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Alzheimer's disease genetic risk, cognition, and brain aging in midlife

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Abstract

We examined associations of an AD genetic risk score (AD-GRS) and midlife cognitive and neuroimaging outcomes in 1,252 middle-aged participants (311 with brain MRI). A higher AD-GRS based on 25 previously identified loci (excluding *APOE*) was associated with worse Montreal Cognitive Assessment (−0.14 SD[95% CI:−0.26,−0.02]), older machine learning predicted brain age (2.35 years[95%CI:0.01,4.69]), and white matter hyperintensity volume (0.35 SD [95% CI:0.00,0.71), but not with a composite cognitive outcome, total brain, or hippocampal volume. *APOE* ε4 allele was not associated with any outcomes. AD risk genes beyond *APOE* may contribute to subclinical differences in cognition and brain health in midlife.

Summary for Social Media If Published

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Author Contributions:

WB, MF, LL, and KY contributed to the conception and design of the study, WB, MF, LL, MH, CD, and KY contributed to the acquisition and analysis of data, and WB contributed to drafting the text and preparing the figures.

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WDB, MF, MH, and KY report grant funding from NIH. None of the funding sources had involvement in the conduct of this research or preparation of the manuscript. Unrelated to this current study, KY is a Board Member of Alector.

1. If you and/or a co-author has a Twitter handle that you would like to be tagged, please enter it here. (format: @AUTHORSHANDLE).—@WillaBrenowitz @KristineYaffe

2. What is the current knowledge on the topic?—Genetic risk scores for Alzheimer's disease (AD-GRS) predict increased risk of dementia, faster rates of cognitive decline, and brain atrophy in late-life. Little is known about the associations in midlife, although accumulating evidence suggest midlife may be a critical window for dementia prevention.

3. What question did this study address?—This study assessed whether an AD-GRS is associated with cognitive outcomes or brain atrophy among a cohort of middled age white adults.

4. What does this study add to our knowledge?—Middle aged participants with a higher AD-GRS, not including *APOE*, was associated with a lower overall cognition, worse age-related brain atrophy, and higher white matter intensity volume compared to participants with a lower AD-GRS, but there were no associations with the *APOE* ε4 allele. This suggests there are subtle cognitive and brain changes in midlife associated with AD genetic risk beyond the effects of *APOE*.

5. How might this potentially impact on the practice of neurology?—AD-GRS may help screen for individuals at high risk of developing dementia. Future work is needed to confirm our results, but AD-GRS may help identify individuals at higher risk of dementia even in middle age, which could inform the timing of screening and intervention strategies.

Introduction

Genetic risk scores for AD are associated with cognitive and neuroimaging outcomes in late-life,[1–3] and could help predict preclinical AD.[4] Few studies have examined associations in midlife. Understanding when AD genes begin to affect cognition or brain structure has implications for when treatment strategies would be most effective.

Midlife is increasingly seen as a window of opportunity for early detection and prevention,[5] yet few studies have examined AD genetic risk and midlife cognitive or neuroimaging outcomes. Recent work in the large UK Biobank suggested the association between higher AD genetic risk and worse cognition may begin in midlife.[6] In a middle-age cohort, several individual AD-risk loci were nominally associated with poor cognition.[7] However, another study found no associations between AD genetic risk or APOE genotype and midlife cognition.[8] Studies in young adults suggest high AD genes may confer early susceptibility to reduced hippocampal volume,[1,9] but none have focused on midlife.

We investigated the association of an AD genetic risk score (AD-GRS) with global cognition and brain MRI outcomes in middle aged adults in the Coronary Artery Risk Development in Young Adults (CARDIA). To understand associations with AD genetic loci beyond APOE genotype, we focus on an AD genetic risk score without *APOE*, and *APOE* genotype separately.

Methods

Study Population

CARDIA is an ongoing prospective cohort of 5,115 white and Black adults ages 18–30 recruited in 1985–86 from four cities who have completed up to eight follow-up examinations spanning 30 years.[10] We focus on Year 30 visit for analyses, as participants were middle-aged, underwent cognitive testing, and a subset had brain MRI. Year 30 MRI participants were enrolled from those who had received an MRI in Year 25, which is described elsewhere in detail.[11] Those with contraindications (e.g., metal implants or body size too large for scanner) were excluded. Year 25 individuals who declined Year 30 MRI were replaced with random samples recruited by each site individually up to the total number of MRIs in Year 25. Recent studies[12] and our preliminary data in CARDIA suggest that the variants used in our genetic risk score are not generalizable Black participants, so we restricted the current study to white participants with European genetic ancestry, complete genetic data, and at least one cognitive measure (n=1,252, n=311 with brain MRI). At each visit, participants provided written informed consent, and study protocols were reviewed by institutional review boards from each study site, the CARDIA Coordinating Center at the University of Alabama, Birmingham and the University of California, San Francisco.

Genotyping and Genetic Risk Score

CARDIA samples were genotyped with the Affymetrix Genome-Wide Human SNP Array 6.0 (Santa Clara, CA, USA), quality controlled, and imputed to 1000 Genomes version 3. The AD genetic risk score (AD-GRS) was calculated based on summary statistics of single nucleotide polymorphisms (SNP) associated with AD. Specifically, we calculated the AD-GRS based on 25 SNPs, each corresponding to a different loci (Table 1) not including the *APOE* region, identified as genome-wide significant in the 2019 International Genomics of Alzheimer's Project meta-analyzed genome-wide association study on late-onset AD in Europeans.[13] This approach is similar to prior studies[1,2,6] and follows recommendations from prior work that found genetic architecture of late-onset AD is oligogenic (e.g. due to a small set of genes),[14] The AD-GRS was calculated in PLINK as a weighted sum of an individual's AD risk allele count; with weights as the β coefficient for AD for each SNP. *APOE* ε4 allele (0, 1+) was derived from APOE phenotype assays. Principal components (PCs) related to genetic population stratification were also calculated.

Global Cognition

A standardized cognitive battery was administered in Year 30.[15] Tests included: the Digit Symbol Substitution Test, the Rey Auditory-Verbal Learning delayed test, the Stroop Interference Test (scores were inversed for analysis); Category and Letter Fluency Tests; and the Montreal Cognitive Assessment (MoCA) a measure of global cognition. Our primary measures were the MoCA and a composite cognitive score, which was a weighted average of each test standardized.

MRI and Data Processing

Brain MRI at Year 30 were collected with 3-T MR scanners, images were processed using standardized QC measures and an automated pipeline,[16] regional brain volumes were derived from T1 and T2 sequences.[11] A measure of predicted "brain age" was separately derived from a machine learning approach using high-dimensional classification developed based on patterns from older samples and applied to CARDIA.[17] The brain age index differentiates individuals exhibiting "advanced brain aging" from those with normal brain aging and captures a more complex spectrum of structural changes than region-specific volumes. Total brain volume, total hippocampal volume, and total white matter hyperintensity (WMH) volume were secondary measures.

Statistical Analysis

Multiple linear regressions evaluated the association between the AD-GRS without *APOE* and each measure of global cognition (MoCA and composite score) and MRI outcomes (for those with brain MRI), with adjustment for age at year 30 visit, sex, education, and 10 principal components. Models for MRI outcomes additionally adjusted for intra-cranial volume, and MRI collection center. We reran analyses with *APOE* ε4 allele as the primary predictor and examined interactions between the AD-GRS and *APOE* ε4 allele. Analyses were conducted in R (version 3.3.2), tests were 2-sided alpha=0.05.

Results

Participants mean age was 55.8 (standard deviation (SD): 3.3), 54.3% were female; 24.4% had at least one *APOE* ε4 allele; and the mean AD-GRS without APOE was −0.18 (SD: 0.31; range: −1.23 to 1.06), corresponding to log odds of AD). In adjusted modes, the continuous AD-GRS without *APOE* was associated with a 0.14 standard deviation (SD) lower MoCA scores (95% CI:−0.26, −0.02) (Table 2) and a graded trend by tertile of the AD-GRS (Figure 1). There was no association with the composite cognitive score, although the estimate was in the same direction. Among 311 participants with MRI; higher AD-GRS without *APOE* was associated with older predicted brain age (Table 2) and demonstrated a graded trend by tertile of the AD-GRS (Figure 1). The AD-GRS without *APOE* was also associated with higher WMH volume (0.35 SD higher [95% CI:0.00, 0.71]), but not total brain volume nor hippocampal volume. Participants with MRI were similar to Year 30 participants without MRI in terms of demographic, clinical, and genetic characteristics AD-GRS (mean: −0.16, SD: 0.31); with the exception of having a lower prevalence of obesity and diabetes ($p<0.05$). *APOE* ε4 allele was not associated with any outcomes (Table 2), there were no interaction between AD-GRS and *APOE* ε4 allele ($P<0.05$); excluding participants with APOE ε4 alleles did not substantively change estimates of the AD-GRS with MoCA, predicted brain age, or WMH but reduced precision (data not shown).

Discussion

We examined whether AD genetic risk associated with cognition and structural MRI as assessed among white middle-aged adults. Higher AD-GRS without *APOE* was associated with a lower MoCA score, worse age-related brain atrophy, and higher WMH volume

compared to lower AD-GRS. These findings are important given that the mean age of CARDIA participants was 55 and the sample was relatively small. However, significant associations with other cognitive tests and brain regions were not found. We also did not find associations with *APOE* genotype. This suggests cognitive and brain changes associated with AD genetic risk in midlife are subtle.

Genetic risk scores are popular tools, but previous studies focus on late-life outcomes,[1–3] our study expands research on midlife outcomes. A prior study in middle-aged adults found several individual AD-risk loci (including *APOE* ε4 allele) were associated with poor cognition, but found no associations with a polygenic risk score.[7] We found associations in an AD-GRS without *APOE*, but no effects for *APOE* alone, suggesting a contribution of multiple SNPs beyond *APOE*. The lack of association with APOE genotype in our study, is surprising but in line with another study in middle-aged adults,[8] and the *APOE* ε4 allele has also been associated with better cognitive performance in early life.[18] It may not be until late life (e.g. 65+) that effects of the *APOE* ε4 allele on cognition develop.

We examined brain health associated with AD genetic risk focusing on a machine learning derived brain aging index.[17] Our lack of findings with total brain volume and hippocampal volume, suggest that participants in this analysis were too young for substantial AD neurodegeneration. However, the AD-GRS without *APOE* was associated with older predicted brain age and a higher volume of WMH. In an a prior study an AD-GRS (based on fewer genetic loci) was not associated with predicted brain age but was associated with AD-atrophy in older ages.[19] The brain aging index and WMH may be more sensitive to early neurodegeneration. WMH are more strongly associated with preclinical AD than other imaging markers including hippocampal volume.[20]

It is unclear whether associations in our study represent early AD-related changes, the effects of other shared pathways, or lifelong susceptibility. Studies in younger adults suggest that high AD genetic risk may confer early susceptibility to lower hippocampal volumes,[1,9] but these results do not match our findings. Our results may represent early pathophysiologic changes associated with AD genetic pathways that increase risk for dementia. Given our small sample size we did not further examine specific genes, however, there may be differences in effect on cognitive or brain outcomes by individual genes, gene-interactions, or implicated genetic pathways (e.g. innate immunity or lipid metabolism). Future work in larger samples involving longitudinal measures of AD biomarkers and in-depth genomic analyses may help elucidate neurophysiologic changes in midlife that promote AD.

This study has several limitations including a small sample and cross-sectional assessments of cognition and MRIs which limits power to detect associations. SNPs used in the GRS represent known and candidate risk loci for AD;[13] however, there may remain inaccuracy in our AD-GRS and not all risk loci are well-established as causal. There are multiple approaches to GRS, including using SNPs from the whole-genome to capture more variance.[3] Such approaches could identify different findings, but prior work suggests prediction of AD is maximized when using GRS based on selecting a smaller number of SNPs[14] as in our approach. We studied white participants and our findings may not be generalizable to other racial or ethnic groupings. Future work is needed to develop

informative AD-GRS for multi-ethnic samples. However, this study has several strengths as well including a population-based sample with genotyping, cognitive assessments, brain MRI, and machine learning derived imaging measures in middle age.

We found that a higher AD genetic risk excluding APOE was associated with detectable but limited cognitive and brain differences in middle-aged white adults. Midlife may be an important window for early identification and intervention to prevent AD. This is preliminary work, and future larger studies are needed to replicate these findings, to extend studies to more diverse aging populations, and to examine associations using longitudinal data.

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Data Availability:

CARDIA data is available for approved research projects, see more details at https://www.cardia.dopm.uab.edu/.

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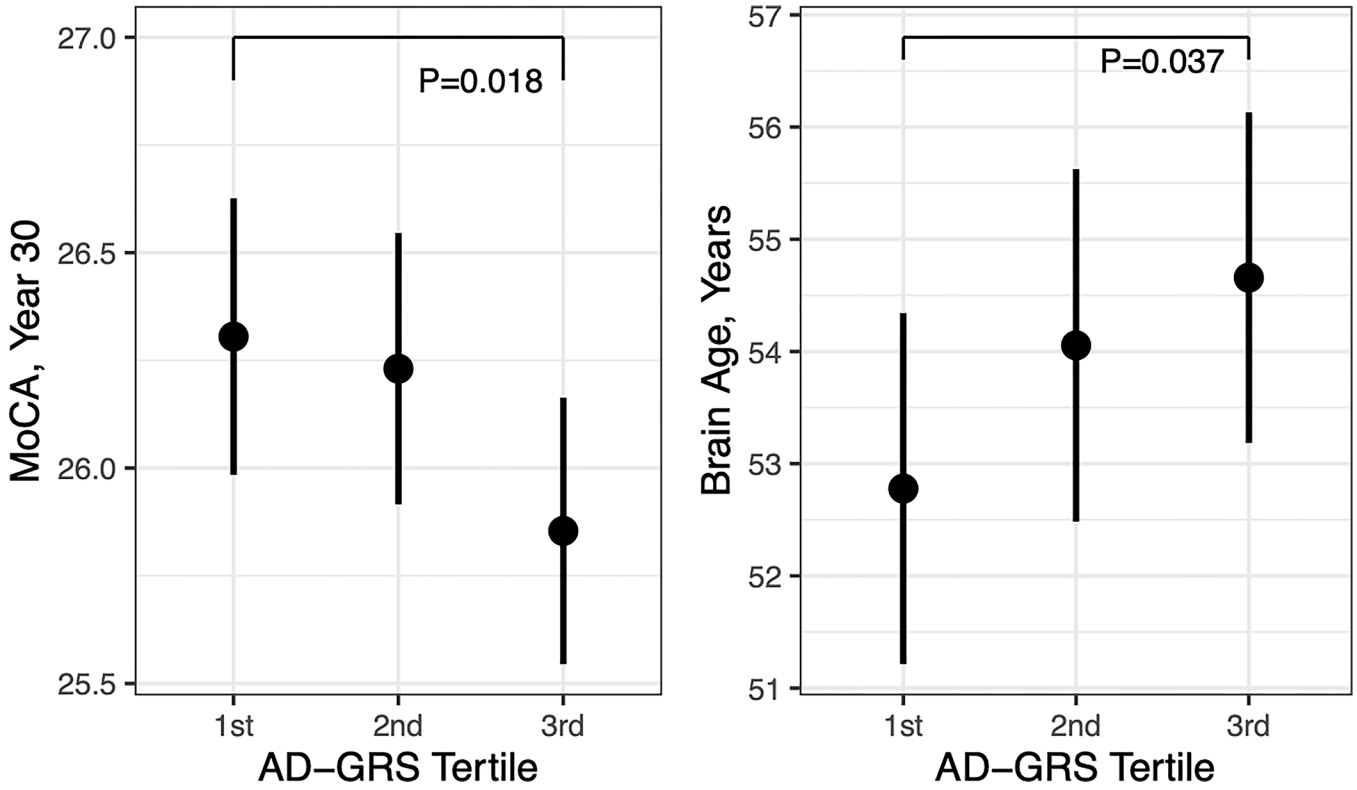

Figure 1.

Association of Alzheimer's Disease Genetic Risk Score (AD-GRS) tertile with midlife Montreal Cognitive Assessment (MoCA) score and predicted brain age based on structural MRI.

Table 1.

SNPs and log odds ratio estimates (weights) for the Alzheimer's Disease Genetic Risk Score (AD-GRS)

Marker Name	Chromosome	Closest gene	Effect Allele	Effect Estimate	Odds Ratio for AD
rs4844610	1	*CR1*	A	0.157	1.17
rs6733839	2	*BIN1*	T	0.182	1.2
rs10933431	2	*INPP5D*	G	−0.094	0.91
rs9271058	6	*HLA -DRB1*	A	0.095	1.1
rs75932628	6	*TREM2*	T	0.732	2.08
rs9473117	6	*CD2AP*	C	0.086	1.09
rs114812713	6	*OARD1*	C	0.278	1.32
rs12539172	7	*NYAP1*	T	−0.083	0.92
rs10808026	7	*EPHA1*	A	−0.105	0.9
rs73223431	8	*PTK2B*	T	0.095	1.1
rs9331896	8	*CLU*	C	−0.128	0.88
rs7920721	10	*ECHDC3*	G	0.077	1.08
rs3740688	11	*SPI1*	G	−0.083	0.92
rs7933202	11	*MS4A2*	C	−0.117	0.89
rs3851179	11	*PICALM*	T	−0.128	0.88
rs11218343	11	*SORL1*	C	−0.223	0.8
rs17125924	14	*FERMT2*	G	0.131	1.14
rs12881735	14	*SLC24A4*	C	−0.083	0.92
rs593742	15	*ADAM10*	G	−0.073	0.93
rs7185636	16	*IQCK*	C	−0.083	0.92
rs62039712	16	WWOX	A	0.148	1.16
rs138190086	17	*ACE*	A	0.262	1.3
rs3752246	19	*ABCA7*	G	0.140	1.15
rs6024870	20	*CASS4*	A	−0.128	0.88
rs2830500	21	*ADAMTS1*	A	−0.073	0.93

Table 2.

Association of AD Genetic Risk Score (GRS) and *APOE* ε4 allele with midlife cognition and brain MRI outcomes

Outcome (in SD unless noted otherwise)	AD-GRS without *APOE (continuous score)*	*APOE* ε4 allele *(any vs none)*
Cognition *	**β (95% CI)**	**β (95% CI)**
MoCA	−0.14 (−0.26, −0.02)	−0.05 (−0.14, 0.05)
Composite Score	−0.03 (−0.10, 0.05)	0.02 (−0.03, 0.07)
Brain Health**		
Brain Age, years	2.35 (0.01, 4.69)	0.44 (−1.28, 2.17)
Total Brain Volume	0.04 (−0.08, 0.02)	0.05 (−0.04, 0.14)
Hippocampal Volume	−0.24 (−0.54, 0.06)	0.18 (−0.04, 0.39)
White Matter Hyperintensity Volume	0.35 (0.00, 0.71)	0.07 (−0.19, 0.32)

MoCA; Montreal Cognitive Assessment; SD: standard deviation

* Models adjusted for age, sex, education, 10 principal components

* Models additionally adjusted for intracranial volume and MRI assessment center