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RESEARCH ARTICLE

Genetic risk score for Alzheimer's disease predicts brain volume differences in mid and late life in UK biobank participants

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Abstract

INTRODUCTION: We estimated the ages when associations between Alzheimer's disease (AD) genes and brain volumes begin among middle-aged and older adults.

METHODS: Among 45,616 dementia-free participants aged 45–80, linear regressions tested whether genetic risk score for AD (AD-GRS) had age-dependent associations with 38 regional brain magnetic resonance imaging volumes. Models were adjusted for sex, assessment center, genetic ancestry, and intracranial volume.

RESULTS: AD-GRS modified the estimated effect of age (per decade) on the amygdala (−0.41 mm^3 [−0.42, −0.40]); hippocampus (−0.45 mm^3 [−0.45, −0.44]), nucleus accumbens (−0.55 mm^3 [−0.56, −0.54]), thalamus (−0.38 mm^3 [−0.39, −0.37]), and medial orbitofrontal cortex (−0.23 mm^3 [−0.24, −0.22]). Trends began by age 45 for the nucleus accumbens and thalamus, 48 for the hippocampus, 51 for the amygdala, and 53 for the medial orbitofrontal cortex. An AD-GRS excluding apolipoprotein E (*APOE*) was additionally associated with entorhinal and middle temporal cortices.

DISCUSSION: *APOE* and other genes that increase AD risk predict lower hippocampal and other brain volumes by middle age.

KEYWORDS
age, Alzheimer's disease, dementia, genetic risk score, magnetic resonance imaging (MRI), neurodegeneration

1 | BACKGROUND

The biological processes leading to late-onset Alzheimer's disease (AD) begin long before dementia onset or diagnosis.[1] Changes in amyloid, tau, and vascular damage occur before cognitive changes are clinically detectable. These neuropathological changes lead to neurodegeneration, atrophy, and eventual cognitive decline.[1] Magnetic resonance imaging (MRI)-detectable atrophy in the limbic structures and gyri of the frontal and temporal cortices are thought to be largest and occur earlier in the disease process.[2] This aligns with *post mortem* neuropathologic Braak staging[3] and models that can predict AD dementia up to a decade before diagnosis using volumes from these specific brain regions.[2] However, when and in which regions AD-related atrophy as measured with structural MRI first becomes detectable has not been firmly established. Identifying the earliest age at which brain changes due to emerging AD pathogenesis are detectable would help determine how to time preventive interventions such that they have the greatest benefit. Identifying specific brain regions indicative of AD-related changes can also inform screening strategies to identify individuals at high risk for dementia.

Observational studies of brain regions associated with AD are often conducted in older adults or over a limited span of the life course.[2] Such studies cannot easily determine the ages at which AD neurodegeneration begins; longitudinal studies with decades of biomarker, MRI, and cognitive data would be needed. In the absence of such data, study designs leveraging genetic information are better equipped to identify regional brain volume differences most strongly associated with the development of AD-related neurodegeneration. Genetic risk scores for AD (AD-GRS) are associated with dementia, cognition, and brain differences in late life.[4–6] While AD-GRS does not explain a large percentage of the variance in AD outcomes, they offer an opportunity to determine the temporal ordering of AD pathological changes since individuals with high genetic risk of AD are more likely to develop AD-related neurodegeneration as they age.[7] This is because genes are assigned at birth, so observed associations are not susceptible to reverse causation or confounding by subsequent life course risk factors that may lead to brain changes.

In prior work, we found AD genetic risk is associated with worse cognition and other AD symptoms emerging in midlife, with strengthening associations in late life.[8,9] AD-GRS may also be associated with brain volume differences in relatively younger (preclinical) cohorts; however, evidence is mixed. Some prior studies in young adults suggested that AD genetic risk might confer life-long susceptibility to reduced hippocampal volume.[10–12] Conversely, two studies on the effects of *APOE* ε4 haplotype on brain volume found no associations between the *APOE* ε4 allele and brain volumes in younger age groups.[13,14] Few studies have comprehensively examined associations between AD-GRS and regional brain volumes in middle-aged and older adults to determine the precise timing of AD-related change. Determining the relationships between AD-GRS and brain volumes as a function of age would help ascertain which volumetric measures are markers for early AD changes, as opposed to life-long brain differences that are associated with increased risk of AD.

We aimed to (1) identify which regions of the brain associated with AD-GRS differ by age and (2) estimate the age when differences begin to emerge in those regions. To do this, we evaluated associations between AD-GRS and regional brain volumes obtained from structural MRI by age and then estimated the youngest age of divergence in brain volumes by the AD-GRS among middle-aged and older adults in the UK Biobank (UKB), a large cohort of middle-aged and older adults in the UK.

RESEARCH IN CONTEXT

1. **Systematic review**: The authors reviewed the literature using PubMed. Few studies have examined the genetic risk of AD and brain outcomes in younger age groups. Three studies found differences in hippocampal volume between those with high and low genetic predisposition to AD, while two other studies found no association between apolipoprotein E APOE-e4 carrier status and regional brain volumes.
2. **Interpretation**: Our findings indicated that there were significant age by AD genetic risk interactions in the nucleus accumbens, hippocampus, amygdala, medial orbitofrontal cortex, and thalamus. In these regions, high-risk individuals exhibited increased atrophy beginning in middle age and becoming more pronounced in late life.
3. **Future directions**: Our study adds to a growing body of literature that indicates that pathological changes in AD begin in midlife. Understanding both the timing of these changes and specific brain regions affected is critical to the effective primary prevention of AD.

2 | METHODS

2.1 | Data source and sample

The UKB is an ongoing prospective study, described in detail elsewhere.[15] Briefly, from 2006 to 2011, the UKB recruited over half a million individuals living in the UK between the ages of 40 and 69; these individuals provided survey responses and biological samples. Starting in 2014, a subset of participants were invited to participate in imaging.[16] Ethics approval was obtained by the UKB study from the National Health Service National Research Ethics Service, with all participants providing written informed consent. Analyses were approved under UK Biobank Resource Project 78748, and the use of UKB data for the current analysis was reviewed by the University of California San Francisco Institutional Review Board.

We included participants with at least one valid MRI (n = 47,502). We also included individuals regardless of ancestry (n = 1354 (3.2%)

non-European ancestry) following recommended approaches[17]; preliminary analyses in UKB suggested no significant differences in time to dementia across different ancestry groups, and we examined this further in sensitivity analyses in this study. We excluded those without genetic data or with imaging data that failed quality control. Our final eligible sample included 45,616 participants.

2.1.1 | Genotyping and AD-GRSs

The UKB genotyped samples in batches of approximately 4700 using two assays (UK BiLEVE array and UKB Axiom array). Single-nucleotide polymorphisms (SNPs) were removed if found to be unreliable across all batches. Similarly, samples were removed only if they were suspected to be duplicates, involved in laboratory mishandling, or asked to be withdrawn by participants. SNPs were imputed using two reference panels, with preference shown for the larger haplotype reference consortium (HRC) panel (n = 32,488; no indels) over a merger of UK10K and 1000 Genomes Phase 3 individuals (n = 6285 individuals, for indels) since the majority of UKB participants are of European descent. The latter panel was used primarily to help phase those of non-European ancestry.[18] The APOE haplotype was derived using the directly genotyped SNPs rs7412 and rs429358.

We calculated AD-GRSs using SNPs identified to be genome-wide significant in the most recent meta-analysis of late-onset AD that was completely independent of UKB.[7] This approach maximizes our ability to interpret findings as a consequence of AD-GRS pathways rather than pleiotropic pathways as previous studies suggested that late-onset AD arose from a small set of genes.[19] Using PLINK 2.0, we calculated the AD-GRS as a weighted sum of 26 SNPs after quality control, weighted by the meta-analyzed effect size (weights for two SNPs in the apolipoprotein E (APOE) region were derived from an earlier genome-wide association study (GWAS) meta-analysis that evaluated all SNPs in the APOE region).[7] Because APOE is the strongest genetic risk factor for AD, we also conducted sensitivity analyses utilizing modified forms of the GRS, one excluding the two APOE SNPs as well as an APOE-only GRS. We standardized each AD-GRS by centering at the full sample's mean and dividing by the standard deviation. In a sensitivity analysis to corroborate findings based on a separate study of AD risk genes, we also calculated an AD-GRS based on 23 genome-wide significant SNPs identified in Lambert et al.'s meta-analysis of AD in 2013.[20]

2.1.2 | MRI outcomes

All surviving participants that continued to live in the UK at the time of the UKB's imaging substudy recruitment were invited to participate; those with contraindications for MRI were excluded.[16] Brain MRI protocols, image processing, and quality control measures were standardized for all participants and are detailed elsewhere.[16] Briefly, A 3-Tesla Siemens Skyra scanner with VD13 software and a 32-channel head coil performed the MRI with exams lasting approximately 35 min. T1-weighted structural imaging and T2-weighted fluid attenuation inversion recovery (FLAIR) were acquired at a 1-mm isotropic resolution using a straight sagittal orientation.[21] An automated processing pipeline conducted brain imaging analyses, based on Oxford Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB's) Software Library, which included a raw, defaced T1-weighted volume, a reduced field-of-view T1-weighted volume, and further processing (skull stripping, bias field correction, gross tissue segmentation, and subcortical structural modeling).[21] Total brain, total white matter, and total gray matter were estimated in UKB from processed T1 images.[21] T1 and T2 FLAIR images were processed using FreeSurfer version 6.0 to generate subcortical volumes using the automatic subcortical segmentation (ASEG)[22] and cortical volume and thickness values based on the Desikan-Killianny-Tourville (DKT) atlas.[21,23] T1 images were also processed using FMRIB's Automated Segmentation Tool (FAST) and FMRIB's Integrated Registration and Segmentation Tool (FIRST). FAST processing provides hard segmentation into grey matter and white matter to generate a fully bias-field-corrected version of T1 images; FIRST allows for subcortical processing.[21]

When participants had multiple brain MRI measures available, we used the earliest available measure. We combined each side of the hemisphere to obtain a single measure for each region of interest (ROI). Our primary set of ROIs were 38 volumes derived from Freesurfer packages: seven volumes in subcortical regions (from ASEG) and 31 cortical regions (from DKT). In secondary analyses, we examined the mean thickness of 31 DKT regions, 66 regional FAST gray matter volumes, seven FIRST subcortical regions, and total white matter hyperintensity volume derived from T1 and T2 FLAIR images.

2.2 | Analysis

2.2.1 | Age interaction models

To identify which areas of the brain showed differences by AD-GRS that increased with age, we ran separate linear regressions with an interaction between age and the AD-GRS for each of the 38 brain ROIs. Models were adjusted for age at MRI, sex, imaging center at MRI visit, total intracranial volume, and the first 10 genetic ancestry principal components (measured in all participants who provided genetic data, to account for confounding by population stratification).

Our primary coefficient of interest was the interaction between age and genetic risk, which provides an estimate of the difference in the association of AD-GRS with brain region volume with increasing age. The interaction term can be interpreted as the change in brain volume in cubic millimeters (mm^3) per standard deviation (SD) increase in AD-GRS per decade of age. To aid interpretability of the coefficient, we also estimated the association between age and each brain region for people with an average AD-GRS (mm^3/decade), as well as the percentage increase in the rate of change with age associated with a SD higher AD-GRS compared to someone with an average AD-GRS from the same models.

2.2.2 | Age divergence models

We fit models to detect the earliest age at which the age-related trends in brain volume differences begin to diverge between individuals with a high compared to low AD-GRS using an approach previously developed by Zimmerman et al. and described in detail elsewhere.[8] Briefly, this method allows for non-linear associations with age and uses cross-validation to compare models specifying different ages of divergence, or the age at which the AD-GRS begins to become associated with the phenotype of interest. Models for each brain volume of interest were fit to data with the following predictors: age and age squared (both centered at 45), the set of covariates used in the age interaction models (represented by W_i), and a step function at the threshold age times cubic age in years exceeding threshold:

$$ROI \sim age^2 + age + ADGRS_Z \times I(age > age_{threshold}) \times (age - age_{threshold})^3 + \sum_i W_i. \quad (1)$$

We evaluated a range of hypothesized ages from 45 to 80 for the age threshold (based on the age range of the study sample). We compared models with different thresholds using mean squared prediction error from 10-fold cross-validation and selected the age threshold from the model with the minimum mean squared predicted error. Below that threshold, the mean AD-GRS would not be associated with brain volume. Above that age threshold, the data are better represented by AD-GRS-specific curves across ages (Formulas 2 and 3 in Supplement 1). We then used this model to predict and plot anticipated average brain volumes across age at median values of covariates, comparing higher (95th percentile) and lower (5th percentile) AD-GRS. For a ROI significantly associated with the interaction of AD-GRS and age, we bootstrapped this process over a smaller window centered around the age of divergence to obtain a 95% confidence interval.

2.3 | Secondary analyses

Secondary analyses examined subcortical volumes, cortical thickness, and regional gray matter volumes in similar areas, as well as total volume of white matter hyperintensities. To better understand the effect of APOE ε4 versus non-ε4 variants, all models were replicated using alternative AD-GRS omitting SNPs in the APOE region as well as a GRS using only APOE polymorphisms. To test whether the age-of-divergence results were sensitive to modeling of age, we repeated the analysis with alternative functional forms for age (Supplement 1). Another sensitivity analysis examined brain volume trajectories without an age threshold for differences by AD-GRS in the quadratic model.

2.4 | Sensitivity analyses

To evaluate the robustness of our primary models, we ran several sensitivity models. The first model adjusted for other factors that may be affected by AD-GRS, including education and several vascular risk factors, including hypertension, diabetes, atrial fibrillation, stroke, hypercholesterolemia, smoking history, and myocardial infarction. These were not included in the main model as these may partially mediate the pathway between genetic risk and brain volume. Secondly, to corroborate our findings, we used results from Lambert 2013's GWAS to construct a separate GRS and reran models with a different AD-GRS.[20]

Although previous studies advocated for inclusion of non-Europeans in genetic studies even with low numbers, genes identified in European samples may not be as predictive among other ancestries.[24] Thus, we evaluated whether associations between AD-GRS and hippocampal volume were similar for participants over the age of 60 by genetic ancestry as defined in UKB (as European and Non-European). We examined overall associations after age 60 rather than the interactions given the small sample sizes of non-Europeans. Individuals were determined to be "genetically Caucasian" if they self-identified as White British and had similar principal components to one another.

We also evaluated our assumptions about the age of divergence by fitting different divergence models. We first assumed a linear relationship between age and regional volume with a second-order divergence and separately evaluated a model with a third-order association and fourth-order divergence (Supplemental Formulas). We further examined models that allowed genetic risk to differ across the entire time range in order to identify trends that did not vary by age and could indicate potentially life-long differences.

3 | RESULTS

The analytic sample comprised 45,616 participants (mean age: 64.8 (SD = 7.7); 52.6% female, 97.1% White) (Table 1). In addition, 25.5% of participants had one APOE ε4 allele and an additional 2.2% had two ε4 alleles. The distribution of each AD-GRS is shown in Supplement 2.

3.1 | Interactions of AD-GRS and age for brain ROIs

Five of the 38 primary MRI outcomes of interest had significant AD-GRSs by age interactions at or below the Bonferroni-corrected p value threshold ($p \leq 1.32 \times 10^{-3}$): the medial orbitofrontal cortex, nucleus accumbens, thalamus, hippocampus, and amygdala. The mean brain region volume per decade increase in age for 1 SD higher AD-GRS increased 7.1% for the medial orbitofrontal, 4.2% for the nucleus accumbens, 3.8% for the thalamus, 5.3% for the hippocampus, and 5.8% for the amygdala (Table 2, full list of results is available in eTable 1).

Findings were overall similar for the AD-GRS without APOE. Age by AD-GRS without APOE interactions for the hippocampus and amygdala met statistical significance, but the nucleus accumbens did not, so the estimate was slightly lower. There were also significant

TABLE 1 Characteristics of UK Biobank MRI study participants included in analyses ($N = 45{,}616$).

Characteristic	Mean (SD) or *n* (%)
Female	23,979 (52.6%)
Age at first MRI (25th percentile, 75th percentile).	65.2 (58.8, 70.7)
Racial/ethnic identity	
White	44134 (97.1%)
Black	336 (1.0%)
Asian	681 (1.5%)
Mixed	72 (0.2%)
Other	240 (0.5%)
AD-GRS	
With APOE	0.004 (0.02)
Without APOE	−0.003, (0.007)
APOE ε4 alleles	
One allele	11659 (25.5%)
Two alleles	1001 (2.2%)

Abbreviations: AD-GRS, Alzheimer's disease genetic risk score; APOE, apolipoprotein E; CI, confidence interval; MRI, magnetic resonance imaging; SD, standard deviation.

interactions for the entorhinal and middle-temporal cortices for the AD-GRS without APOE, regions that did not quite meet the threshold for significance and had slightly lower effect estimates when using the AD-GRS with APOE (eTable 2). For an AD-GRS constructed using only two SNPs in APOE region, age by AD-GRS interactions were statistically significant for same regions of the brain as the primary analysis of AD-GRS with APOE except for the thalamus (eTable 3).

In sensitivity models controlling for vascular factors and education, the effect estimates in primary models did not significantly change, suggesting that our findings would not be explained by genetic effects on educational attainment or cardiovascular disease (eTable 4).

We also evaluated differences in the effects on hippocampal volume stratified by race/ethnicity and genetic ancestry for participants over 70. Estimates were only statistically significant in White participants and European ("Caucasian") ancestry. Otherwise, the estimates were largely in the expected same direction as the main results; however, estimates for Asian and Black participants were less consistent, but findings were very imprecise given the small sample sizes (eTable 5). The full set of primary results were not substantially changed when excluding non-White participants, so we present estimates for the overall sample.

In the 104 secondary regions, five met the Bonferroni-corrected significance ($p < 4.8 \times 10^{-4}$) threshold for age by AD-GRS interactions: the medial thickness of entorhinal cortex (DKT), hippocampal volume (FIRST), and gray matter volumes found in the amygdala (FAST), hippocampus (FAST), and anterior parahippocampal gyrus (FAST) (eTable 6). The age by AD-GRS interaction was not significantly associated with white matter hyperintensity volume (T1 and T2 FLAIR derived) (p value = .958).

3.2 | Estimated age of divergence in AD-GRS trends

The youngest estimated age of divergence in brain volume for the five ROIs for which AD-GRS modified the association with age between people with higher (95th percentile) and lower (5th percentile) AD-GRS is shown in Figure 1 (full results in eTable 7a). Each region showed similar trends (Figure 1), with no significant differences by the AD-GRS for youngest ages (45) of the sample with increasing differences by the AD-GRS among older ages. The nucleus accumbens (−0.547 mm^3 per decade) and thalamus (−0.380 mm^3 per decade) provided evidence for divergence at the youngest testable age available in our sample, 45 years, with differences by the AD-GRS becoming statistically significantly different at age 60 and 56 years, respectively. In the hippocampus (−0.449 mm^3 per decade) and amygdala (−0.409 mm^3 per decade), the earliest age of divergence by AD-GRS was at age 48 and 51 years, respectively (Table 3; Figure 2), with differences becoming statistically significant at ages 59 and 61, respectively. Lastly, the medial orbitofrontal (−0.230 mm^3 per decade) was found to begin diverging at age 53, with differences becoming significantly different at 63.

We bootstrapped estimates for the age of divergence in the regions found to be significantly associated with the interaction between age and AD-GRS (eTable 7b). The intervals were narrow and varied at most by a year and a half for the hippocampus. The regions that were found to diverge at the earliest age available in our analysis (age 45) yielded confidence intervals for the same age. (The age of divergence for the secondary regions can be found in eTable 8.)

Sensitivity analyses modeling divergence with a linear form of age (Supplemental Formula S2) identified older ages of divergence for these regions. Conversely, models incorporating a cubic form for age (Supplemental Formula S3) identified an age of divergence at or younger than 45 for all of the primary regions. When the threshold was removed completely, allowing the volumes to differ along the entire range of ages, the ages of divergence appeared virtually identical to Figure 1, showing no associations at age 45 but diverging associations that increase at older ages.

The models that excluded APOE and that were composed only of APOE found ages of divergence largely similar to the primary model, except the medial orbitofrontal cortex diverged a decade later (eTable 7a). Models that evaluated the effect of Lambert's 2013 GRS found the same regions to be significant with a similar magnitude of effect (eTables 9a and 9b).

Finally, we re-examined the two most significant cognitive findings from our prior work (eTables 10a and 10b).[8] We largely observe similar ages of divergence to brain volumes by age 45 to 49 even in this smaller sample.

4 | DISCUSSION

This study comprehensively examined how genetic risk for late-onset AD modified age-related trends in brain volumes between mid and late life. Higher genetic predisposition to AD including APOE ε4 was

TABLE 2 Effect modification of age-slope by AD-GRS for each brain region with a statistically significant age by AD-GRS interaction in linear regression models (*z*-scored).

Brain region	Age effect per decade at mean AD-GRS [95% CI]	Difference in age effect for person with 1 SD higher AD-GRS (interaction) [95% CI]	Percentage acceleration associated with 1 SD higher AD-GRS
Nucleus accumbens	−0.547 [−0.557, −0.537] $p = .000$	−0.022 [−0.033, −0.013] $p = 4.47E-06$	4.2%
Hippocampus	−0.449 [−0.454, −0.436] $p = .000$	−0.024 [−0.033,−0.013] $p = 7.86E-07$	5.3%
Amygdala	−0.409 [−0.418, −0.400] $p = .000$	−0.024 [0.033, −0.015] $p = 2.44E-07$	5.8%
Medial obitofrontal	−0.2297 [−0.2388, −0.2206] $p = .00$	−0.0162 [−0.0253, −0.0071] $p = 5e-04$	7.1%
Thalamus	−0.3797 [−0.3877, −0.3716] $p = .00$	−0.0143 [−0.0224, −0.0062] $p = 5e-04$	3.8
Entorhinal cortex[NS]	−0.0607 [−0.0719, −0.0495] $p = 2.97E-26$	−0.0166 0.0279, −0.0054] $p = .0037$	27.4
Middle temporal cortex[NS]	−0.276 [−0.2845, −0.2676] $p = .0000$	−0.0104 $p = 0.0154$ [0.0188, −0.002]	3.8

Abbreviations: AD-GRS, Alzheimer's disease genetic risk score; CI, confidence interval; SD, standard deviation.

significantly associated with greater age-related divergence in volumes for five of 38 brain regions (nucleus accumbens, hippocampus, medial orbitofrontal cortex, thalamus, and amygdala). Brain volumes began to diverge between those with high and low AD-GRS in middle age (estimated ≤ 45 years for nucleus accumbens and the thalamus, 48 for hippocampus, 51 for the amygdala, and 53 for the medial orbitofrontal), with differences becoming statistically significant about a decade later. MRI measures from secondary analyses showed similar trends with significant effects for medial temporal lobe structures. The AD-GRS without APOE identified significant interactions between age and AD-GRS for the hippocampus and amygdala, as well as the entorhinal and middle temporal cortices but not the nucleus accumbens, thalamus, or medial orbitofrontal. For these models, the age of divergence either remained the same or increased slightly for the ROIs compared with the full AD-GRS. Consistency across these results suggests that, in those with high genetic predisposition to AD, there are detectable differences in volume of specific brain regions that emerge in midlife.

Our results build upon prior studies examining associations between genetic risk and dementia-related neuroimaging outcomes. These studies were typically limited to samples of older adults,[4,6] and we extend these findings to middle-aged adults in a large cohort. Our findings are in contrast to several studies examining genetic associations with brain volumes in younger adults that reported associations of AD-GRS or the APOE ε4 allele with lower hippocampal volume in young adults.[25,10,11] However, our findings are consistent with several studies that reported no associations between APOE genotype and brain volumes in younger age groups.[13,14,26] Other studies found increased cognitive performance and neuroimaging markers in the youngest populations (under 30),[12,27] consistent with the "antagonistic pleiotropy hypothesis," which postulates that a gene may have varying

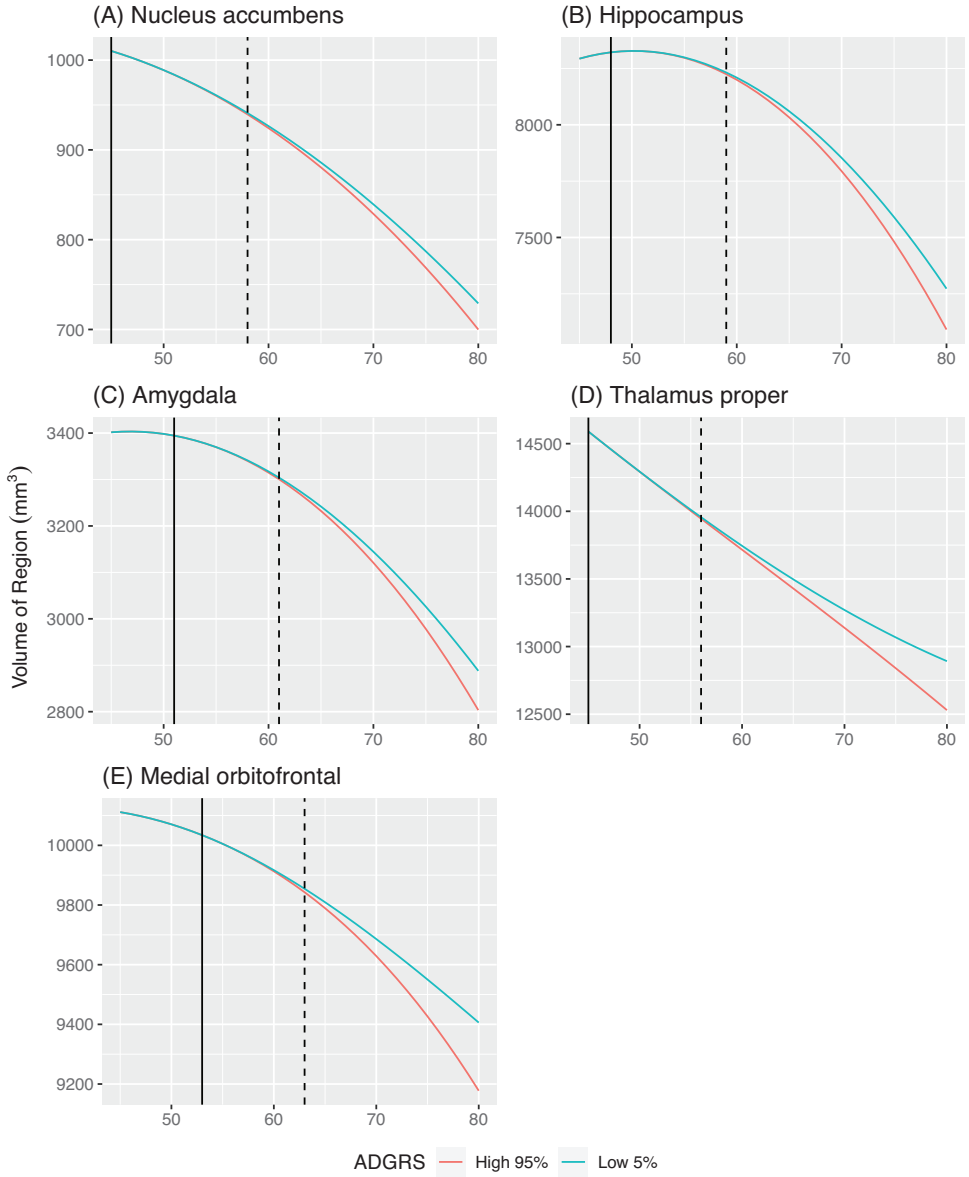

FIGURE 1 Age-related curves for (A) nucleus accumbens, (B) hippocampus, (C) amygdala, (D) thalamus proper, and (E) medial orbitofrontal cortex for high and low Alzheimer's disease genetic risk score (AD-GRS). Predicted curves for 5th (low) versus 95th (high) percentile of AD-GRS (score including APOE variants is shown here). In each panel, the solid line denotes the estimated age of divergence in curves, and the dotted line denotes the age at which there is a significant difference for high versus low AD-GRS.

effects on health outcomes during different life stages (eg, may be beneficial during early life but harmful in late life). Although our study did not include younger adults, we found no evidence for volumetric associations with the AD-GRS in "early" middle-aged adults in our sample but rather a divergence based on age. While we do find evidence for age differences, we posit that this is due to AD pathogenesis.

Similarly, our study highlights an important contribution of non-APOE risk alleles on brain volume differences that emerge in midlife. Most differences in the effect estimates obtained between the GRS that included APOE and the GRS that excluded it were in the same direction and within each other's confidence intervals; the similarities in findings are a bit surprising given APOE has a much stronger effect on AD risk compared to other genes. Though the exact pathways remain unclear, AD genes likely affect development of AD (or dementia more broadly) through multiple pathways, including innate immunity and lipid metabolism.[7] This may partially explain why estimates and significance levels for some regions (eg, entorhinal cortex and nucleus accumbens) differed between the AD-GRS including APOE and excluding APOE. Our findings add to evidence suggesting that biological processes that lead to AD begin decades prior to the average dementia diagnosis. Future longitudinal work may help elucidate differences in effects and timing of effects arising from specific AD risk genes.

Our findings indicate associations between certain volumes and genetic risk of AD appear in middle age and grow over time. Atrophy in the medial temporal lobe, including the hippocampus, is a hallmark of

TABLE 3 Estimated earliest age of divergence by AD-GRS.

	AD-GRS with APOE	AD-GRS without APOE	APOE-only AD-GRS
MRI	Age of estimated divergence (age of significant difference)		
Nucleus accumbens	≤45 (58)	≤45 (66)[a]	≤45 (60)
Hippocampus	48 (59)	≤45 (59)	47 (62)
Amygdala	51 (61)	51 (65)	52 (63)
Thalamus	≤45 (56)	≤45 (58)[a]	≤45 (59)[a]
Medial orbitofrontal	53 (63)	63 (70)[a]	52 (63)
Entorhinal cortex	≤45 (56)[a]	≤45 (58)	≤45 (60)[a]
Middle temporal cortex	63 (69)[a]	72 (75)	62 (70)[a]

Note: Earliest age of divergence in predicted regional volume trends determined by model with lowest mean squared error calculated using a 10-fold cross-validation. Significant differences in volumes determined by *t* test at each age between high and low AD-GRS groups.
Abbreviations: AD-GRS, Alzheimer's disease genetic risk score; APOE, apolipoprotein E; MRI, magnetic resonance imaging.
[a]Not statistically significant for given AD-GRS.

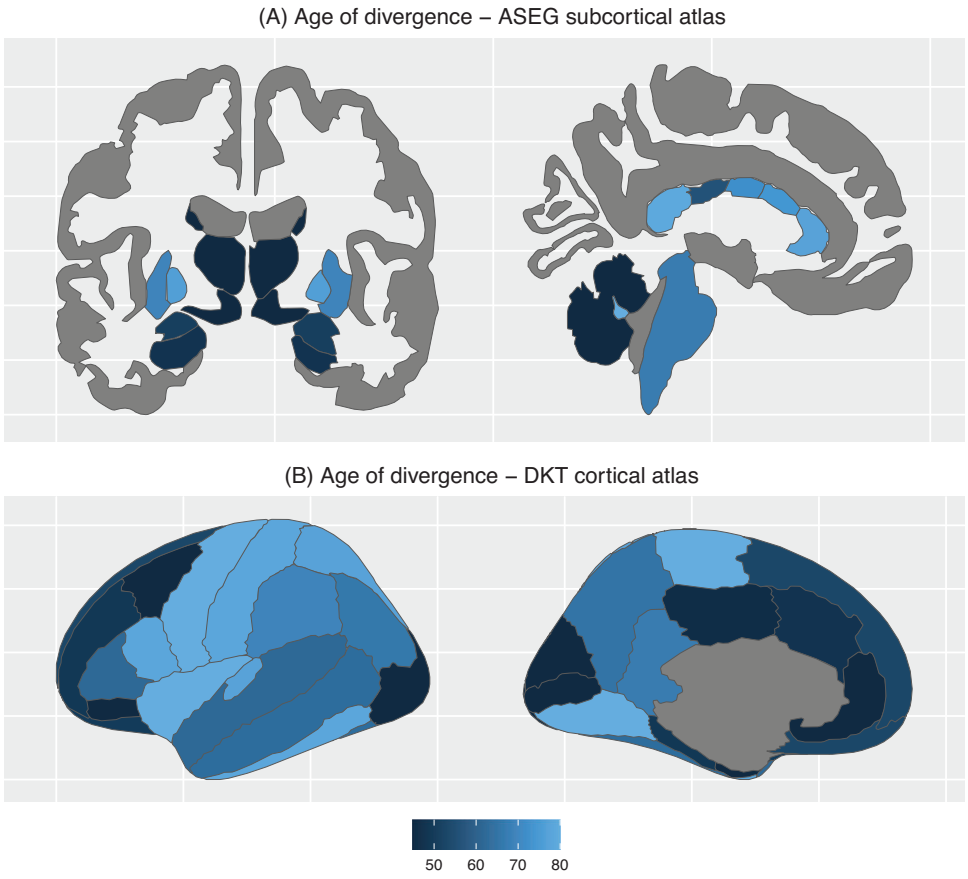

FIGURE 2 Estimated age of divergence for all brain regions of interest plotted to brain atlas regardless of significance. Cortical and subcortical atlas for brain regions of interest shows a range of estimated age of divergence in AD-GRS trends, with many regions diverging prior to age 50. However, only the medial orbitofrontal cortex and nucleus accumbens, hippocampus, thalamus, and amygdala (shown in ASEG atlas) met a Bonferroni-corrected threshold for significant age-related divergence by the AD-GRS.

AD. Although MRI-derived signatures of AD dementia in older adults also generally include atrophy in neocortical regions,[2] our findings are consistent with hypothesized brain changes at earlier stages of the AD continuum.[3] Tau proteins forming neurofibrillary tangles are hypothesized to begin in the entorhinal cortex and hippocampus, later spreading to the amygdala, inferior-lateral temporal regions, and then other cortical areas.[3] The AD-GRS with only APOE haplotypes was associated with increased risk of atrophy with age in the nucleus

accumbens. Similarly, other studies found that atrophy in this area was associated with poorer cognitive function[28] and that amyloid beta oligomer activity in the region may play a role in AD progression.[29]

Although the AD pathophysiologic cascade hypothesis posits that neurodegeneration develops prior to cognitive decline, our previous findings of divergence in cognition and BMI were around the same ages.[8,9] We observed similar ages of divergence for cognition in this sample. This suggests that slight cognitive deficits occur even prior to substantial neurodegeneration measured by brain volumes, perhaps due to changes in brain function or other mechanisms. However, given the cross-sectional nature of these findings, future longitudinal work must be conducted to determine the ordering of events.

This study has a number of strengths. The UKB's large sample size conferred substantial increases in statistical power compared with smaller cohorts used in prior work. Using AD genetic risk as a proxy to study AD-related changes in brain regions avoids traditional confounding structures by environmental risk factors for AD diagnosis, as genetic variants precede traditional confounders. This approach takes advantage of existing imaging without the need for decades-long follow-up periods. Furthermore, the cross-validated model comparison procedure allows us to estimate the age at which AD begins to influence each brain region. We conducted several sensitivity analyses, which supported the robustness and consistency of our primary findings and highlight the role of non-APOE genetic variants in predicting brain volumes.

This study also has limitations. First, this is a cross-sectional study; however, the ideal longitudinal study would be expensive and results would not be available in the near term. Second, UKB is not representative of the general UK population; however, previous studies did not find evidence of selection bias using the AD-GRS in UKB.[9] Third, the exact age of MRI changes for an individual will likely differ by etiology and risk profile, as illustrated with slight differences in our findings between AD-GRSs that included versus excluded APOE. Fourth, the GRS is based on genes identified in exclusively European ancestry cohorts; we have some evidence to suggest that the GRS predicts AD similarly in non-White populations; however, stratified estimates within this sample were imprecise, and future studies in large diverse populations are needed. Finally, our findings may be driven in part by pleiotropic effects of AD genes on multiple pathways that increase dementia risk. We do not fully understand how AD genes cause dementia, and while AD genes are associated with AD-related pathologies,[30] other neurogenerative, cerebrovascular, or other processes may contribute to these findings.[30] However, our findings were robust to multiple risk scores, adjustment for education, and vascular conditions. Furthermore, our primary interest for this study was in the collective impact of AD genes on neurodegeneration and increased risk for dementia.

5 | CONCLUSION

We conducted a comprehensive evaluation of the association between AD genetic risk and regional brain volumes in mid to late life. Our findings identified volumetric differences for five regions (the accumbens area, hippocampus, amygdala, medial orbitofrontal, and thalamus) that were inversely associated with higher genetic risk for AD, with divergence beginning in middle age and subsequently growing. When examining genetic risk excluding SNPs in APOE, two additional regions (entorhinal cortex and middle temporal cortex) differed significantly by age and AD-GRS. We determined that volumes in those with high risk began to diverge in midlife. This work adds to a growing body of evidence that AD changes begin decades prior to dementia onset, suggesting individuals at high risk for dementia in late life may already be developing atrophy in midlife. Primary prevention of AD may be most effective if begun in midlife or earlier.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts to declare. None of the authors' funding organizations contributed to the design or conduct of the study; collection, management, analysis, or interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication. All authors are independent from the funders. Author disclosures are available in the supporting information.

CONSENT STATEMENT

Ethics approval was obtained by the UKB study from the National Health Service National Research Ethics Service, with all participants providing written informed consent. Use of UKB data for the current analysis was reviewed by the University of California San Francisco Institutional Review Board.

DATA AVAILABILITY STATEMENT

Data are available for approved research from UK Biobank (https://www.ukbiobank.ac.uk/enable-your-research/apply-for-access).

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SUPPORTING INFORMATION

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

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