussian distribution.[32] We used linear mixed-effects regression models (i.e., lmer) for models with PACC scores as the outcome as these continuous cognitive measures approximated a Gaussian distribution. Sex (male, female) and *APOE* ε4 status (carrier, non-carrier) were categorical. Age and CL values were standardized across the entire dataset and treated as continuous measures.

Cross-sectional Models 1 through 3 included both timepoints with participant ID as a random intercept. Longitudinal Models 4 and 5 used difference scores as outcomes with assessment interval as a covariate. Multiple comparisons were controlled using Benjamini–Hochberg false discovery rate correction within each model, treating all fixed effects as one family of tests. Three-way interactions were specified a priori to guide targeted follow-up analyses of group differences; interpretation is therefore based on these subsequent analyses rather than the interaction terms alone.

To investigate spatial distributions of brain outliers, the percentage of participants with outliers (i.e., *Z* scores ≤ −1.96) was determined for each region. This allowed for visualization of the degree of overlap or divergence in regional outlier patterns. Brain surface mapping was performed using the Destrieux (cortical regions) and aseg (subcortical regions) atlas with the R package ggseg.[33]

2.8.1 | Associations among age, sex, and tOC/PACC

We first tested the effects of age and sex on tOC and PACC scores:

Model 1 is:

$$DV = \beta_0 + \beta_1 Sex + \beta_2 Age + \beta_3 Sex \times Age + u + \epsilon$$

where DV represents the tOC or PACC scores of participants and *u* represents the modelling of Participant ID as a random intercept, and

ϵ is the error term. The global intercept is denoted by β_0, while the regression coefficients for *Sex*, *Age*, and the interaction between *Sex* and *Age* are denoted as β_1, β_2, and β_3, respectively. As sex differences in PACC scores were previously examined in this cohort,[26,31] we uniquely tested whether there were sex differences in the effect of age on PACC scores.

2.8.2 | Associations among age, sex, AD risk, and tOC/PACC scores

We then tested whether there were sex differences in the effect of AD risk (*APOE* ε4, CL) on tOC across timepoints using the following separate models.

Model 2 is:

$$tOC = \beta_0 + \beta_1 Sex + \beta_2 Age + \beta_3 AD\ Risk + \beta_4 Sex \times Age \times AD\ Risk + u + \epsilon$$

These models also test the underlying two-way interactions; we also ran dedicated two-way interaction models as a cross-check. To determine whether the effect of greater brain pathology, from brain outliers and amyloid accumulation, on cognitive scores varied by sex, we examined the interaction among sex, CL, and tOC on PACC scores, with participants' age at the time of the scan as a covariate.

Model 3 is:

$$PACC = \beta_0 + \beta_1 Sex + \beta_2 Amyloid\ Centiloid + \beta_3 tOC + \beta_4 Age + \beta_5 Sex \times Amyloid\ Centiloid \times tOC + u + \epsilon$$

For Model 3, we ran stratified analyses by *APOE* ε4 status to assess whether sex differences in the relationship between brain pathology and cognition varied by genetic risk.

2.8.3 | Associations among age, sex, and AD risk on longitudinal tOC/PACC changes

We performed simple linear regressions to explore the associations among age, sex, AD risk and longitudinal changes in tOC/PACC in participants with data from both timepoints (n = 309; Section S1, Table S1 in supporting information for sample demographics). We calculated change using difference scores (Timepoint 2 − Timepoint 1), and included assessment interval as a covariate so that observed changes in tOC are not biased by differences in time between assessments (mean assessment interval = 2.4 years, standard deviation = 0.2, range = 2.0 to 3.5).

Model 4 is:

$$DV\ Change = \beta_0 + \beta_1 Sex + \beta_2 Age Timepoint1 + \beta_3 Sex \times Age\ Timepoint1 + \beta_4 Assessment\ Interval + \epsilon$$

Model 5 is:

$$DV\ Change = \beta_0 + \beta_1 Sex + \beta_2 Age\ Timepoint\ 1 + \beta_3 AD\ Risk + \beta_4 Sex \times Age\ Timepoint\ 1 \times AD\ Risk + \beta_5 Assessment\ Interval + \epsilon$$

In Model 5, amyloid PET status (negative/positive) at each timepoint was used to classify participants by change in amyloid status: persistently negative (n = 212), persistently positive (n = 70), or converters from negative to positive (n = 19). No participants reverted from positive to negative.

2.8.4 | Sensitivity analyses

Supplementary analyses included: (1) alternative change score analyses, rerunning Models 4 and 5 using timepoint 2 values with timepoint 1 values regressed out (modelling changes in DV independent of its baseline value); (2) matched longitudinal subsample to assess within-individual effects over time; (3) binary amyloid status (positive/negative; 12-CL threshold) and stratified analyses by amyloid status, though CL was modeled continuously in primary analyses to preserve power; and (4) Pearson correlations between baseline tOC and longitudinal changes in total brain volume and mean cortical thickness to assess relationships with conventional structural metrics. Diagnostic checks across linear mixed effects models assessed residual normality (Kolmogorov–Smirnov test) and robustness using rlmer, which downweighs outliers without exclusion.[34]

3 | RESULTS

3.1 | Associations among age, sex, and tOC/PACC scores

Model 1 revealed a significant interaction between age and sex on tOC (β = −0.13, standard error [SE] = 0.05, z = −2.39, p = 0.02, $p$corr = 0.03), indicating that males had higher tOC than females at younger ages. PACC scores were greater in females compared to males (β = −0.33, SE = 0.06, t = −5.26, $p < 0.005$, $p$corr < 0.05). There was no significant effect of age (β = −0.02, SE = 0.02, t = −1.40, p = 0.16, $p$corr = 0.22) or interaction between age and sex on PACC (β = 0.02, SE = 0.02, t = 0.84, p = 0.40, $p$corr = 0.40). Section S2, Figure S2 in supporting information shows the relationships between age and tOC and PACC scores in both sexes.

Figures 1 and 2 show the proportion of participants with outliers in each brain region, for females and males at each timepoint. See Section S2, Figures S3 and S4 in supporting information for outlier maps with truncated color scales to enhance visibility of regional variations, and list of brain regions most affected by sex across timepoints. While tOC captures the total number of outlier regions per individual, these maps reflect group-level variation across regions, highlighting how the spatial distribution of outliers differs within and between groups.

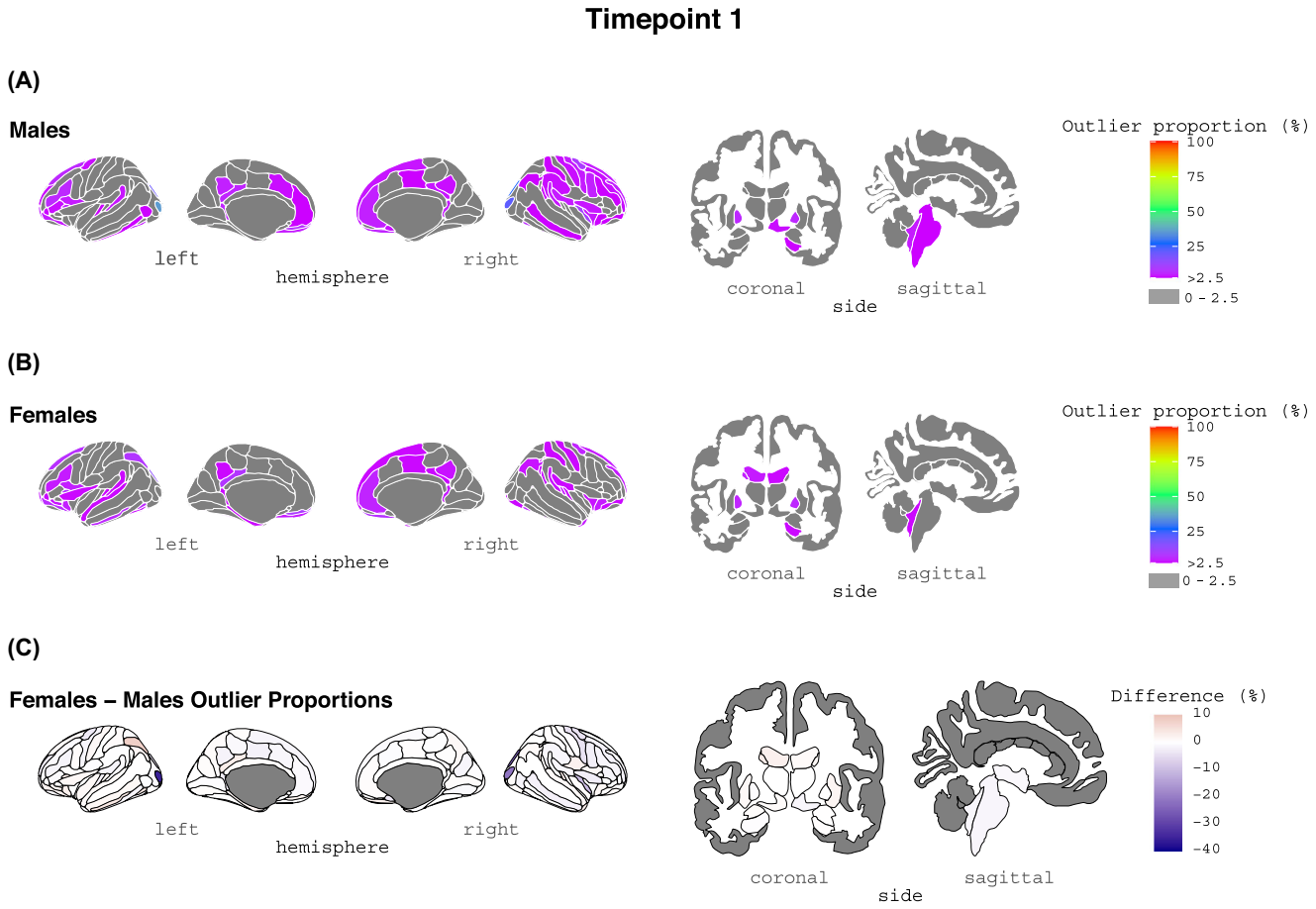

FIGURE 1 The percentage of outliers present within (A) males and (B) females at timepoint 1. The color bar represents the outlier proportion (thresholding of *Z* scores). Regions in gray reflect areas where participants did not have any outliers (≤ 2.5%). C, The arithmetic difference in outlier proportions between females and males; it does *not* represent a statistical test of group differences. The color gradient indicates the direction and magnitude of the difference: dark blue represents regions where males have more outliers than females, white indicates no difference between sexes, and dark red represents regions where females have more outliers than males. Color scales are adjusted to reflect the range of group differences at each timepoint. See Figure S3 in supporting information for an outlier map with the color scale truncated to enhance visibility of regional variations.

3.2 | Associations among age, sex, AD risk, and tOC

Model 2 showed no significant three-way interaction among age, sex, and *APOE* ε4 status on tOC ($\beta = 0.13$, SE = 0.12, $z = 1.14$, $p = 0.26$, *Pcorr* = 0.68), nor among age, sex, and CL on tOC ($\beta = -0.02$, SE = 0.05, $z = -0.36$, $p = 0.72$, *Pcorr* = 0.82). See Section S3, Tables S2–S7 in supporting information for full regression outputs.

3.2.1 | Associations among sex, amyloid burden, and tOC on cognitive outcomes

Model 3 revealed a significant three-way interaction among sex, CL, and tOC on PACC scores ($\beta = 0.11$, SE = 0.04, $t = 2.52$, $p = 0.01$, *Pcorr* = 0.03; Section S3, Figure S5 in supporting information). In females, greater amyloid was associated with poorer cognitive performance at higher tOC levels ($\beta = -0.10$, SE = 0.04, $p = 0.007$). This association was not observed in males ($\beta = 0.01$, SE = 0.02, $p = 0.69$; based on the model re-estimation with male as the reference category). When this model was run within *APOE* ε4 non-carriers, no significant three-way interaction was observed ($\beta = 0.04$, SE = 0.09, $t = 0.41$, $p = 0.68$). However, among *APOE* ε4 carriers, females with both greater tOC and amyloid showed worse cognitive outcomes ($\beta = -0.11$, SE = 0.05, $p = 0.04$), whereas this association was not observed in male carriers ($\beta = 0.005$, SE = 0.03, $p = 0.86$). Figure 3 illustrates the relationship between tOC and PACC scores by *APOE* ε4 status. See Section S3, Tables S8–S19 in supporting information for full regression outputs.

3.3 | Associations among age, sex, and AD risk on longitudinal tOC/PACC changes

Model 4 revealed a significant interaction between age and sex on changes in tOC ($\beta = 1.89$, SE = 0.34, $t = 5.58$, $p \leq 0.01$, *Pcorr* ≤ 0.01), indicating that an older age was related to a greater increase in tOC,

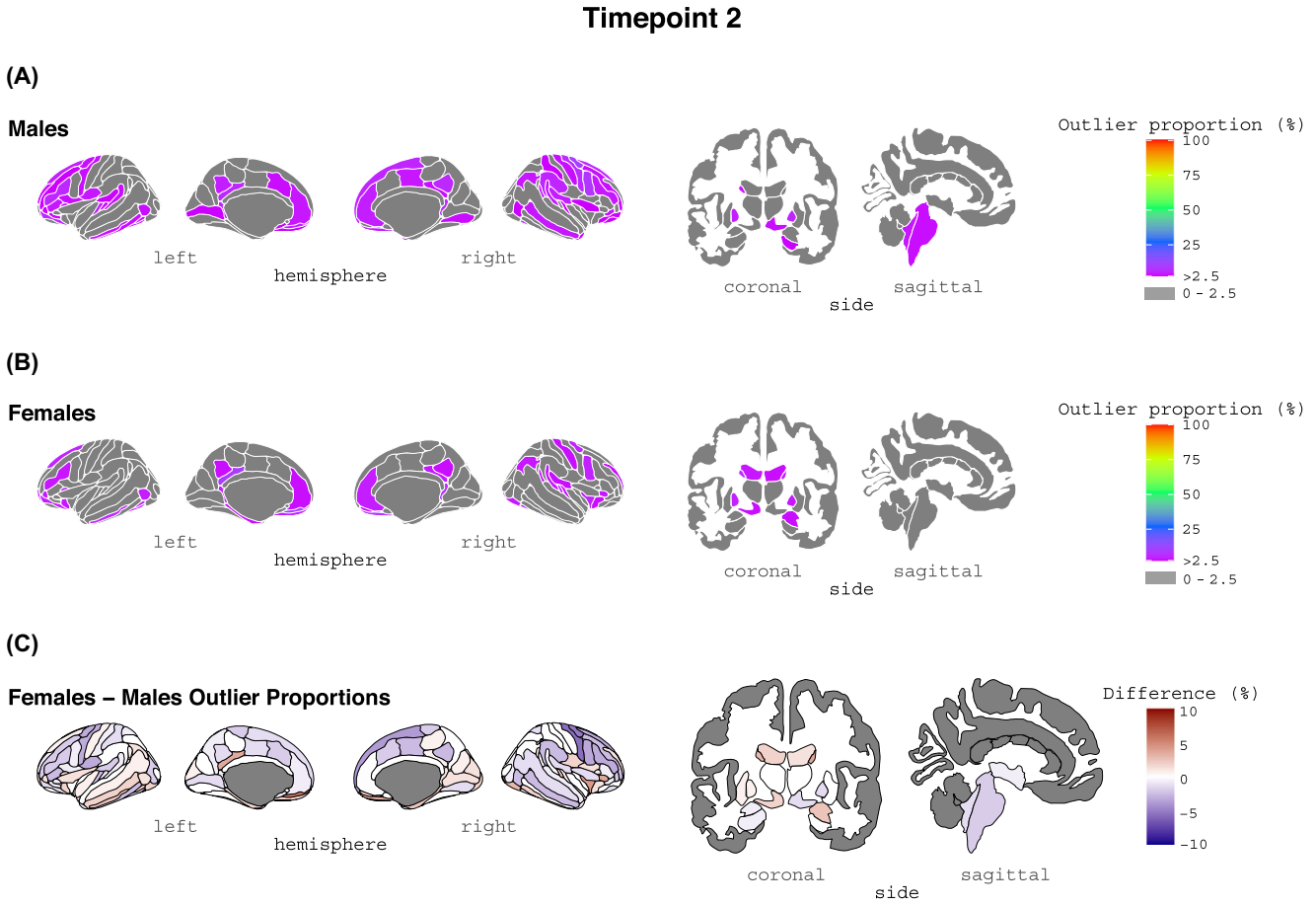

FIGURE 2 The percentage of outliers present within (A) males and (B) females at timepoint 2. The color bar represents the outlier proportion (thresholding of *Z* scores). Regions in gray reflect areas where participants did not have any outliers (≤ 2.5%). C, The arithmetic difference in outlier proportions between females and males; it does *not* represent a statistical test of group differences. The color gradient indicates the direction and magnitude of the difference: dark blue represents regions where males have more outliers than females, white indicates no difference between sexes, and dark red represents regions where females have more outliers than males. Color scales are adjusted to reflect the range of group differences at each timepoint. At timepoint 1, group differences were larger but observed in fewer regions; at timepoint 2, differences were smaller in magnitude but present across more regions, resulting in higher visual contrast under the narrower scale. See Figure S4 in supporting information for an outlier map with the color scale truncated to enhance visibility of regional variations.

with stronger effects in males compared to females (Figure 4). When changes in PACC scores were used as the outcome, this model did not reveal any significant effects of age ($\beta = -0.01$, SE = 0.03, t = −0.41, $p = 0.69$, *P*corr = 0.74), sex ($\beta = 0.01$, SE = 0.05, $t = 0.33$, $p = 0.74$, *P*corr = 0.74), or their interaction ($\beta = 0.04$, SE = 0.05, $t = 0.86$, $p = 0.39$, *P*corr = 0.68; Figure 4).

Model 5 showed no significant interactions among age, sex, and *APOE ε4*/amyloid status on changes in tOC/PACC (Section S3, Tables S20–S23 in supporting information for regression outputs).

3.4 | Sensitivity analyses

Alternative change score analyses (Section S4, Tables S24–S27 and Figure S6 in supporting information) and matched samples (Section S5, Tables S28–S34 in supporting information) were consistent with primary findings. Binary amyloid and stratified analyses confirmed findings were primarily driven by amyloid-positive individuals (Section S6, Tables S35–S42 in supporting information). Correlations between baseline tOC and changes in brain volume ($r = 0.01$, $p = 0.83$) and cortical thickness ($r = 0.11$, $p = 0.06$) were small. Model diagnostics indicated no significant deviation from residual normality (Kolmogorov–Smirnov tests: all $p > 0.05$), and robust regression methods confirmed consistency with primary analyses (Section S7, Tables S43–S46 in supporting information). However, when excluding one visually distinct observation, the effect was attenuated and no longer statistically significant (Tables S47–S49 in supporting information).

4 | DISCUSSION

This longitudinal birth-cohort study highlights variation in brain and cognitive patterns across sex and AD risk groups among cognitively

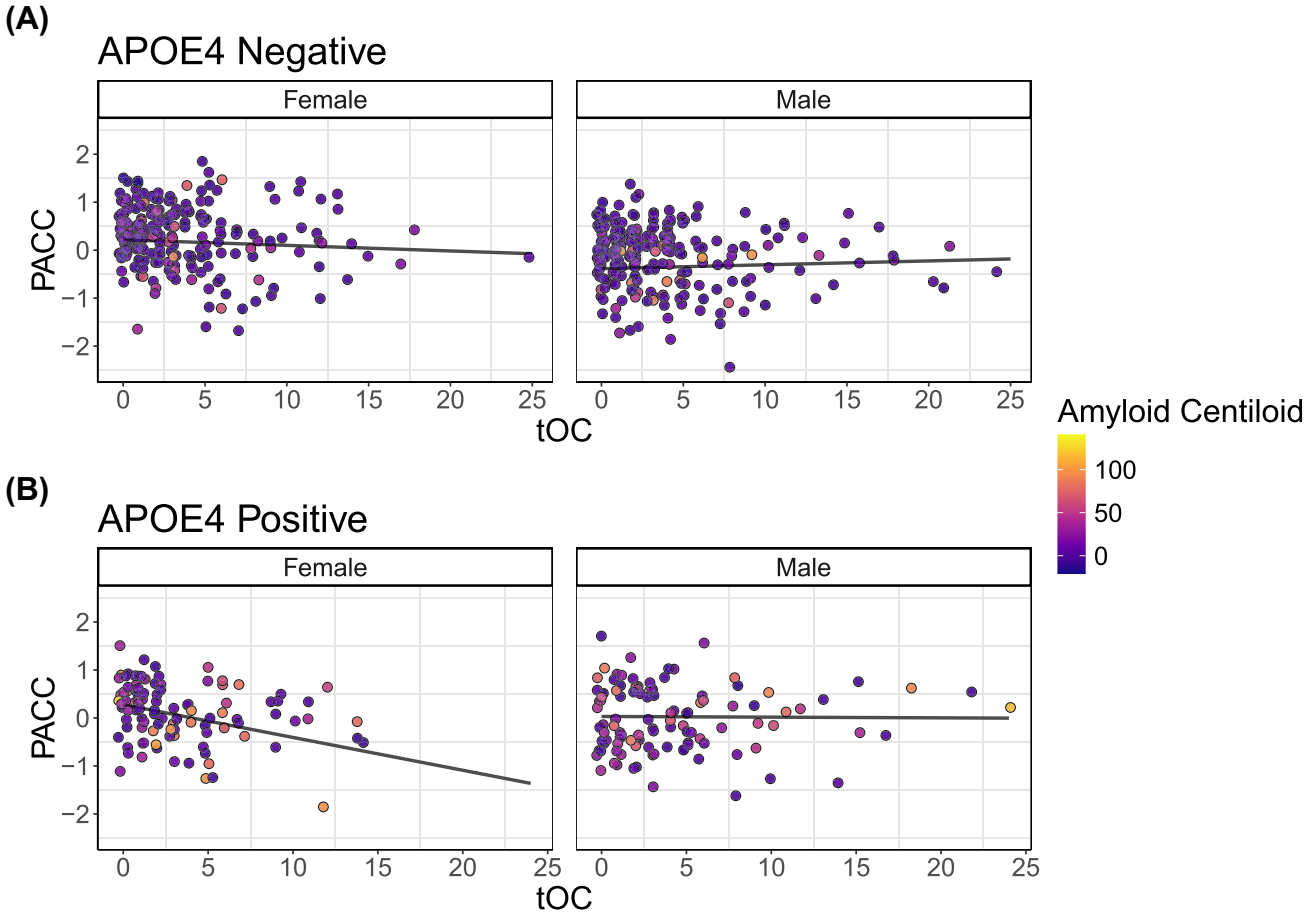

FIGURE 3 Fitted linear relationships between tOC and PACC scores in *APOE* ε4 (A) non-carriers and (B) carriers, with their corresponding 95% confidence intervals (model 3). PACC scores were computed as the average of *Z* scores across four neuropsychological tests (episodic memory, processing speed, global cognition), with higher scores reflecting better cognitive performance. Data points on the plots represent raw data from the dataset and are color-coded based on amyloid Centiloid. *APOE*, apolipoprotein E; PACC, Preclinical Alzheimer Cognitive Composite; tOC, total outlier count.

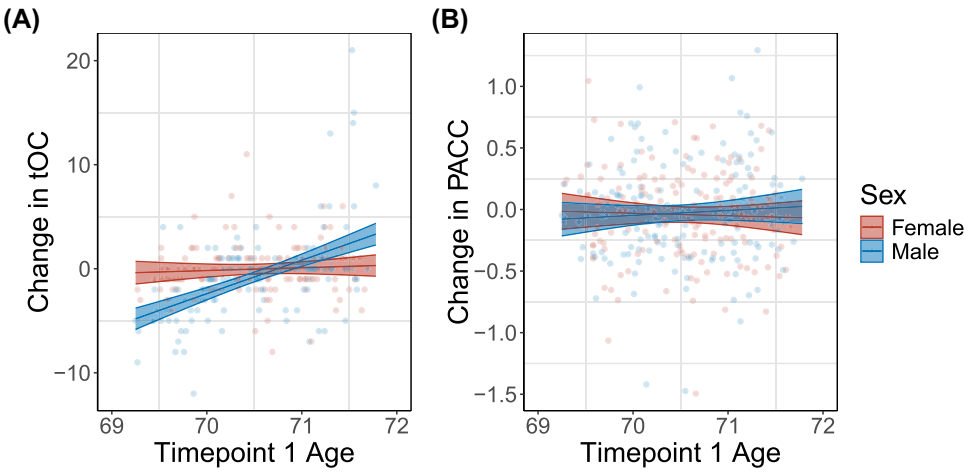

FIGURE 4 Fitted relationships between age at timepoint 1 and changes in tOC (A) or PACC (B), with corresponding 95% confidence intervals (model 4). PACC scores were computed as the average of *Z* scores across four neuropsychological tests (episodic memory, processing speed, global cognition), with higher scores reflecting better cognitive performance. Change was measured using difference scores (Timepoint 2 values – Timepoint 1 values). Data points on the plots represent raw data from the dataset, while lines of best fit and confidence intervals are model derived. PACC, Preclinical Alzheimer Cognitive Composite; tOC, total outlier count.

normal older adults. Males showed more brain outliers than females, primarily at younger ages. At baseline, males had outliers in more regions, although high outlier proportions were mostly confined to occipital areas. By follow-up, sex differences became more spatially distinct, with males and females showing deviations in distinct regions. Older males exhibited steeper increases in total outliers over time, reflected in an age-by-sex interaction on tOC change. Females showed higher PACC scores overall, but there were no sex differences in cognitive change over time. Greater tOC and amyloid were associated with poorer cognition cross-sectionally, with the strongest association observed in female *APOE ε4* carriers; however, this effect was modest and partially driven by one deviating data point. We found no evidence that AD risk influenced age-related changes in tOC or cognition over the follow-up period. Together, these findings suggest early sex-specific variation in brain aging that may precede overt cognitive decline.

Cross-sectional sex differences in tOC were evident primarily at younger ages, suggesting earlier structural brain vulnerability in males. Previous studies have shown that males exhibit steeper age-related declines in cortical thickness and gray matter volume beginning in midlife, potentially driven by faster vascular changes.[18,35–37] Although attrition in this cohort was more likely among individuals with lower cognition and socioeconomic status,[18] supplementary analyses restricted to participants with data at both timepoints yielded consistent results, and participants lost after baseline did not show substantially greater outliers. Our longitudinal analyses further revealed that males who were older at baseline showed greater increases in tOC over time compared to females of the same age, indicating steeper structural decline with advancing age. While the short follow-up window limits interpretation of long-term trajectories, this suggests that sex differences in the timing of structural brain decline may emerge even within a narrow age range in later life.

Sex differences were also evident in the spatial distribution of brain deviations. Males showed greater deviations in visuospatial and sensorimotor areas, while females showed more deviations in memory and default mode areas. While both sexes showed deviations in regions vulnerable in preclinical AD,[38–40] the spatial patterns differed, pointing to sex-specific aging trajectories. Importantly, group-average maps masked substantial inter-individual variability: although males showed higher overall outlier burden at baseline, only a small number of regions exhibited consistent overlap across individuals. This heterogeneity suggests that elevated outlier counts reflect focal rather than widespread structural vulnerability, reinforcing the value of individual-level analyses, consistent with prior work in AD-diagnosed samples.[13,14,41]

Consistent with previous reports from this cohort,[26,31] females showed a cognitive advantage on the PACC, likely influenced by its strong verbal memory component.[42] When stratifying data by sex and AD risk, female *APOE ε4* carriers with higher amyloid and outlier burden showed lower cognitive performance than males with similar risk profiles, though effects were modest. Although effects were modest, this underscores how group-level averages may mask emerging deficits in high-risk subgroups. We observed no sex differences in cognitive change over time, though this may change when pathological burden thresholds are met.[11,43] Longer follow-up is essential to determine whether these patterns predict subsequent decline. Sensitivity analyses indicated that associations with cognition were driven primarily by the amyloid-positive subgroup; within these individuals, continuous amyloid measures revealed dose–response relationships, supporting continuous rather than binary classification, though the modest amyloid-positive sample likely limited power in binary analyses. Given the closer link between tau and cognitive decline,[44] larger samples with broader amyloid ranges and tau PET data will be critical to clarify these relationships. Additionally, because several outliers localized to frontal regions, future work should examine whether regional outlier patterns relate to executive function measures that may be more sensitive than PACC.

Several limitations warrant consideration. The predominantly White, highly educated UK-based sample limits generalizability. Sex-specific biological factors, including menopause and hormone therapy,[45] as well as interactions with vascular and inflammatory risk,[46,47] may contribute to observed differences in brain aging.[48] Prior work in this cohort has shown stronger associations between vascular risk and brain health in females compared to males,[35] suggesting that vascular factors may partially contribute to the observed differences in brain and cognitive patterns across sex and AD risk groups.[49] Future research should prioritize the inclusion of underrepresented groups and broader risk profiles to better capture the complexities of sex- and gender-related factors in brain aging and disease risk.[48,50]

In summary, our findings reveal a nuanced picture of brain and cognitive health in older adulthood, shaped by sex and AD risk. Although males showed greater brain outliers than females at younger ages, outlier maps highlighted greater sex-specific heterogeneity in the spatial distribution of structural deviations at follow-up. Stratified analyses revealed that the overall female cognitive advantage may mask early deficits in at-risk females. The observed effects, though small, underscore the need for longitudinal, sex-stratified research to characterize the influence of genetic risk and disease markers on brain aging trajectories.

ACKNOWLEDGMENTS

Open access publishing facilitated by Universite de Lausanne, as part of the Wiley - Universite de Lausanne agreement via the Consortium Of Swiss Academic Libraries. The authors received funding from the Swiss National Science Foundation (PZ00P3_193658 to A.M.d.L.; TMPFP3_217174 to S.S.); the Natural Sciences and Engineering Research Council of Canada (Postdoctoral Fellowship Grant to S.S.). F.B. is supported by the NIHR biomedical research centre at UCLH. J.H.C. and S.V. are supported by the Alzheimer's Society (grant reference 634). J.M.S. is a National Institute for Health Research (NIHR) Senior Investigator and acknowledges the support of the NIHR University College London Hospitals Biomedical Research Centre and the UCL Centre of Research Excellence, an initiative funded by British Heart Foundation (RE/24/130013). He has grant funding from Alzheimer's Research UK, Brain Research UK, Weston Brain Institute, Medical Research Council, British Heart Foundation, Wolfson

Foundation, UK Dementia Research Institute, and Alzheimer's Association. This work uses data provided by study participants or patients and collected through clinical studies or as part of their care and support. Insight 46 is funded by grants from Alzheimer's Research UK (ARUK-PG2014-1946, ARUK-PG2017-1946 principal investigators (PIs) J.M.S., N.C.F., M.R.), Alzheimer's Association (SG-666374-UK BIRTH COHORT PI J.M.S.), the Medical Research Council Dementias Platform UK (CSUB19166 PIs J.M.S., N.C.F., M.R.), The Wolfson Foundation (PR/ylr/18575 PIs N.C.F., J.M.S.), The Medical Research Council (MC-UU-12019/1 PI MR, MC-UU-12019/3 PI M.R.), Selfridges Group Foundation (22/3/18 PI J.M.S.) and Brain Research Trust (UCC14191, PI J.M.S.). This work was initiated while S.S. and A.-M.G.d.L. were affiliated with the Department of Clinical Neurosciences, Lausanne University Hospital (CHUV) and University of Lausanne, Switzerland.

Open access publishing facilitated by Universite de Lausanne, as part of the Wiley - Universite de Lausanne agreement via the Consortium Of Swiss Academic Libraries.

CONFLICT OF INTEREST STATEMENT

F.B. is on the steering committee or Data Safety Monitoring Board for Biogen, Merck, Eisai, and Prothena. He is an advisory board member for Combinostics, Scottish Brain Sciences, and Alzheimer Europe; a consultant for Roche, Celltrion, Rewind Therapeutics, Merck, and Bracco; has research agreements with ADDI, Merck, Biogen, GE Healthcare, and Roche; and is the co-founder and shareholder of Queen Square Analytics LTD. J.M.S. has received research funding and PET tracer from AVID Radiopharmaceuticals (a wholly owned subsidiary of Eli Lilly) and Alliance Medical; has consulted for Roche, Eli Lilly, Biogen, MSD, and GE; and received royalties from Oxford University Press and Henry Stewart Talks. He is Chief Medical Officer for Alzheimer's Research UK.

All other authors declare that they have no conflicts of interest.

CONSENT

The Insight 46 study received ethical approval from the National Research Ethics Service Committee London (14/LO/1173). All participants provided informed written consent.

ORCID

Sivaniya Subramaniapillai https://orcid.org/0000-0003-3207-0700

REFERENCES

1. Castro-Aldrete L, Einsiedler M, Novakova Martinkova J, et al. Alzheimer disease seen through the lens of sex and gender. *Nat Rev Neurol*. 2025;21(5):235-249. doi:10.1038/s41582-025-01071-0
2. Neu SC, Pa J, Kukull W, et al. Apolipoprotein E genotype and sex risk factors for Alzheimer Disease: a meta-analysis. *JAMA Neurology*. 2017;74(10):1178-1189. doi:10.1001/jamaneurol.2017.2188
3. Nemes S, Logan PE, Manchella MK, et al. Sex and APOE ε4 carrier effects on atrophy, amyloid PET, and tau PET burden in early-onset Alzheimer's disease. *Alzheimers Dement*. 2023;19(S9):S49-S63. doi:10.1002/alz.13403
4. Sundermann EE, Panizzon MS, Chen X, et al. Sex differences in Alzheimer's-related tau biomarkers and a mediating effect of testosterone. *Biol Sex Diff*. 2020;11(1):33. doi:10.1186/s13293-020-00310-x
5. Dang C, Harrington KD, Lim YY, et al. Relationship between amyloid-β positivity and progression to mild cognitive impairment or dementia over 8 years in cognitively normal older adults. *J Alzheimers Dis*. 2018;65(4):1313-1325. doi:10.3233/JAD-180507
6. Mormino EC, Papp KV. Amyloid accumulation and cognitive decline in clinically normal older individuals: implications for aging and early Alzheimer's Disease. *J Alzheimers Dis*. 2018;64(s1):S633-S646. doi:10.3233/JAD-179928
7. Mormino EC, Papp KV, Rentz DM, et al. Early and late change on the preclinical Alzheimer's cognitive composite in clinically normal older individuals with elevated β-amyloid. *Alzheimers Dement*. 2017;13(9):1004-1012. doi:10.1016/j.jalz.2017.01.018
8. Sundermann EE, Biegon A, Rubin LH, Lipton RB, Landau S, Maki PM. Does the female advantage in verbal memory contribute to underestimating AD pathology in women versus men? *J Alzheimers Dis*. 2017;56(3):947-957. doi:10.3233/JAD-160716
9. Sundermann EE, Maki P, Biegon A, et al. Sex-specific norms for verbal memory tests may improve diagnostic accuracy of amnestic MCI. *Neurology*. 2019;93(20):e1881-e1889. doi:10.1212/WNL.0000000000008467
10. Beinhoff U, Tumani H, Brettschneider J, Bittner D, Riepe MW. Gender-specificities in Alzheimer's disease and mild cognitive impairment. *J Neurol*. 2008;255(1):117-122. doi:10.1007/s00415-008-0726-9
11. Emrani S, Sundermann EE. Sex/gender differences in the clinical trajectory of Alzheimer's disease: insights into diagnosis and cognitive reserve. *Front Neuroendocrinol*. 2025;77:101184. doi:10.1016/j.yfrne.2025.101184
12. Buckley RF, Mormino EC, Amariglio RE, et al. Sex, amyloid, and *APOE* ε4 and risk of cognitive decline in preclinical Alzheimer's disease: findings from three well-characterized cohorts. *Alzheimers Dement*. 2018;14(9):1193-1203. doi:10.1016/j.jalz.2018.04.010
13. Verdi S, Kia SM, Yong KXX, et al. Revealing individual neuroanatomical heterogeneity in Alzheimer Disease using neuroanatomical normative modelling. *Neurology*. 2023;100(24):e2442-e2453. doi:10.1212/WNL.0000000000207298
14. Loreto F, Verdi S, Kia SM, et al. Alzheimer's disease heterogeneity revealed by neuroanatomical normative modelling. *Alzheimers Dement(Amst)*. 2024;16(1):e12559. doi:10.1002/dad2.12559
15. Keuss SE, Coath W, Cash DM, et al. Rates of cortical thinning in Alzheimer's disease signature regions associate with vascular burden but not with β-amyloid status in cognitively normal adults at age 70. *J Neurol Neurosurg Psychiatry*. 2024;95(8):748-752. doi:10.1136/jnnp-2023-332067
16. Donohue MC, Sperling RA, Salmon DP, et al. The preclinical Alzheimer cognitive composite: measuring amyloid-related decline. *JAMA Neurol*. 2014;71(8):961-970. doi:10.1001/jamaneurol.2014.803
17. Lane CA, Parker TD, Cash DM, et al. Study protocol: insight 46 – a neuroscience sub-study of the MRC National Survey of Health and Development. *BMC Neurol*. 2017;17(1):75. doi:10.1186/s12883-017-0846-x
18. James SN, Lane CA, Parker TD, et al. Using a birth cohort to study brain health and preclinical dementia: recruitment and participation rates in Insight 46. *BMC Res Notes*. 2018;11(1):885. doi:10.1186/s13104-018-3995-0
19. Murray-Smith H, Barker S, Barkhof F, et al. Updating the study protocol: insight 46 - a longitudinal neuroscience sub-study of the MRC National Survey of Health and Development—phases 2 and 3. *BMC Neurol*. 2024;24(1):40. doi:10.1186/s12883-023-03465-3
20. Coath W, Modat M, Cardoso MJ, et al. Operationalizing the centiloid scale for [18F]florbetapir PET studies on PET/MRI. *Alzheimers Dement (Amst)*. 2023;15(2):e12434. doi:10.1002/dad2.12434
21. Reuter M, Schmansky NJ, Rosas HD, Fischl B. Within-subject template estimation for unbiased longitudinal image analysis. *NeuroImage*. 2012;61(4):1402-1418. doi:10.1016/j.neuroimage.2012.02.084

22. Destrieux C, Fischl B, Dale A, Halgren E. Automatic parcellation of human cortical gyri and sulci using standard anatomical nomenclature. *Neuroimage*. 2010;53(1):1-15. doi:10.1016/j.neuroimage.2010.06.010
23. de Boer AAA, Bayer JMM, Kia SM, et al. Non-Gaussian normative modelling with hierarchical Bayesian regression. *Imaging Neurosci*. 2024;2:1-36. doi:10.1162/imag_a_00132
24. Kia SM, Huijsdens H, Rutherford S, et al. Closing the life-cycle of normative modelling using federated hierarchical Bayesian regression. *PLOS ONE*. 2022;17(12):e0278776. doi:10.1371/journal.pone.0278776
25. Lawry Aguila A, Lorenzini L, Janahi M, Barkhof F, Altmann A. Deep normative modelling reveals insights into early-stage Alzheimer's disease using multi-modal neuroimaging data. *Alz Res Therapy*. 2025;17(1):107. doi:10.1186/s13195-025-01753-3
26. Lane CA, Barnes J, Nicholas JM, et al. Associations between blood pressure across adulthood and late-life brain structure and pathology in the neuroscience substudy of the 1946 British birth cohort (Insight 46): an epidemiological study. *Lancet Neurol*. 2019;18(10):942-952. doi:10.1016/S1474-4422(19)30228-5
27. Wechsler D. Wechsler Memory Scale-Revised. Psychological Corporation. Published online 1987. Accessed June 22, 2025. https://cir.nii.ac.jp/crid/1573105974508393472
28. Papp KV, Amariglio RE, Dekhtyar M, et al. Development of a psychometrically equivalent short form of the face-name associative memory exam for use along the early Alzheimer's disease trajectory. *Clin Neuropsychol*. 2014;28(5):771-785. doi:10.1080/13854046.2014.911351
29. Wechsler. WAIS-R: Manual: Wechsler adult intelligence scale-revised. Published online 1981. Accessed June 22, 2025. https://cir.nii.ac.jp/crid/1370567187534350980
30. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12(3):189-198. doi:10.1016/0022-3956(75)90026-6
31. Lu K, Nicholas JM, Collins JD, et al. Cognition at age 70: life course predictors and associations with brain pathologies. *Neurology*. 2019;93(23):e2144-e2156. doi:10.1212/WNL.0000000000008534
32. Brooks ME, Kristensen K, Benthem KJ van, et al. glmmTMB balances speed and flexibility among packages for zero-inflated generalized linear mixed modelling. *The R Journal*. 2017;9(2):378-400.
33. Mowinckel AM, Vidal-Piñeiro D. Visualisation of brain statistics with R-packages ggseg and ggseg3d. *arXiv*. Preprint posted online December 17, 2019. doi:10.48550/arXiv.1912.08200
34. Koller M. robustlmm: An R package for robust estimation of linear mixed-effects models. *J Stat Soft*. 2016;75(6):1-24. doi:10.18637/jss.v075.i06
35. Subramaniapillai S, Schindler LS, Redmond P, et al. Sex-dependent effects of cardiometabolic health and APOE4 on brain age. *Neurology*. 2024;103(6):e209744. doi:10.1212/WNL.0000000000209744
36. Nowell J, Gentleman S, Edison P. Cardiovascular risk and obesity impact loss of grey matter volume earlier in males than females. *J Neurol Neurosurg Psychiatry*. 2025;96(6):546-557. doi:10.1136/jnnp-2024-333675
37. Driscoll I, Davatzikos C, An Y, et al. Longitudinal pattern of regional brain volume change differentiates normal aging from MCI. *Neurology*. 2009;72(22):1906-1913. doi:10.1212/WNL.0b013e3181a82634
38. Javitt DC, Martinez A, Sehatpour P, et al. Disruption of early visual processing in amyloid-positive healthy individuals and mild cognitive impairment. *Alzheimers Res Therapy*. 2023;15(1):42. doi:10.1186/s13195-023-01189-7
39. Bai S, Liu W, Guan Y. The visuospatial and sensorimotor functions of posterior parietal cortex in drawing tasks: a review. *Front Aging Neurosci*. 2021;13:717002. doi:10.3389/fnagi.2021.717002
40. Ficek-Tani B, Horien C, Ju S, et al. Sex differences in default mode network connectivity in healthy aging adults. *Cereb Cortex*. 2022;33(10):6139-6151. doi:10.1093/cercor/bhac491
41. Verdi S, Rutherford S, Fraza C, et al. Personalizing progressive changes to brain structure in Alzheimer's disease using normative modelling. *Alzheimers Dement*. 2024;20(10):6998-7012. doi:10.1002/alz.14174
42. Emrani S, Sundermann EE. Sex/gender differences in the clinical trajectory of Alzheimer's disease: insights into diagnosis and cognitive reserve. *Frontiers in Neuroendocrinology*. 2025;77:101184. doi:10.1016/j.yfrne.2025.101184
43. Barnes LL, Wilson RS, Bienias JL, Schneider JA, Evans DA, Bennett DA. Sex differences in the clinical manifestations of Alzheimer Disease pathology. *Arch Gen Psychiatry*. 2005;62(6):685-691. doi:10.1001/archpsyc.62.6.685
44. Nelson PT, Alafuzoff I, Bigio EH, et al. Correlation of Alzheimer disease neuropathologic changes with cognitive status: a review of the literature. *J Neuropathol Exp Neurol*. 2012;71(5):362-381. doi:10.1097/NEN.0b013e31825018f7
45. Needham LP, Lu K, Nicholas JM, Schott JM, Richards M, James SN. A comprehensive assessment of age at menopause with well-characterized cognition at 70 years: A population-based British birth cohort. *Maturitas*. 2023;170:31-38. doi:10.1016/j.maturitas.2023.01.009
46. Caldwell JZK, Kinney JW, Ritter A, et al. Inflammatory cytokine levels implicated in Alzheimer's disease moderate the effects of sex on verbal memory performance. *Brain Behav Immun*. 2021;95:27-35. doi:10.1016/j.bbi.2020.12.001
47. Fatih N, Chaturvedi N, Lane CA, et al. Sex-related differences in whole brain volumes at age 70 in association with hyperglycemia during adult life. *Neurobiol Aging*. 2022;112:161-169. doi:10.1016/j.neurobiolaging.2021.09.008
48. Arenaza-Urquijo EM, Boyle R, Casaletto K, et al. Sex and gender differences in cognitive resilience to aging and Alzheimer's disease. *Alzheimers Dement*. 2024;20(8):5695-5719. doi:10.1002/alz.13844
49. Keuss SE, Coath W, Nicholas JM, et al. Associations of β-amyloid and vascular burden with rates of neurodegeneration in cognitively normal members of the 1946 British Birth Cohort. *Neurology*. 2022;99(2):e129-e141. doi:10.1212/WNL.0000000000200524
50. Sivaniya Subramaniapillai, Galea LAM, Einstein G, de Lange AMG. Sex and gender in health research: intersectionality matters. *Front Neuroendocrinol*. Published online 2024:101104. doi:10.1016/j.yfrne.2023.101104

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Subramaniapillai S, Verdi S, Keuss S, et al. Mapping sex differences in brain and cognition in relation to *APOE* ε4 and amyloid burden: A longitudinal normative modelling study. *Alzheimer's Dement*. 2026;12:e70223. https://doi.org/10.1002/trc2.70223