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Genetic overlap between vascular pathologies and Alzheimer's dementia and potential causal mechanisms

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Abstract

INTRODUCTION: We sought to examine the genetic overlap between vascular pathologies and Alzheimer's disease (AD) dementia, and the potential mediating role of vascular pathologies between AD-related genetic variants and late-life cognition.

METHODS: For 2,907 stroke-free older individuals, we examined the association of polygenic risk scores for AD dementia (ADPRS) with vascular pathologies and with cognition. Mediation analyses addressed whether association between ADPRS and cognition was mediated by a vascular pathology.

RESULTS: ADPRS was associated with lobar cerebral microbleeds (CMB), white matter lesion load (WML) and coronary artery calcification (CAC), mostly explained by SNPs in the 19q13 region. The effect of ADPRS on cognition was partially but significantly mediated by CMB, WML, and CAC.

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Declarations of interest: none

DISCUSSION: Our findings provide evidence for genetic overlap, mostly due to *APOE,* between vascular pathologies and AD dementia. The association between AD polygenic risk and late-life cognition is mediated in part via effects on vascular pathologies.

Keywords

Alzheimer's dementia; Polygenic risk score; Cerebral microbleeds; White matter lesions; Coronary calcification; Cognitive impairment; Causal mediation

1. BACKGROUND

The etiology of Alzheimer's disease (AD) dementia is complex and multifactorial. AD dementia refers to the clinical diagnosis of dementia considered likely to be due to underlying AD pathology, the accumulation of amyloid plaques and neurofibrillary tangles, which may lead to neurodegeneration and neuronal cell death. However, it is well-established that a large fraction of those with a diagnosis of AD dementia also have cerebrovascular pathology [1]. Systematically collected cohort-based autopsy data have shown that vascular pathology often coexists with AD pathology, adds to the likelihood of cognitive impairment, and lowers the threshold of AD pathology for the development of clinically diagnosed AD dementia [2].

A variety of cerebral small vessel diseases (SVD) have been associated with AD dementia. Cerebral microbleeds (CMB) are more prevalent in individuals with dementia [3–5]. The presence of CMB in deep and infratentorial regions is generally ascribed to hypertensive vasculopathy, while a lobar distribution of CMB is associated with cerebral amyloid angiopathy (CAA) [6], which has been considered a major contributor to the pathogenesis of AD dementia [7]. White matter lesions (WML), an imaging marker of cerebral SVD, may also play a role in the development of AD dementia [8, 9]. A metaanalysis found that WML predicted an increased risk of AD and other dementia [10]. Retinal venular diameter (RVD), an indicator to visualize microcirculation in vivo, has been related to WML, brain atrophy, and increased risk of dementia [11–13].

Research efforts have also been devoted to the association between large vessel disease (LVD) and AD dementia. Possible mechanisms linking large-vessel atherosclerosis to AD dementia include shared etiology and brain hypoperfusion [14]. Several longitudinal studies suggest that carotid intima-media thickness (CIMT), a marker of atherosclerosis, is associated with brain atrophy [15] and a later incidence of AD dementia [16, 17]. Atherosclerotic coronary artery calcification (CAC) is another marker of LVD. Although there have been few reports on the relation between CAC and AD , current evidence suggests that larger volume of CAC is associated with brain atrophy, worse cognitive function, and all-cause dementia [18–20].

Genetic studies may provide clues to the biological link of AD dementia with cerebro- and cardio-vascular disease (collectively "CVD"). Apolipoprotein E *(APOE),* the major susceptibility gene for AD [21], has been reported to be a risk factor for hyperlipidemia, lobar CMB, WML, ischemic stroke, and coronary heart disease [22–25]. In addition to *APOE,* genome-wide association studies (GWAS) of AD dementia have identified single

nucleotide polymorphisms (SNPs) with known or hypothesized relationships to lipid metabolism, such as *CLU, ABCA7,* and *SORL1* [26]. Recent studies using large-scale GWAS data suggest that AD dementia may be genetically correlated with levels of biomarkers for CVD risk (plasma lipids and C-reactive protein) [27] and small vessel stroke [28]. A gene-based pathway approach to GWAS data has also identified shared genetic pathways between CVD and AD dementia [29].

A recent study found that the effect of APOE-e4 on late-life cognition was partially mediated by cerebrovascular pathologies [30]. In the present study, we expand to additional vascular pathologies beyond the brain and full genome data to more fully understand the relationship of AD genes and vascular pathology in the development of cognitive impairment. We generated genome-wide polygenic risk scores for AD dementia (GW-ADPRS) to examine the polygenic overlap between AD dementia and each of the following vascular pathologies: lobar CMB, WML, RVD, CIMT, and CAC. We also generated two partitioned ADPRS, estimating genetic risk for AD dementia contributed separately by the 19q13 region that includes *APOE* and SNPs in linkage disequilibrium (LD) with *APOE,* and all other SNPs outside of the APOE-linkage region. We tested each ADPRS separately for association with cognition scores and with each vascular pathology. For vascular markers observed to be genetically correlated with AD dementia, we performed mediation analyses to explore the causal relationship among ADPRS, vascular pathology, and cognitive function.

2. METHODS

2.1. Study Sample

The analyses were performed in data from the Age, Gene/Environment Susceptibility—Reykjavik Study (AGES-Reykjavik), a population-based cohort in Iceland [31] (see Supplementary Methods). For our phenotypic analyses, from the full AGES-Reykjavik sample of 5,764 participants, we excluded those with a history of stroke or vascular dementia, leaving 5,161. Of these participants, the 2,907 with clean genotype data available constituted the sample for our genetic analyses (see Supplementary Figure S1). Genotyping was performed using the Illumina HumanCNV370-Duo (Illumina Inc.; San Diego, CA, USA). Rigorous quality control procedures were performed on the genotyped markers and individuals. Non-genotyped markers were imputed using the 1000 Genomes-V3-phase I reference panel (see Supplementary Methods).

2.2. Vascular Pathology Markers

Markers of vascular pathologies were measured with standard protocols and assessed by well-trained raters (see Supplementary Methods). We systematically examined cerebrovascular and cardiovascular markers in our analyses, including lobar CMB (binary; multiple [>=2] versus non-multiple [0 or 1]), WML load (binary; the highest quartile versus the lower three), RVD (continuous), CIMT (continuous; log-transformed), and CAC (continuous; log-transformed).

2.3. Measures of Cognitive Function

Participants received a comprehensive cognitive assessment battery including tests of memory, executive function, and processing speed. Based on the scores of domain-specific cognitive tests, we calculated the Z-score of the composite memory score and the Z-score of the composite global cognition score, as the main cognitive outcomes for our analyses (see Supplementary Methods and Supplementary Figure S2).

2.4. Other Covariates

Other covariates used in the analyses included age, sex, education, smoking status, midlife physical activity, diet quality, prevalent diabetes, hypertension, high LDL level, and obesity (see Supplementary Methods).

2.5. Polygenic Risk Scores for AD Dementia (ADPRS)

2.5.1. Genome-wide ADPRS (GW-ADPRS)—We used the summary statistics from the Alzheimer's Disease Genetics Consortium (ADGC) GWAS (8,309 AD cases and 7,366 controls of European ancestry) [32] as the discovery dataset to calculate GW-ADPRS in our study sample. We applied an LD clumping procedure to the discovery datasets, retaining the SNP with smallest P-value in each 250kb window and removed all those in LD ($r^2 > 0.2$) with this SNP. We used three association P-value thresholds (P_Ts), 0.0001, 0.001, and 0.01, to select index SNPs from the clumped independent SNPs for generating the PRSs. For each individual, and each P_T, we calculated GW-PRS by summing the risk allele counts of the index SNPs, weighted by the log of their association odds ratios estimated from the ADGC GWAS results.

2.5.2. 19q13-ADPRS and non-19q13-ADPRS—Because *APOE* is the strongest risk gene for AD dementia, we further partitioned the GW-ADPRS into an *APOE region* score and a *non-APOE* region score to separately assess the polygenic effects of SNPs in the APOE-linkage region 19q13 (ch19:4500000–4580000) and all other SNPs. We followed the same steps as for the calculation of the GW-ADPRS to generate a 19q13-ADPRS (the summation of log-odds-ratio weighted risk allele counts of the index SNPs in the 19q13 region) and a non-19q13-ADPRS (the summation of log-odds-ratio weighted risk allele counts of the index SNPs across whole genome except 19q13) for each individual.

2.6. Data Analysis

2.6.1. Phenotypic associations of vascular markers with cognition—We used univariate and multivariate linear regressions to assess the associations of each vascular marker with the cognitive outcomes. Multivariate models adjusted for age, sex, education, diabetes, hypertension, high LDL level, obesity, physical activity, diet quality, and smoking status.

2.6.2. Association of ADPRS with vascular and cognitive phenotypes—We examined if any of the P_Ts generates an ADPRS significantly associated with each of the cognitive outcomes and vascular pathologies. We used linear (for continuous phenotypes) or logistic (for binary phenotypes) regression models to test the association of each phenotype

with each of GW-ADPRS, 19q13-ADPRS, and non-19q13-ADPRS, adjusting for age and sex. The Wald test P-value for each association test was reported, and squared semi-partial correlations (R^2) were calculated to estimate the proportion of variance explained by the PRSs. We used Bonferroni correction to adjust for multiple testing (see Supplementary Methods).

2.6.3. Causal Mediation Analyses—We performed mediation regression analyses [33], based on the counterfactual framework for causal inference [34], to examine how much of the effect of an ADPRS on cognition score was mediated by a vascular pathology observed to be genetically correlated with AD dementia.

For each ADPRS (GW-ADPRS, 19q13-ADPRS, or non-19q13-ADPRS) as the predictor, we estimated the direct and indirect (mediated) effects of each vascular pathology as the mediator, and Z-score of the composite memory or global cognition score as the outcome. In order to gain more statistical power, the ADPRS predictors used in the mediation analyses were those with the P_T that showed the highest association with each cognitive outcome. We adjusted for potential mediator-outcome confounders, including age, sex, smoking status, midlife physical activity, diet quality, and other genetic risk scores if necessary. A counterfactual outcome variable denotes the outcome that would have been observed had a predictor been set to a particular value. In order to compare high and low values of each ADPRS in our estimates of the direct and the indirect effects, we chose to compare the 75^{th} percentile and the 25^{th} percentile of each.

Finally, we conducted sensitivity analyses of unmeasured confounding and the choice of 75^{th} versus 25^{th} percentile comparison (see Supplementary Methods).

All the mediation analyses were performed by using the PARAMED module in STATA [35]. We used bootstrap procedures with 200 replications to compute a 95% bias-corrected bootstrap confidence interval (95% BCCI) for the direct and indirect effects.

3. RESULTS

3.1. Sample Characteristics

Table 1 presents descriptive statistics for the AGES sample used here. The mean age of all subjects without stroke or vascular dementia (n=5,161) was 76.7 (5.8) years. Vascular pathologies were relatively rare: for example, only 2% had multiple lobar CMB. Subjects with genotype data available (n=2,907) were similar to the full sample but had somewhat lower coronary calcification score (with vs. without genotypes; Mann Whitney U test, P=0.01).

3.2. Phenotypic Associations

Table 2 presents phenotypic associations between each vascular pathology and cognitive outcomes. All unadjusted associations were significant. After adjusting for potential confounders, CMB, CAC, and WML were significantly associated with memory score, whereas the former two were significantly associated with global cognition score.

3.3. Associations of GW-ADPRS with Cognitive or Vascular Phenotypes

Results are shown in Figure 1 and Table 3. Lower memory score was significantly associated with higher GW-ADPRS with a P-value threshold of 0.0001 ($GW\text{-}ADPRS_{PT = 0.0001}$; P = 0.006, R^2 = 0.22%) and higher GW-ADPRS with a P-value threshold of 0.01 ($GW\text{-}ADPRS_{PT = 0.01}$; P = 0.001, R^2 = 0.29%), after the Bonferroni correction. We also found nominal associations of lower global cognition score with higher $GW\text{-}ADPRS_{PT = 0.0001}$ and higher $GW\text{-}ADPRS_{PT = 001}$. In terms of the association between the GW-ADPRSs and vascular pathologies, we found that higher GW-ADPRS at all three P_T were nominally associated with multiple lobar CMB. There were also nominal associations between higher $GW\text{-}ADPRS_{PT = 0.01}$ and greater WML and between higher $GW\text{-}ADPRS_{PT = 0.0001}$ and higher CAC.

3.4. Associations of 19q13-ADPRS and non-19q13-ADPRS with Cognitive or Vascular Phenotypes

Our data showed that higher 19q13-ADPRS at all three P_Ts were significantly associated with having lobar CMB. We also found nominal associations of higher 19q13-ADPRS with greater WML, higher CAC, and poorer performance on both cognitive outcomes (Table 3). For non-19q13-ADPRS, the only association was that between higher non-19q13-$ADPRS_{PT = 0.01}$ and lower memory score (Table 3).

3.5. Mediation Analyses

The PRS that most associated with each cognitive outcome was selected as the predictor ($GW\text{-}ADPRS_{PT = 0.01}$, $19q13\text{-}ADPRS_{PT = 0.001}$, and non-$19q13\text{-}ADPRS_{PT = 0.01}$ for memory; $GW\text{-}ADPRS_{PT = 0.0001}$, $19q13\text{-}ADPRS_{PT = 0.001}$, non-$19q13\text{-}ADPRS_{PT = 0.01}$ for global cognition). Vascular pathologies with a p-value lower than 0.05 for PRS associations with AD dementia were tested as potential mediators (CMB, WML, and CAC).

Results are shown in Table 4. The proportion mediated (PM) was obtained by dividing the estimated indirect effect by the estimated total effect, as an index of the degree of mediation. The total effect of GW-ADPRS on memory score was significantly mediated by multiple lobar CMB and WML load. CMB, WML, and CAC were all identified as significant mediators of the effects of GW-ADPRS on global cognition score. The total effect of 19q13-ADPRS on memory score was significantly mediated by CMB and WML, and its effect on global cognition was mediated by CMB, WML, and CAC. The total effect of non-19q13-ADPRS on both memory and global cognition was mediated by CMB.

When an interaction between the PRS and the vascular mediator was included in each mediation model, there was very little change in the estimated direct and indirect effects, so we decided not to include the interaction in the mediation models, as suggested by Vanderweele [33].

3.6. Sensitivity Analyses

Sensitivity analyses of unmeasured confounding suggest that under the seemingly more likely scenarios of unmeasured confounders associated with better cognition and less severe vascular pathology, or unmeasured confounders associated with poorer cognition and more

severe vascular pathology, our estimated PMs would underestimate the true mediation effects of vascular pathologies (see Figure 2, Supplementary Results, Table S1, and Figure S3). Sensitivity analyses for selection of predictor levels for comparison found that mediation analyses comparing the effects of the 90th percentile and the 10th percentile of each ADPRS yielded very similar PMs as those shown in Table 4 (see Supplementary Table S2).

4. DISCUSSION

In a community-based sample of 5,161 stroke-free older individuals, we found that multiple lobar CMB, higher WML load, and greater CAC --but not RVD nor CIMT--were associated with poorer late-life memory and global cognition. In the 2,907 genotyped individuals, we found that a higher genetic risk score for AD dementia, driven primarily by *APOE,* was associated with these three vascular pathologies and two cognition outcomes. In mediation analyses, we found that the effects of *APOE* and SNPs near *APOE* on memory may be partially mediated by CMB and WML, and their effects on global cognition may be partially mediated by CMB, WML, and CAC. With the possible exception of CMB, there was little evidence of an effect of *non-APOE* AD dementia-associated alleles on either memory or global cognition.

In a relatively large sample of older adults, our phenotypic analyses replicated previously reported phenotypic associations of cerebral SVD [36, 37] and atherosclerosis [18]with cognitive function. We further examined if shared genetic factors contribute to these associations, and found genetic overlap between AD dementia, vascular pathologies, and late-life cognition (Table 3 and Figure 1). Our data showed that lobar CMB, WML load, and CAC score were associated with GW-ADPRS, and were even more strongly associated with 19q13-ADPRS. Our findings of the strongest genetic overlap between AD dementia and CMB are consistent with recently reported genetic correlation between AD and cerebral SVD but not LVD [28]. Lobar CMB may be caused by CAA [38, 39], which is highly prevalent in post-mortem analyses of brains of persons with clinical diagnosis of AD dementia [40]. In addition, the APOE-e4 allele has been associated with the presence of CAA [41, 42]. These previous findings support the possible genetic overlap between lobar CMB and AD dementia observed in our data. Since WML [43] and CAC [44] may share some common risk factors with CMB, and both have been related to dementia (although the evidence is not as strong as that for CMB), a genetic overlap of AD dementia with WML and CAC makes sense. On the other hand, we found no association between ADPRS and RVD, which has been reported as an indicator of cerebral small-vessel pathology [12] and a predictor of dementia [11]. One possible explanation is that the central retinal venular equivalent is observer-dependent and may not accurately reflect the degree of retinal venular dilatation, but there is no indication of even an attenuated signal.

Our results suggest that the *APOE* gene explains most of the SNP-based genetic overlap of AD dementia with the vascular pathologies (see Supplementary Methods and Results on ‘Conditional Regression Analyses’ and Supplementary Table S6). *APOE* has been related to cerebrovascular dysfunction by affecting cerebral blood flow, blood-brain-barrier integrity, and neuronal-vascular coupling [45]. As mentioned above, the *APOE-e4* allele is a risk

factor for CAA [41, 42]. In terms of peripheral vascular disease, *APOE* has been shown to be an important factor in the development of hyperlipoproteinemia and atherosclerosis [45, 46]. Our data also showed no association between the non-19q13-ADPRS and any of the examined vascular pathologies, despite previously reported associations of non-APOE AD risk genes with inflammation and abnormal lipid metabolism, which are both risk factors for vascular disease [47]. Future research with larger samples are needed to test for association between vascular pathologies and AD dementia-associated alleles outside of the APOE-linkage region.

In our sample, we observed associations of the APOE-ADPRS with both memory and global cognition, whereas the non-APOE-ADPRS was associated with memory, but not global cognition. A previous meta-analysis including 77 studies of the association between *APOE* and cognitive function suggested that carriers of *APOE-e4* performed worse on multiple domains of cognitive tests, including memory, executive functioning, perceptual speed, and overall global cognition [48]. On the other hand, non-APOE-ADPRS calculated by using summary statistics from the International Genomics of Alzheimer's Project (IGAP) was found to be associated with memory impairment but not executive function in non-demented subjects, with mean age of 75.3 years, in the Alzheimer's Disease Neuroimaging Initiative (ADNI) [49]. It is possible that impaired memory was more likely to be detected than deficits in other cognitive domains for individuals in the early stage of cognitive decline. However, more research is needed on the relationship between specific genes and different domains of cognitive function.

Having established a SNP-based genetic overlap between AD dementia, vascular pathologies, and late-life cognition, we then sought to identify the causal relationships between ADPRS, vascular pathologies, and cognition scores. Our findings indicate that AD dementia-associated SNPs affect late-life cognition partially through pathways involving vascular pathologies, providing insight into potential pathogenic mechanisms in clinical AD dementia. The results also may lend further support to interventions to reduce vascular pathologies may be of value in the prevention of AD dementia. It is worth noting that we separately examined the mediation effects of CMB, WML, and CAC. Although measures of these vascular pathologies were correlated with each other, their correlations were relatively weak in our sample (Kendall's tau-b=0.07 for CMB-WML, Point-Biserial correlation coefficient=0.08 for CMB-CAC and 0.12 for WML-CAC). Thus, it is reasonable to believe that a certain proportion of AD dementia-associated SNP effects on cognitive function were mediated by vascular pathologies when considering all vascular mediators together.

The only previous study investigating the mediation role of cerebrovascular imaging markers between genetic variants and cognitive function, which used an overlapping sample from the same cohort (the AGES-Reykjavik), reported that about 9% of the total effect of *APOE4* carriership on global cognition was mediated by CMB and WML volume together [30]. Our analyses revealed similar but stronger mediation effect of vascular pathologies on the relationship between SNPs and cognition. The major strength of the present study is that we assessed the effects of PRS, aggregating multiple possible risk alleles for AD across the whole genome, within or beyond the APOE-linkage region, weighted by their estimated effect sizes. Moreover, we considered both cerebral small-vessel and systemic large-vessel

imaging markers, which have been previously associated with dementia or poor cognition, as potential mediators.

Several limitations in the present study should be noted. In the population-based sample, in which most subjects were cognitively normal or mildly impaired, mean scores of cognitive tests reflect both lifelong cognitive variability and recent pathological changes, and the former may overwhelm the latter. However, with our relatively large sample size, we were able to detect small signals and parse these signals into what appear to be meaningful mediation relationships. Nonetheless, the sample may have only been large enough to detect ^POF-related signals, even if other causal SNPs are present. In any event, in the setting of small signals, another major limitation is the possible violation of the no-unmeasured-confounding assumption necessary for causal mediation analyses. However, our sensitivity analyses suggest that given the expected direction of unmeasured confounding, our estimated indirect effects may underestimate the true mediated effects. In addition, the ADPRS, including only common genetic variants, cannot account for all the genetic effects on cognitive performance and AD dementia. Although our SNP-based PRS were strongly associated with vascular and cognitive phenotypes, and PRS for AD dementia has been reported to be capable of capturing nearly all common genetic risk for AD [50], there are still causal genomic variants (e.g., rare variants) that are not well-tagged by GWAS SNPs. However, the genetic effects not captured by SNP-based risk scores can also be seen as a type of unmeasured mediator-outcome confounding. Therefore, the sensitivity analyses mentioned above may help minimize these concerns. Finally, although our use of causal mediation analysis appears to imply mechanistic causality, we note that our design is ultimately correlational. In future research, an experimental-causal-chain approach may help to develop a more fundamental understanding of causal mechanisms.

This is the first study, to our knowledge, that combined polygenic profiling and causal mediation methods to identify the causal relationship between two genetically correlated phenotypes and their shared genetic factors. Our findings support the hypothesis of a genetic overlap, mostly due to *APOE,* between AD dementia and vascular pathologies, especially SVD. Our results also showed that in older individuals, CMB, WML, and CAC may causally affect cognitive function and partially mediate the polygenic effects of AD-related genes on cognition, underscoring the potential role of vascular factors in cognitive decline, and suggesting vascular pathologies as a target for future mechanistic research in this area.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Research in Context

Systematic review:

A large literature, updated with a recent PubMed search, includes extensive epidemiological and neuropathological evidence suggesting shared mechanisms between vascular pathologies and Alzheimer's disease (AD) dementia. However, few studies have examined their polygenic overlap, and no published research has focused on whether vascular pathologies mediate the relationship between AD-associated genes and late-life cognition.

Interpretation:

Our findings support the hypothesis of a genetic overlap, mostly due to *APOE,* between AD dementia and vascular pathologies. The cumulative effect of AD-related genes on late-life cognition was partially but significantly mediated by cerebral microbleeds, white matter lesions, and coronary calcification, underscoring the potential role of vascular factors in cognitive decline.

Future directions:

These results should be confirmed in larger samples. Research is also needed on the relationship of specific genes and pathways with different domains of cognitive function. In the meantime, these findings suggest vascular pathologies as a target for future mechanistic research on AD.

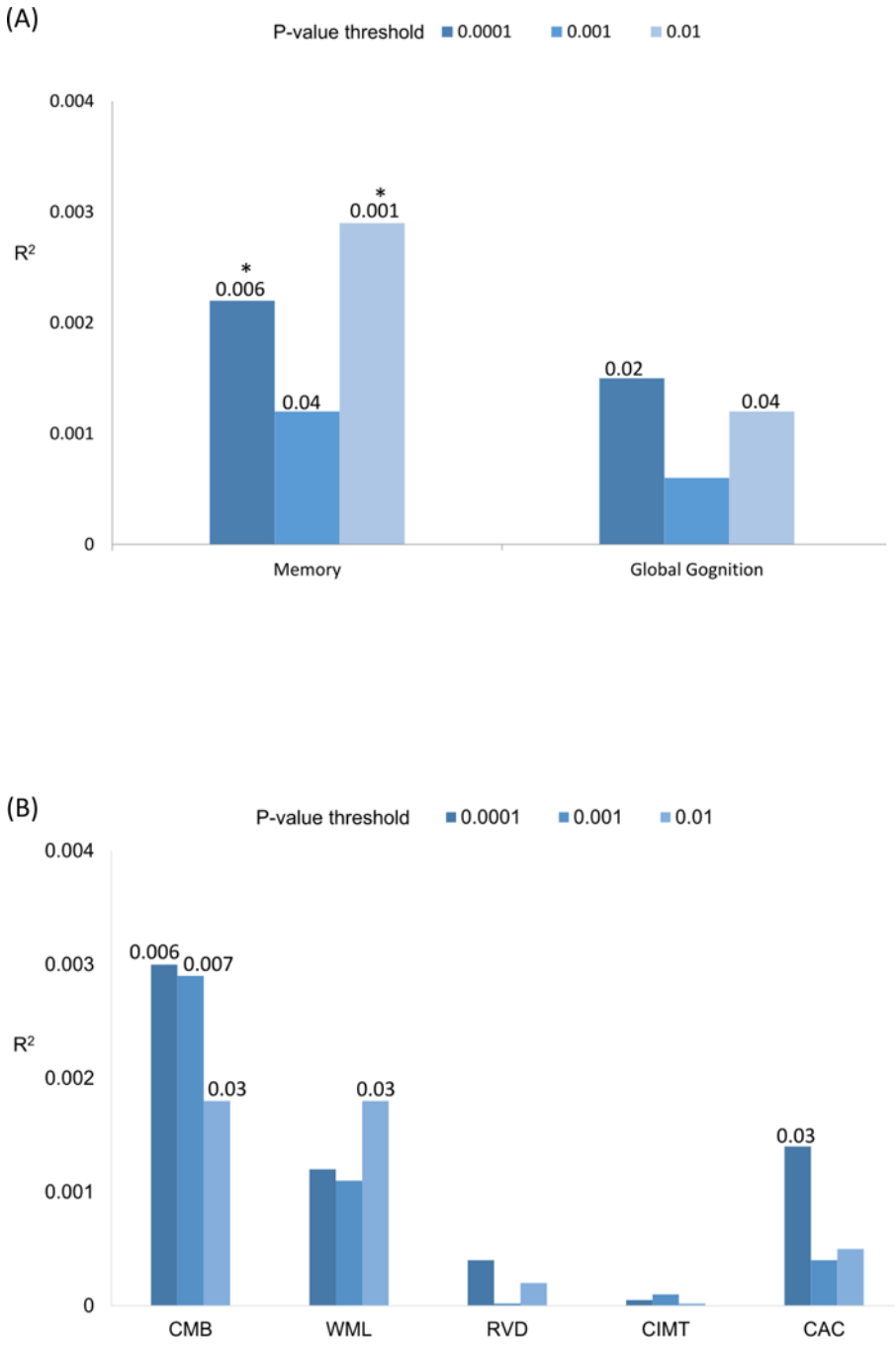

Figure 1. Pair-wise polygenic association analyses between GW-ADPRS and (A) cognition scores, (B) vascular pathologies

We derived genome-wide PRS for AD dementia using ADGC GWAS as the discovery sample with three different P-value thresholds (PT used to select training set SNPs: 0.0001, 0.001, and 0.01) and apply them to (A) Z-score of the composite memory or global cognition score; and (B) each of the markers of vascular pathologies. Age and sex were included as covariates in the association analyses.

Each pair is shown on the x-axis and the proportion of variance explained for each phenotype (estimated via partial correlation R^2) on the y-axis.

Unadjusted P-values are shown on the top of the bars if < 0.05.
An asterisk indicates Bonferroni-corrected P-value < 0.05.

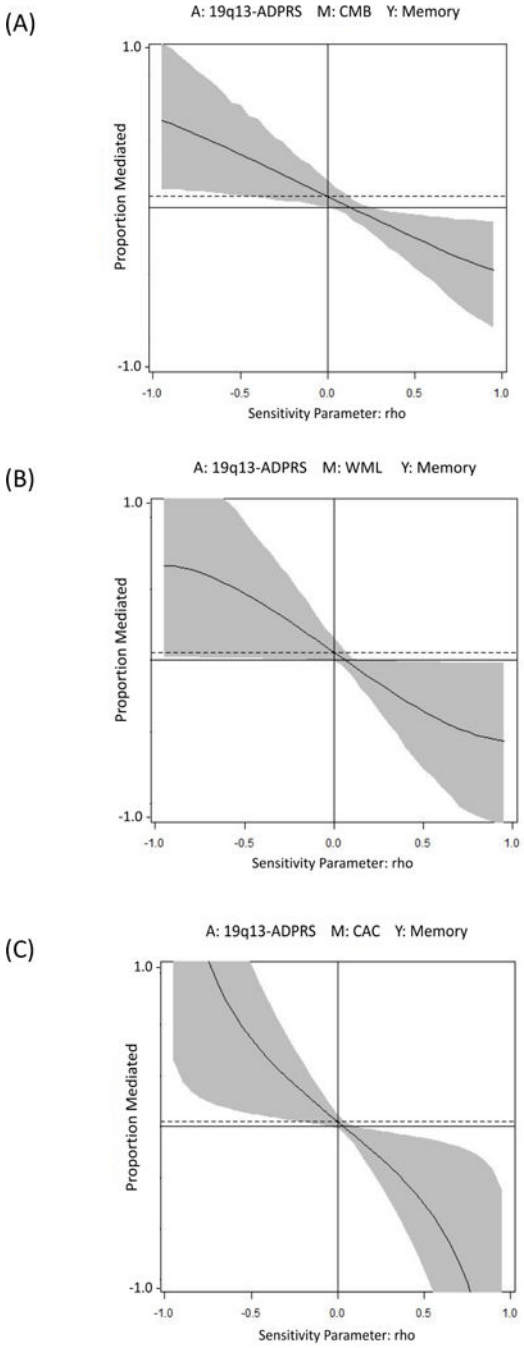

Figure 2. Sensitivity analyses of unmeasured confounding for the relationship between 19q13-ADPRS and memory score mediated by (A) CMB, (B) WML, or (C) CAC

Figure 2 presents how the PM would change if unmeasured confounding of a specified direction and magnitude is allowed for in the mediation relationship between 19q13-ADPRS, vascular markers, and memory score. Detailed results of sensitivity analyses of unmeasured confounding for all other mediation analyses are described in Supplementary Results, Table S1, and Figure S3.

A: predictor; 19q13-ADPRS

M: mediator; (A) CMB, (B) WML, or (C) CAC

Y: outcome; memory score

The y-axis is the proportion mediated The x-axis, denoted by rho, is the degree of hypothetical unmeasured confounding, estimated by the size of the correlation between the residuals in the equation predicting M and the equation predicting Y. The larger the absolute value of rho, the stronger the confounding.

The solid curve shows the estimated proportion mediated for different values of the correlation between the residuals in equations. The shaded part of the plot represents the 95% intervals surrounding the mediated effect. The x-intercept represents the value of rho at which proportion mediated equals to 0.

The horizontal broken line denotes the proportion mediated without considering unmeasured confounding. When rho is equal to zero, the reported proportion mediated is the same as that we estimated in the mediation analysis without considering unmeasured confounding. For other values of rho, the proportion mediated is calculated under different levels of unobserved confounding. When rho<0, which means there is unmeasured confounding associated with better cognition and less severe vascular pathology or unmeasured confounding associated with poorer cognition and more severe vascular pathology (seemly more likely), our estimated PMs would underestimate the true mediation effects of vascular pathologies.

Table 1.

Descriptive statistics of demographic and clinical characteristics

Characteristics	All subjects (N=5161)	Subjects with genotype data (N=2907)
Demoaraphic		
Age at AGES I (years), *mean (SD)*	76.73 (5.83)	76.20 (5.43)
Sex		
Female, *N (%)*	3022 (58.6)	1706 (58.7)
Education		
Secondary, *N (%)*	2406 (49.9)	1441 (49.7)
College, *N (%)*	755 (15.7)	451 (15.6)
University, *N (%)*	547 (11.4)	334 (11.5)
Vascular Patholoaies, Baseline Lobar cerebral microbleeds		
Count>=2, *N(%)*	110 (2.1)	69 (2.7)
White matter lesion load, *median(Q1, Q3)*	1.91 (0.51, 5.64)	1.92 (0.50, 5.59)
Central retinal venular equivalent, *mean(SD)*	202.19 (19.56)	202.14 (19.50)
Carotid intima-media thickness, *median(Q1,Q3)*	0.97 (0.88, 1.06)	0.97 (0.88, 1.06)
Coronary calcification score, *median(Q1, Q3)*	271.23 (43.61, 898.78)	253.52 (38.94, 841.53)
Other Covariates, Baseline Midlife physical activity		
Intermediate, *N(%)*	2166 (46.6)	1327 (47.5)
Poor, *N(%)*	909 (19.5)	524 (18.8)
Diet quality		
Intermediate, *N(%)*	4011 (84.6)	2418 (84.8)
Poor, *N(%)*	354 (7.5)	205 (7.2)
Smoking		
Ever, *N(%)*	2111 (43.9)	1303 (44.8)
Current, *N(%)*	593 (12.3)	372 (12.8)
Diabetes, *N(%)*	640 (12.4)	324 (11.2)
Hypertension		
Prehypertension, *N(%)*	758 (14.8)	445 (15.3)
Hypertension, *N(%)*	4112 (80.3)	2318 (79.8)
LDL level >=130 mg/dL, *N(%)*	2830 (54.9)	1643 (56.6)
BMI>=30, *N(%)*	1139 (22.3)	642 (22.1)

Subjects with GWAS genotype data available (n=2,907) had lower coronary calcification score than those without genotype data (n=2,254) (Mann-Whitney U test, P=0.01). No significant difference was observed in the distribution of any other characteristic listed in the Table between subjects with and without genotype data available.

Table 2.

Phenotypic associations between vascular pathologies and late-life cognitive function

Vascular pathologies	Memory				Global Cognition			
	Unadjusted		Adjusted		Unadjusted		Adjusted	
	Beta (S.E.)	P	Beta (S.E.)	P	Beta (S.E.)	P	Beta (S.E.)	P
Lobar CMB	−0.368 (0.097)	1.5E-04*	−0.187 (0.086)	0.03*	−0.443 (0.100)	8.9E-06*	−0.268 (0.083)	0.001*
WML	−0.193 (0.036)	1.1E-07*	−0.070 (0.033)	0.03*	−0.244 (0.037)	6.0E-11*	−0.060 (0.032)	0.06
RVD	0.002 (0.001)	0.01*	−0.001 (0.001)	0.53	0.003 (0.001)	0.001*	0.0004 (0.0007)	0.56
CIMT	−1.110 (0.105)	6.3E-26*	−0.107 (0.102)	0.29	−1.004 (0.109)	4.5E-20*	0.073 (0.099)	0.46
CAC	−0.086 (0.006)	1.5E-46*	−0.015 (0.006)	0.01*	−0.087 (0.006)	2.4E-45*	−0.023 (0.006)	7.8E-05*

Lobar CMB: Multiple lobar cerebral microbleeds; count >=2 vs. 0 or 1.

WML: White matter lesion load; highest quartile vs. other three quartiles of the total volume of white matter lesions. RVD: Retinal venular diameter; represented by central retinal venular equivalent, continuous.

CIMT: Carotid intima-media thickness; log-transformed, continuous.

CAC: Coronary artery calcification score; log-transformed, continuous.

All multivariate models adjusted for age, sex, education, diabetes, hypertension, high LDL level, obesity, physical activity, diet quality, and smoking status.

*Asterisk indicates significance at P<0.05.

If all potential confounders remain constant, those with multiple lobar CMB had, on average, 0.19 SD lower memory score and 0.26 SD lower global cognition score than those with 0 or 1 lobar CMB. Individuals in the highest quartile of WML load had 0.07 SD lower memory score than others. For each one-unit increase in log-transformed CAC, the mean memory and global cognition scores declined by 0.015 SD and 0.023 SD, respectively.

Table 3.

Associations between polygenic risk scores for AD dementia and each target phenotype

PRS for AD dementia			Cognitive Outcomes		Vascular Marker Mediators				
Genomic region	**P-threshold**	**nSNP**	**Memory (n=2752)**	**Global Cognition (n=2582)**	**Lobar CMB (n=2562)**	**WML (n=2559)**	**RVD (n=2682)**	**CIMT (n=2777)**	**CAC (n=2869)**
GW-ADPRS	$P_T < 0.0001$	190	R^2=0.0022 P=0.006†	R^2=0.0015 P=0.02	R^2=0.0030 P=0.006*	R^2=0.0012 P=0.07	R^2=0.0004 P=0.29	R^2<0.0001 P=0.71	R^2=0.0014 P=0.03*
	$P_T < 0.001$	1342	R^2=0.0012 P=0.04*	R^2=0.0006 P=0.14	R^2=0.0029 P=0.007*	R^2=0.0011 P=0.09	R^2<0.0001 P=0.90	R^2=0.0001 P=0.61	R^2=0.0004 P=0.24
	$P_T < 0.01$	8918	R^2=0.0029 P=0.001†	R^2=0.0012 P=0.04*	R^2=0.0018 P=0.03*	R^2=0.0018 P=0.03*	R^2=0.0002 P=0.49	R^2<0.0001 P=0.99	R^2=0.0005 P=0.19
19q13-ADPRS	$P_T < 0.0001$	40	R^2=0.0015 P=0.02*	R^2=0.0013 P=0.04*	R^2=0.0038 P=0.002†	R^2=0.0014 P=0.05	R^2=0.0003 P=0.40	R^2=0.0002 P=0.46	R^2=0.0012 P=0.04*
	$P_T < 0.001$	54	R^2=0.0015 P=0.02*	R^2=0.0013 P=0.04*	R^2=0.0035 P=0.003†	R^2=0.0018 P=0.03*	R^2=0.0002 P=0.48	R^2=0.0002 P=0.48	R^2=0.0015 P=0.02*
	$P_T < 0.01$	76	R^2=0.0012 P=0.04*	R^2=0.0011 P=0.06	R^2=0.0040 P=0.002†	R^2=0.0019 P=0.02*	R^2=0.0002 P=0.46	R^2=0.0003 P=0.30	R^2=0.0015 P=0.02*
Non-19q13-ADPRS	$P_T < 0.0001$	150	R^2=0.0008 P=0.10	R^2=0.0002 P=0.39	R^2<0.0001 P=0.94	R^2<0.0001 P=0.82	R^2=0.0002 P=0.50	R^2=0.0001 P=0.50	R^2=0.0001 P=0.49
	$P_T < 0.001$	1288	R^2=0.0002 P=0.45	R^2<0.0001 P=0.81	R^2=0.0004 P=0.30	R^2=0.0001 P=0.68	R^2=0.0001 P=0.67	R^2<0.0001 P=0.94	R^2<0.0001 P=0.71
	$P_T < 0.01$	8842	R^2=0.0020 P=0.008†	R^2=0.0006 P=0.15	R^2=0.0005 P=0.27	R^2=0.0008 P=0.14	R^2=0.0004 P=0.31	R^2<0.0001 P=0.70	R^2=0.0001 P=0.59

P-threshold (P_T): the P-value threshold used in the training dataset to select SNPs for calculating the PRS for AD dementia. nSNP: different number of independent SNPs included for calculating the PRS for AD dementia, which is determined by the selection of P_T.

Lobar CMB: lobar cerebral microbleeds (count >=2 vs. 0 or 1).

WML: total brain white matter lesion load (highest quartile vs. other three quartiles of the total volume of white matter lesions).

RVD: the average retinal venular diameter, represented by central retinal venular equivalent (continuous).

CIMT: mean of carotid intima-media thickness (log-transformed, continuous).

CAC: coronary artery calcification score (log-transformed, continuous).

R^2: squared semi-partial correlation, the proportion of variance in the target phenotype explained by the PRS for AD dementia.

P: the P-value of the test for association between the PRS and the target phenotype, before multiple testing correction.

Associations were tested using linear (for continuous phenotype) or logistic (for binary phenotype) regression models with age and sex as covariates.

The missing data status of each vascular marker was associated neither with memory / global cognition scores nor with any of the PRS (all P > 0.20).

*An asterisk indicates significance at P-value <0.05.

†A dagger indicates significance after Bonferroni-correction. We considered a PRS-wise significant threshold for the correction of multiple comparisons (P< 0.008, after Bonferroni correction for the 6 association tests between 2 cognitive outcomes and 3 ADPRS for each genomic region; and P<0.003, Bonferroni correction for the 15 association tests between 5 vascular pathologies and 3 ADPRS).

Table 4.

Total, direct and indirect effects of PRS for AD dementia on late-life cognitive function mediated by vascular pathologies

			Memory				Global Cognition			
Predictor	**Mediator**	**N**	**Total effect (95% BCCI)**	**Direct effect (95% BCCI)**	**Indirect effect (95% BCCI)**	**PM**	**Total effect (95% BCCI)**	**Direct effect (95% BCCI)**	**Indirect effect (95% BCCI)**	**PM**
GW-ADPRS	CMB	2308	−.074 (−.117, −.025)	−.072 (−.115, −.023)	−.002 (−.006, −.001)	3.2% *	−.038 (−.081, .008)	−.034 (−.076, .013)	−.004 (−.009, −.002)	10.8% *
	WML	2307	−.078 (−.124, −.033)	−.076 (−.123, −.032)	−.002 (−.007, −.00004)	2.7% *	−.041 (−.087, .011)	−.039 (−.085, .013)	−.002 (−.006, −.0003)	4.0% *
	CAC	2577	−.069 (−.112, −.023)	−.067 (−.110, −.022)	−.001 (−.006, .0001)	1.6%	−.048 (−.093, −.003)	−.046 (−.092, −.001)	−.002 (−.006, −.0001)	4.4% *
19q13-ADPRS	CMB	2308	−.038 (−.087, .013)	−.035 (−.085, .017)	−.003 (−.008, −.001)	7.4% *	−.036 (−.090, .009)	−.032 (−.079, .015)	−.004 (−.013, −.001)	11.3% *
	WML	2307	−.043 (−.091, .007)	−.041 (−.088, .010)	−.002 (−.008, −.0004)	5.6% *	−.040 (−.091, .008)	−.038 (−.088, .012)	−.002 (−.007, −.0002)	4.8% *
	CAC	2577	−.048 (−.096, −.001)	−.046 (−.093, .002)	−.002 (−.005, .0004)	3.6%	−.048 (−.100, −.003)	−.045 (−.096, −.0004)	−.002 (−.006, −.0001)	5.0% *
Non-19q13ADPRS	CMB	2308	−.068 (−.118, −.022)	−.067 (−.116, −.020)	−.001 (−.005, −.0001)	2.1% *	−.028 (−.075, .016)	−.026 (−.074, .019)	−.002 (−.006, −.0001)	7.5% *
	WML	2307	−.070 (−.115, −.022)	−.069 (−.114, −.021)	−.001 (−.005, .0003)	2.0%	−.029 (−.075, .017)	−.028 (−.073, .018)	−.001 (−.005, .0003)	3.7%
	CAC	2577	−.058 (−.102, −.013)	−.057 (−.101, −.012)	−.001 (−.004, .001)	0.9%	−.031 (−.078, .015)	−.031 (−.077, .015)	−.001 (−.004, .001)	2.2%

Predictor: GW-ADPRS, 19q13-ADPRS, and non-19q13-ADPRS (the 75th percentile vs. the 25th percentile).

Mediator: CMB (lobar cerebral microbleeds; >=2 vs. 0 or 1), WML (total brain white matter lesion load; highest quartile vs. other three quartiles of the total volume of white matter lesions), or CAC (coronary artery calcification score; log-transformed, continuous).

Outcome: z-score of the memory composite score (left panel) or z-score of the global cognition composite score (right panel).

Values for total, direct and indirect effects indicate changes in each outcome.

BCCI: bias-corrected confidence interval.

PM: proportion mediated=indirect effect beta coefficient/ total effect beta coefficient. An asterisk indicates that the PM is significantly greater than 0. Models for the effects of GW-PRS adjusted for age, sex, smoking status, midlife physical activity, and diet quality.

Models for the effects of 19q13-ADPRS adjusted for age, sex, smoking status, midlife physical activity, diet quality, and non-19q13-ADPRS.

Models for the effects of non-19q13-ADPRS adjusted for age, sex, smoking status, midlife physical activity, diet quality, and 19q13-ADPRS.

*An asterisk indicates that the estimated indirect effect is significantly different from zero at the 5% level.