

## RESEARCH ARTICLE

# A genome-wide association meta-analysis of all-cause and vascular dementia

## The Mega Vascular Cognitive Impairment and Dementia (MEGAVCID) consortium

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[Correction added on July 26, 2024, after first online publication: The byline was revised to list only the consortium name. Bernard Fongang is acting as the contact for correspondence for the consortium and had been incorrectly listed in the byline.]

### Funding information

National Heart, Lung, and Blood Institute, Grant/Award Numbers: R01HL105756, RC2HL102419; National Institute on Aging, Grant/Award Number: AG033193; UT Health San Antonio Center for Biomedical Neuroscience, Grant/Award Numbers: AG059421, AG054076, AG049607, AG033090, AG066524, P30 AG066546, 5P30AG059305-03, RF1 AG061729A1, 5U01AG052409-04; NINDS, Grant/Award Numbers: NS017950, UF1NS125513, K01NS126489

### Abstract

**INTRODUCTION:** Dementia is a multifactorial disease with Alzheimer's disease (AD) and vascular dementia (VaD) pathologies making the largest contributions. Yet, most genome-wide association studies (GWAS) focus on AD.

**METHODS:** We conducted a GWAS of all-cause dementia (ACD) and examined the genetic overlap with VaD. Our dataset includes 800,597 individuals, with 46,902 and 8702 cases of ACD and VaD, respectively. Known AD loci for ACD and VaD were replicated. Bioinformatic analyses prioritized genes that are likely functionally relevant and shared with closely related traits and risk factors.

**RESULTS:** For ACD, novel loci identified were associated with energy transport (*SEMA4D*), neuronal excitability (*ANO3*), amyloid deposition in the brain (*RBFox1*), and magnetic resonance imaging markers of small vessel disease (SVD; *HBEGF*). Novel VaD loci were associated with hypertension, diabetes, and neuron maintenance (*SPRY2*, *FOXA2*, *AJAP1*, and *PSMA3*).

**DISCUSSION:** Our study identified genetic risks underlying ACD, demonstrating overlap with neurodegenerative processes, vascular risk factors, and cerebral SVD.

### KEYWORDS

all-cause dementia, Alzheimer's disease, cross-ancestry, genome-wide association study (GWAS), GWAS meta-analysis, vascular dementia

### Highlights

- We conducted the largest genome-wide association study of all-cause dementia (ACD) and vascular dementia (VaD).
- Known genetic variants associated with AD were replicated for ACD and VaD.
- Functional analyses identified novel loci for ACD and VaD.
- Genetic risks of ACD overlapped with neurodegeneration, vascular risk factors, and cerebral small vessel disease.

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## 1 | BACKGROUND

Traditionally, Alzheimer's disease (AD) is considered the most common dementia subtype, followed by vascular dementia (VaD). The two conditions are considered clinically distinct. VaD is diagnosed based on the presence of stroke or extensive cerebral vascular disease, with atherosclerosis and arteriosclerosis considered the underlying pathologies.<sup>1</sup> However, a wealth of evidence from recent years has emphasized a broad role for brain vascular damage, beyond that of lacunar and larger cerebral infarcts, as a major mechanism for cognitive impairment.<sup>2</sup> It is now increasingly recognized that a component of vascular pathology is prominent in all major dementias and acts synergistically with amyloid beta ( $A\beta$ ), tau, and other neurodegenerative pathologies to affect dementia risk.<sup>3</sup> Moreover, a new hypothetical model of dementia dynamics suggests that damage to brain vasculature is an early process in the dementia continuum that precedes brain atrophy, neurodegeneration, and the emergence of amyloid and tau biomarker abnormalities.<sup>4</sup> Recent genetic studies using methods that are relatively immune to reverse causation also suggest a putative causal relationship between brain imaging markers of cerebral small vessel disease (SVD) and AD.<sup>5</sup>

Hence there is a strong rationale to examine the "vascular contributions to cognitive impairment and dementia" (VCID), a term that includes a broad range of vascular mechanisms and phenotypes and represents the multifactorial nature of dementia and related disorders as a pathway for reducing dementia burden.<sup>6</sup> In particular, genetic exploration of VCID may highlight important mechanisms across the wide spectrum of pathologies, including vascular pathways, which, in turn, are considered to be a major and modifiable target for the prevention of dementia, including the Alzheimer's type.<sup>7</sup>

Emerging evidence suggests that VCID is highly heritable.<sup>8</sup> Mutations in the *NOTCH3* gene known to cause monogenic cerebral SVD and early cognitive impairment also influence later onset polygenic manifestations of VCID by acting through common, less pathogenic variations in the same genes. Other examples are several point mutations in the amyloid precursor protein (APP) gene that lead to cerebral amyloid angiopathy (CAA)<sup>9</sup> as well as mutations in HtrA Serine Peptidase 1 (*HTRA1*) and Collagen Type IV Alpha 1 Chain (*COL4A1*) or *COL4A2* genes.<sup>10</sup> Further support for the strong genetic basis of VCID stems from heritability and genome-wide association studies (GWASs) of cerebral SVD endophenotypes that are closely related to VCID, including ischemic stroke (IS),<sup>11</sup> and white matter hyperintensities (WMHs).<sup>12</sup> In contrast to the over 70 loci identified as being associated with AD genetic variance, the genetic architecture of "sporadic" VCID is largely unknown. Most genetic studies of VCID have utilized a candidate gene approach, which did not yield consistent and replicable findings.<sup>13</sup>

GWASs of VCID are sparse. In 2012, a GWAS of VaD conducted among the participants of the Rotterdam Study ( $N = 67$  cases and 5700 controls) identified a novel locus associated with VaD, located near the androgen receptor on the X chromosome<sup>14</sup>; however, this finding could not be replicated.<sup>15</sup> More recently, a GWAS of dementia and its clinical endophenotypes was conducted as part of the GR@ACE

### RESEARCH IN CONTEXT

- 1. Systematic review:** While findings from genome-wide association studies (GWASs) of Alzheimer's disease (AD) highlighted multiple genetic risk variants, the genetics of all-cause dementia (ACD) and vascular dementia (VaD) has been rarely studied. In this meta-analysis of unpublished GWASs, we utilized data from 21 cohorts and consortia for a total of 46,902 and 8702 cases of ACD and VaD, respectively.
- 2. Interpretation:** Known genetic variants for AD were identified as risk factors for ACD and VaD. Downstream bioinformatics revealed novel genetic loci functionally associated with ACD and VaD, including *SEMA4D*, *RBFOX1*, and *SPRY2*.
- 3. Future directions:** These results should be validated in additional datasets. Particularly, studies are warranted to explore the genetic variation of ACD and VaD in non-European individuals.

study.<sup>16</sup> This study demonstrated the differential biological pathways associated with clinical AD subgroups based on the degree of vascular burden. It identified a variant near *CNTNAP2* associated with probable or possible VCID ( $N = 373$ ). However, this finding did not reach genome-wide (GW) significance.

The multifactorial nature of VaD and the heterogeneity of the clinicopathological criteria used to define this entity have hampered the identification of genetic polymorphisms underlying VCID. To overcome these limitations, large-scale studies with sufficient power to detect genetic signals specific to VCID are needed.<sup>17</sup> In this study, we investigate the genetic predisposition to VCID specifically. Hence, we explored the genetic variability associated with ACD as a broad phenotype, as well as VaD as an extreme phenotype of the dementia continuum characterized by increased vascular burden. Our findings were then analyzed in light of the knowledge already gained from previous large-scale GW and sequencing studies on the genetic determinants of AD, stroke, and additional phenotypes along the VCID spectrum.<sup>10</sup>

## 2 | METHODS

### 2.1 | Study population

A total of 800,597 participants from 21 cohorts and consortia contributed to 46,902 and 8702 cases of ACD and VaD, respectively. The overall sample included individuals from four different ethnicities (European, African, Asian, and Hispanic) from North America, Europe, and Asia. The mean age ranged between 54 and 80 years, with 54% to 68% females. The summary demographics are described in Table 1 (also

**TABLE 1** Demographics: Data from 17 CHARGE cohorts were included in our meta-analysis, as were the UKBB, ADGC, and EADB for the replication of our VaD results in European ancestry.

Study	N/Control	ACD	VaD	Percentage VaD	Age (mean)	Sex, % (percentage female)
<b>European ancestry</b>						
3C	6475	808	162	20.1	74.2	61.0
AGES	5656	1501	118	7.9	76.1	61.0
ARIC	3145	165	36	21.8	75.5	60.0
ASPREE	12,480	319	NA	NA	75.0	55.0
CHS	2169	508	156	30.7	74.9	61.5
FVG	804	73	NA	NA	58.2	58.3
FHS	4175	679	167	24.5	54.6	54.3
GRACE	12,599	7516	1953	26.0	78.8	68.2
GREAT-AGE	1504	138	7	5.1	73.7	50.3
HUNT	69,633	3982	681	17.1	67.7	57.4
MEMENTO	2050	263	36	13.7		
MYHAT	865	50	NA	NA	83.7	59.5
ROSMAP	1335	626	NA	NA	79.8	69.7
RS (1,2,3)	11,390	1715	178	10.4	63.6	56.8
ADGC-NAJ-2011	15,675	8309	NA	NA	75.4	59.5
UKBB	314,278	17,008	332	NA	66.1	63.1
<b>Total European</b>	<b>466,606</b>	<b>44,009</b>	<b>3892</b>			
<b>African ancestry</b>						
ARIC	905	101	31	30.7	75.5	60.0
CHS	514	194	65	33.5	74.9	61.5
ADGC-Reitz (2013)	5896	1968	NA	NA	80.5	63.9
<b>Total African</b>	<b>7315</b>	<b>2263</b>	<b>96</b>			
<b>Asian ancestry</b>						
HKOS	2373	349	66	18.9	60.1	67.9
Harmonization	385	153	49	32.0	73.6	55.0
<b>Total Asian</b>	<b>2758</b>	<b>502</b>	<b>115</b>			
<b>Hispanic ancestry</b>						
SALSA	1271	128	35	27.3	68.9	58.6
<b>Total Stage 1 for ACD and VaD</b>	<b>477,950</b>	<b>46,902</b>	<b>4138</b>			
<b>Replication of VaD results in EADB</b>						
EADB	275,745	NA	4,564			
<b>Total</b>	<b>753,695</b>	<b>46,902</b>	<b>8702</b>			

Note: Overall, 800,597 individuals were included in this study, accounting for 46,902 and 8702 cases of ACD and VaD, respectively. For UKBB, we used the proxy-AD (familial AD) for ACD analysis and assessed VaD cases using ICD10 codes (see Methods). We also used ADGC-NAJ-201118 and ADGC-Reitz-201319 for ACD in European and African ancestry, respectively, to avoid overlap with CHARGE samples. We subsequently replicated our VaD results in EADB.

Abbreviations: ACD, all-cause dementia; ADGC, Alzheimer's Disease Genetics Consortium; EADB, the European Alzheimer Disease Biobank; UKBB, the UK Biobank.

detailed in Table S1 of Supplementary File 1). Each study obtained written informed consent from participants or, for those with substantial cognitive impairment, from a caregiver, legal guardian, or other proxy. Study protocols for all cohorts were reviewed and approved by the appropriate institutional review boards.

## 2.2 | Phenotype definition

The primary study outcomes are ACD and VaD, measured by each participating cohort as described in Supplementary File 2. Briefly, to diagnose ACD and VaD, a neurological evaluation and diagnosis based on validated criteria were required. These criteria, as shown in Table S1 of Supplementary File 1, include the use of International Statistical Classification of Diseases and Related Health Problems (ICD) codes in most cohorts, as well as additional criteria such as the Diagnostic and Statistical Manual of Mental Disorders, Third to Fifth editions (DSM-III to V), National Institute of Neurological Disorders and Stroke-Alzheimer's Disease and Related Disorders Association, National Institute of Neurological Disorders and Stroke-the Association Internationale pour la Recherche et l'Enseignement en Neurosciences, and dementia by proxy for United Kingdom Biobank (UKBB). Additionally, VaD cases were included in ACD, and the proportion of ACD classified as VaD is reported in Table S1 of Supplementary File 1. Moreover, to increase the sensitivity, cohorts were asked to run separate association analyses for (a) incident ACD, (b) prevalent ACD, (c) incident VaD, (d) prevalent VaD, (e) incident probable and definite VaD, and (f) prevalent probable whenever possible. To address the overlap with AD, we included all VCID (including persons with possible VCID) and separately analyzed only cases of "pure" (probable and autopsy-proven definite) VCID and requested that all cohorts provide the most accurate, detailed description of their diagnostic algorithm. Although VaD in UKBB was defined based on ICD-10 codes, we used the family history of dementia GWAS ("imputed dementia") recently published by Marioni et al.<sup>18</sup> for ACD. Imputed dementia was defined as individuals at least 65 years old reporting a history of dementia in one or both parents. As explained in Ghosh et al.,<sup>19</sup> the effect sizes and standard errors of the imputed dementia GWASs were doubled to analytically correct for the use of proxy phenotypes.

## 2.3 | Genotyping and imputation

Genotyping was performed using cohort-specific genotyping arrays as described in Supplementary File 2. Genetic variants were imputed using 1000 Genomes Project (1KG), the Haplotype Reference Consortium (HRC),<sup>20</sup> and the National Heart, Lung, and Blood Institute Trans-Omics for Precision Medicine (TOPMed). UKBB imputed the genotypes to HRC, 1KG, and UK10K. Details on study-specific quality control (QC) filters and software used for phasing and imputation are provided as supplementary materials (Supplementary File 2). Briefly, rare variants (minor allele frequency [MAF] < 1%) and poorly imputed variants (imputation quality,  $R_{sq} < 0.3$ ) were excluded, as were vari-

ants mapping to sex chromosomes or mitochondria. Samples with poor genotyping call rate (<95%) and Hardy-Weinberg  $p$  values <  $1 \times 10^{-6}$  were removed. All genetic positions are reported in genome build 37 (GRCh37, hg19). Moreover, we used HRC version 1.2 as the main reference panel, and only variants in this panel were subsequently used in the association analyses. Additional details on the genotyping and imputation methods and QC are provided in Supplementary File 2.

## 2.4 | Genome-wide association analyses, QC, and meta-analysis

### 2.4.1 | Study-level association analyses

We conducted study and ethnicity-specific association analyses adjusting for age, sex, sites, and population structure to test the association of each variant with VaD and ACD. Cohorts were asked to run logistic regression and Cox proportional hazard models for prevalent and incident VaD/ACD, respectively, assuming additive allelic effects and imputed dosages. The UKBB association analyses were performed with linear mixed models (LMMs) using the BOLT-LMM software.<sup>21</sup> BOLT-LMM has the advantage over other methods in that it accounts for cryptic relatedness and population structure and, thus, allows the inclusion of related individuals in models, which increases the overall sample size. Details on the methods and software used for study-level association analyses are provided in Supplementary File 2.

### 2.4.2 | QC of study-level summary statistics

We performed a stringent QC check of the summary statistics from each cohort using EasyQC.<sup>22</sup> We mapped each variant from the non-European ancestry (EA) cohort to the appropriate 1KG project phase 3 reference panel and all EA to HRC (details in Table S1). Then the following steps were performed to ensure proper QC of each file before the meta-analysis: (a) remove all structural variants and INDELS; (b) filter out variants with missing or unusual values ( $p$  value < 0 or > 1, effect size > 10, effect allele frequency < 0 or > 1, imputation quality < 0 or > 1); (c) filter out variants with effective allele count (EAC,  $2 \times$  minor allele frequency  $\times N \times$  imputation quality) < 10; (d) filter out variants with low imputation quality (eg, INFO scores reported by the imputation software); (e) filter out variants with MAF < 1%; (f) align variants to the main reference panel (HRC for EA, and ethnicity-specific 1KG for others); remove variants with absolute difference between its allele frequencies in the cohort and reference panel greater than 0.2. All variants were assigned a unique identifier as a combination of the chromosome, position, reference, and alternative alleles separated by semi-colons (CHR:POS:REF:ALT) to avoid issues with chromosomal positions mapping to multiple marker IDs. The foregoing steps were repeated until satisfactory results were obtained after visual inspection of the different diagnostic QC plots (AF, P-Z, Q-Q, and SE plots) generated by EasyQC as explained in Winkler et al.<sup>22</sup>

### 2.4.3 | Meta-analysis of GWAS results

#### *Ancestry-specific meta-analysis*

The meta-analyses were conducted using the fixed-effect inverse variance-weighted method implemented in METAL.<sup>23</sup> Post-analysis results were filtered to retain only variants present in more than 40% of the overall cohorts and the effective sample size greater than 40% of the study sample size. We evaluated the heterogeneity across cohorts using the  $I^2$  statistic provided by METAL, which represents the percentage of variation across studies that is due to heterogeneity rather than chance. We used the standard  $p$  value thresholds for GW significance,  $p < 5e-8$ , and suggestive  $p < 1e-6$ . Since there was no evidence of genomic inflation in the cohort summary statistics ( $\lambda = 0.98$  to  $1.06$ ), no genomic control was applied during the meta-analysis. Genomic loci were defined as the region  $\pm 500$  kb around the single nucleotide polymorphism (SNP) with the lowest  $p$  value, considered as the index SNP. We assessed the heterogeneity across studies using the  $I^2$  statistics of METAL (HetPVal output), which represents the percentage of variation across cohorts that is due to genetic heterogeneity rather than chance. Except for the APOE region (defined as SNPs located on chromosome 19 between positions 45,000,000 and 45,800,000 base pairs according to GRCh37 [hg19]), for which the HetPVal was  $> 1e-8$ , significant SNPs were selected with HetPVal  $> 0.01$ . We conducted ancestry-specific meta-analyses of VaD and ACD for EA, African ancestry (AA), Asian ancestry (SA), and Hispanic ancestry (HA). In addition, we used linkage disequilibrium (LD) score regression to quantify the contribution of true polygenicity and biases such as cryptic relatedness and population stratification of the meta-analysis results.

#### *Cross-ancestry meta-analysis*

We performed cross-ancestry meta-analyses to assess whether the increase in sample size could lead to adequate power to identify additional GW significant loci associated with ACD and VaD. To this end, we used Meta-Regression of Multi-Ancestry Genetic Association (MR-MEGA) software, which has proven more efficient than others when dealing with genetic heterogeneity.<sup>24</sup> MR-MEGA uses a matrix of mean pairwise allele frequency differences to quantify the genetic similarity between studies and estimate the effect of each SNP after adjusting for ancestry principal components. We applied study-specific filters, as previously described in the QC section, with EAC  $> 20$ , for studies with small sample sizes to reduce the amount of noise in the results-driven rare SNPs in small cohorts. We fitted three principal components, as suggested by MR-MEGA authors, which proved sufficient to separate the cohorts into self-reported ancestry groups (Figure S1). As in the ancestry-specific meta-analysis, we retained only SNPs that were present in over 40% of cohorts, with  $> 40\%$  total sample size. GW significant SNPs had  $p < 5e-8$  and showed evidence of allelic heterogeneity across populations (MR-MEGA P-Het  $> 1e-5$ ).

### 2.5 | Shared genetic susceptibility with complex disease traits

A gene-based association test was conducted using MAGMA,<sup>25</sup> with  $p < 2.8e-6$  as a genome-wide significance threshold. Gene regions with SNPs not reaching GW significance for ACD or VaD in the primary GWAS analysis and additionally not in LD ( $r^2 < 0.10$ ) with the lead SNP were considered novel.

We first explored the association of lead risk variants with related vascular, neurological traits and metabolic traits, excluding the APOE region. For each related trait, association statistics of SNPs falling in a window of  $\pm 250$  kb around each lead SNP were queried,<sup>26</sup> and SNPs satisfying the GW significance threshold in the original study were retained. Leveraging the polygenicity of ACD (mean chi-squared = 1.1) and VaD (mean chi-squared = 1.06), we systematically explored the genetic overlap of ACD and VaD (in European-only analysis) with (i) neurological and neurodegenerative traits (any stroke [AS], IS, small vessel stroke [SVS], large artery stroke [LAS], cardioembolic stroke [CES], general cognitive function [GCF], and Alzheimer-type dementia [AD]); (ii) common magnetic resonance imaging (MRI) marker of cerebral SVD (WMHs)<sup>5</sup>; and (iii) vascular risk factors (systolic blood pressure [SBP], diastolic blood pressure [DBP], pulse pressure [PP], high-density lipoprotein [HDL], low-density lipoprotein [LDL]).<sup>27</sup> We acquired summary statistics of the largest European-only GWAS for these traits.

Using LD score regression (LDSR) analysis,<sup>28</sup> genetic correlation estimates between ACD/VaD and the aforementioned complex traits were obtained. A similar and potentially powerful approach called genetic covariance analyzer (GNOVA)<sup>29</sup> was additionally used to study the shared genetic covariance across the genome between a given pair of complex traits. LDSR and GNOVA compute genetic correlation and covariance, respectively, while adjusting for potential sample overlap and accounting for the LD of genetic variants. Though LDSR and GNOVA are substantially similar, differences in the minor allele frequency thresholds may influence genetic correlation estimates and significance to some extent. A  $p$  value  $< 8.3e-3$  correcting for six independent phenotypes was considered significant. Additionally, for the traits with significant genetic overlap, we performed causal inference analysis in the Mendelian randomization (MR) framework with ACD/VaD as the outcome. Using the MR-LAP method,<sup>30</sup> we addressed potential bias in the causal effects due to sample overlap between the exposure and the outcome variables. Briefly, MR-LAP utilizes the LDSR intercept estimates – a measure of the degree of sample overlap, polygenic architecture, and the heritability of the genetic instruments of the exposures – to account for the sample overlap bias and other biases (weak instrument and winner's curse bias) that push the causal estimates toward the null.

Since GW correlation estimates may miss significant correlations at the regional level (balancing effect),<sup>31</sup> a Bayesian pairwise GWAS approach (GWAS-PW) was applied.<sup>32</sup> GWAS-PW identifies trait pairs

with high posterior probability of association (PPA) with a shared genetic variant (Model 3,  $PPA3 \geq 0.90$ ). To ensure that PPA3 is unbiased by sample overlap, fgwas version 0.3.6 was run on each pair of traits, and the correlation estimated from regions with null association evidence ( $PPA < 0.20$ ) was used as a correction factor.<sup>32</sup> We then calculated Spearman's rank correlation for regions showing  $PPA3 > 0.90$ , approximating the direction of effect.

Finally, using a Bayesian method – *ashR*<sup>33</sup> – we studied the effect-size distribution for ACD and VaD and related risk factors. Briefly, *ashR* tests the probability of non-zero effect conferred by SNPs as a function of LD score, measuring the true effect size that is not zero and the underlying polygenic background. Using MTAG,<sup>34</sup> traits falling in similar polygenic profile to ACD or VaD are jointly analyzed in a bivariate scheme leveraging the pairwise trait genetic correlation to boost power to discover new loci. The significance threshold in the MTAG analysis is determined based on the number of traits sharing a similar polygenic profile and was additionally restricted to SNPs that also had nominal significance ( $p < 0.05$ ) for each phenotype separately in the pre-existing univariate GWAS.

## 2.6 | Transcriptome-wide association study and colocalization

We performed transcriptome-wide association studies (TWASs) using the association statistics from the ACD and VaD (European-only) and weights from 22 publicly available gene expression reference panels from blood (Netherlands Twin Registry [NTR], Young Finns Study [YFS]), arterial (genotype-tissue expression [GTEx]), brain (GTEx, CommonMind Consortium [CMC]), and peripheral nerve tissues (GTEx). For each gene in the reference panel, precomputed SNP-expression weights in the 1-Mb window were obtained, including the highly tissue-specific splicing quantitative trait loci (sQTLs) information on gene isoforms in the dorsolateral prefrontal cortex (DLPFC) derived from the CMC. TWAS-Fusion<sup>35</sup> was used to estimate the TWAS z-score (association statistic between predicted expression and ACD or VaD), derived from the SNP-expression weights, SNP-trait effect estimates, and the SNP correlation matrix. Transcriptome-wide (TW) significant genes (eGenes) and the corresponding QTLs (expression QTLs [eQTLs]) were determined using Bonferroni correction in each reference panel, based on the average number of features (4235 genes) tested across all the reference panels.<sup>35</sup> eGene regions with eQTLs not reaching GW significance in association with ACD or VaD and not in LD ( $r^2 < 0.01$ ) with the lead SNP for GW significant risk loci were considered novel. Finally, a colocalization analysis (COLOC)<sup>36</sup> was carried out at each locus to estimate the posterior probability of a shared causal variant ( $PP4 \geq 0.75$ ) between the gene expression and trait association, using a prior probability of  $1.1 \times 10^{-5}$ . Furthermore, functional validation of the eGenes was performed by testing for positional overlap of the best eQTLs from TWAS with enhancer (H3K4me1, H3K27ac) and/or promoter (H3K4me3/H3K9ac) elements across a broad category of relevant tissue types (blood [BLD], brain/neurological [BRN]) using Haploreg version 4.1.<sup>37</sup>

## 2.7 | Identification of independent case–case loci with case–case GWAS

Leveraging summary statistics from our GWAS of ACD and VaD, as well as from publicly available existing GWASs of AD<sup>38</sup> and stroke,<sup>39</sup> we examined genetic uniqueness between these highly correlated though distinct disorders using case–case GWAS (CC-GWAS), a method that tests for differences in allele frequency between cases of two disorders without individual-level data.<sup>40</sup> By allowing for sample overlap between the two case-control GWASs, CC-GWAS can increase the power to detect signals otherwise missed in case-control GWASs. We used a LD threshold of 0.2 ( $r^2 < 0.2$ ) to distinguish CC-GWAS-specific loci from genome-wide significant variants identified in the input case-control GWAS.

## 3 | RESULTS

Our analysis included 800,597 individuals comprising 46,902 and 8702 cases of ACD and VaD, respectively. They were recruited from the 19 Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) cohorts, the Alzheimer's Disease Genetics Consortium (ADGC), the European Alzheimer Disease Biobank (EADB), and the UK Biobank (UKBB), encompassing four different reported ancestries: European (98.5%), African (1.0%), Asian (0.4%), and Hispanics/Latino (0.1%). Association analyses were performed in each cohort following a predefined analysis plan, using logistic regression and Cox proportional hazards models for prevalent and incident cases, respectively. We performed study-specific QC of the summary statistics data, followed by ancestry-specific meta-analyses and cross-ancestry meta-analyses of ACD and VaD, as described in the Methods section. For each cohort, a description, association analysis method, QC parameters, and cutoffs are provided in Supplementary File 2.

### 3.1 | Meta-analyses of ACD and VaD GWAS in European ancestry populations replicated known AD loci

We conducted fixed-effects inverse variance-weighted meta-analyses of the 14 European ancestry cohorts ( $N = 466,606$ ,  $N_{ACD} = 44,009$ ,  $N_{VaD} = 3892$ ) from the CHARGE consortium, ADGC, and the UKBB. Furthermore, we replicated significant and suggestive signals from our VaD GWAS in the EADB consortium VCID data ( $N = 275,745$ ,  $N_{VaD} = 4564$ ). The complete list of cohorts included in this study is provided in Table S1.

A total of 11,596,629 and 9,878,961 SNPs passed the study-level QC criteria and were tested for association with ACD and VaD, respectively. After post-meta-analysis QC, we identified 10 GW significant loci associated with ACD (GWS,  $p < 5 \times 10^{-8}$ ), all of which had been previously associated with AD (Table 2, extended results in Table S2). Significant loci associated with ACD included signals in or around known AD genes such as *APOE*, *BIN1*, *MS4A6A*, *PICALM*, *CR1*, *CD2AP*,

**TABLE 2** Genome-wide significant ( $p < 5 \times 10^{-8}$ ) and suggestive ( $p < 1 \times 10^{-6}$ ) variants associated with all-cause dementia in European populations.

rsID	Nearest gene	CHR	POS	EA/NEA	EAF	BETA	p value	HetISq	HetChISq	HetPVal
rs429358	APOE	19q13.32	45411941	C/T	0.1515	1.1728	6.87E-305	98.3	1104.478	2.534E-222
rs4663105	BIN1	2q14.3	127891427	C/A	0.4151	0.156	5.856E-34	63.4	51.892	0.00006868
rs12453	MS4A6A	11q12.2	59945745	C/T	0.3998	-0.0933	1.116E-16	13.2	23.037	0.287
rs10792832	PICALM	11q14.2	85867875	A/G	0.3585	-0.0857	8.234E-14	61.8	52.41	0.0000992
rs10948367	CD2AP	6p12.3	47585615	G/A	0.2712	0.0886	4.041E-13	4.2	20.88	0.4042
rs4295	ACE	17q23.3	61556298	C/G	0.3897	-0.0784	1.014E-11	10.8	22.43	0.3176
rs4844610	CR1	1q32.2	207802552	A/C	0.1846	0.0961	1.245E-11	71.4	66.468	3.519E-07
rs2906644	PILRB	7q22.1	99956290	G/C	0.1294	-0.1016	7.627E-09	0	8.219	0.9616
rs3764650	ABCA7	19p13.3	1046520	G/T	0.0957	0.1141	1.125E-08	35	24.604	0.07712
rs9323877	SLC24A4	14q32.12	92934269	G/A	0.2521	0.0699	3.804E-08	0	19.881	0.4654
rs1532278	CLU	8p21.1	27466315	T/C	0.3819	-0.0629	6.262E-08	66.2	59.185	9.516E-06
rs7912495	USP6NL	10p14	11718713	G/A	0.4612	0.0684	6.774E-08	0	15.343	0.7006
rs17125924	FERMT2	14q22.1	53391680	G/A	0.0928	0.1009	9.38E-08	2.6	19.508	0.4247
rs11767557	EPHA1	7q34	143109139	C/T	0.1998	-0.0742	9.721E-08	31.2	29.052	0.08675
rs1854554	SEMA4D	9q22.2	92155871	A/G	0.409	0.0598	1.096E-07	4	20.83	0.4072
rs7118826	ANO3	11p14.2	261955535	G/C	0.4585	0.0686	1.238E-07	18.7	23.368	0.2215
rs79832570	SPATC1	8q24.3	145097720	C/T	0.086	0.1433	1.385E-07	37.3	19.147	0.08504
rs13010870	RBM43	2q23.3	151765163	C/T	0.2162	-0.0732	1.649E-07	0	18.774	0.5366
rs1354106	CD33	19q13.41	51737991	G/T	0.3441	-0.0614	1.673E-07	6.4	21.373	0.3755
rs6014724	CASS4	20q13.2	54998544	G/A	0.0874	-0.1071	1.863E-07	0	18.603	0.4825
rs897150	TRIB1	8q24.13	126576702	A/G	0.3016	-0.0634	2.33E-07	4	20.842	0.4065
rs11168036	HBEGF	5q31.3	139707439	T/G	0.4933	0.0572	2.336E-07	0	18.21	0.5735
rs17269688	NCK2	2q12.2	106469267	G/A	0.025	-0.1937	2.389E-07	41.8	27.478	0.03647
rs677649	RNU6-11P	7	123439244	T/G	0.1756	0.0851	2.505E-07	9.9	19.987	0.3336
rs8081878	ZNF652	17q21.32	47436812	T/A	0.4634	0.057	2.609E-07	9.9	22.19	0.3303
rs4654450	RP1-37J18.2	1	4667378	G/A	0.3314	-0.0697	2.684E-07	16.2	22.679	0.2518
rs11218343	SORL1	11q24.1	121435587	C/T	0.0364	-0.1658	2.909E-07	20.7	21.432	0.2076
rs2297508	SREBF1	17p11.2	17715317	C/G	0.3659	-0.0585	4.604E-07	31.9	29.367	0.08078
rs442495	ADAM10	15q21.3	59022615	C/T	0.3245	-0.0599	4.722E-07	41	33.895	0.02684
rs13316744	AC091493.2	3	16742711	C/G	0.4544	-0.0549	7.609E-07	0	15.72	0.7338
rs7068231	ANK3	10q21.2	61784928	T/G	0.4005	-0.0579	7.833E-07	11.1	22.503	0.3139
rs834398	GABRB2	5q34	160528276	G/A	0.1971	0.0793	8.951E-07	0	11.885	0.8905
rs62013908	RBFOX1	16p13.3	5991314	G/C	0.2547	0.0724	9.422E-07	3.9	19.767	0.4087

Note: Genome-wide significant variants are highlighted in orange.

**TABLE 3** Genome-wide significant ( $p < 5 \times 10^{-8}$ ) and suggestive ( $p < 1 \times 10^{-6}$ ) variants associated with vascular dementia in European populations.

rsID	Nearest gene	CHR	POS	EA/NEA	EA/NAF	BETA CHARGE	p value CHARGE	p value EADB	p value COMBINED	Direction
rs429358	APOE	19q13.32	45411941	C/T	0.1549	0.8794	2.67E-86	5.66E-113	2.9E-196	++
rs11911	SPRY2	13q31.1	80910851	C/A	0.3756	-0.1466	2.60E-06	0.0653	0.0000335	-
rs7101996	GALNT18	11	11259298	T/C	0.4198	-0.1362	3.06E-06	0.48	0.00452	-+
rs2845990	LINC02113	5	98907502	C/T	0.352	-0.1383	3.24E-06	0.872	0.00131	-+
rs117904289	FOXA2	20p11.21	22782154	G/A	0.0858	0.2516	3.35E-06	0.987	0.00112	+--
rs838941	SCARB1	12q24.31	125183316	A/G	0.4261	0.1344	3.56E-06	0.33	0.0000654	++
rs17418160	ERBB4	2q34	213119022	C/T	0.0396	0.3341	3.58E-06	0.882	0.00171	+--
rs77542509	TRPC6	11q22.1	101415824	C/T	0.058	-0.3038	4.77E-06	0.137	0.0000213	-
rs6127311	DOK5	20q13.2	53501017	C/T	0.0532	-0.3141	4.83E-06	0.294	0.0144	+--
rs35945091	LCN1P2	9	136185411	C/T	0.2227	0.164	5.15E-06	0.855	0.00176	+--
rs17059857	ZNF236	18q23	74469493	C/T	0.0403	0.358	5.41E-06	0.417	0.00934	+--
rs143750890	AJAP1	1p36.32	4602505	C/T	0.0273	0.4283	5.56E-06	0.163	0.0000334	++
rs9510987	SPATA13	13	24575243	G/T	0.2525	0.1466	6.28E-06	0.291	0.0000744	-
rs55709546	PHACTR3	20q13.32	58261107	C/A	0.0484	0.3044	6.53E-06	0.645	0.000496	++
rs12667855	TMEM106B	7p21.3	12124166	T/G	0.0981	0.225	6.59E-06	0.542	0.000299	++
rs281219	SEMA6D	15q21.1	47711652	A/G	0.1954	0.1641	6.65E-06	0.316	0.0129	+--
rs138352554	GBP1	1p22.2	89517105	G/A	0.0359	0.3761	6.95E-06	0.573	0.000406	++
rs16967121	RASGRP1	15q14	38923007	G/A	0.0658	0.2605	7.31E-06	0.916	0.00126	++
rs11007123	WAC	10p12.1	28763005	C/T	0.2804	0.1395	7.70E-06	0.292	0.0139	+--
rs4794009	GIP	17q21.32	47051955	A/G	0.4412	0.1274	8.17E-06	0.797	0.000746	++
rs35448830	PRKCE	2p21	46080762	C/T	0.0368	0.3346	8.48E-06	0.631	0.000579	++
rs2233754	PSMA3	14q23.1	58755574	C/A	0.07	0.2575	9.39E-06	0.601	0.00604	+--

Note: The meta-analysis includes 11 cohorts from the CHARGE consortium and the UK Biobank (UKBB) GWAS. Direction denotes the direction of association in CHARGE and EADB. The genome-wide significant variant is highlighted in orange.

Abbreviations: ADGC, Alzheimer's Disease Genetics Consortium; CHARGE, Cohorts for Heart and Aging Research in Genomic Epidemiology; EADB, European Alzheimer Disease Biobank; UKBB, UK Biobank.

ABCA7, PILRB, SLC24A4, and ACE. For VaD, only one variant located near the APOE gene reached GW significance (Table 3, extended results in Table S3). The genomic inflation coefficients ( $\lambda$ ) were 1.05 and 1.07 for ACD and VaD, respectively. The  $\lambda$  intercept computed with the LDSC software was 1.01 for both analyses, suggesting no systematic inflations of association statistics. The Manhattan and quantile-quantile (QQ) plots for both analyses are provided in Figures 1–3 (Forest and locusZoom plots for prominent signals are provided in Figures S2 to S65).

For the VaD trait, we selected all variants with a  $p$  value less than  $1 \times 10^{-5}$  and meta-analyzed with EADB summary results using a weighted sum of  $z$ -scores approach. Only one variant near the APOE gene was statistically significant and had the same direction of effect in both studies (Table 3).

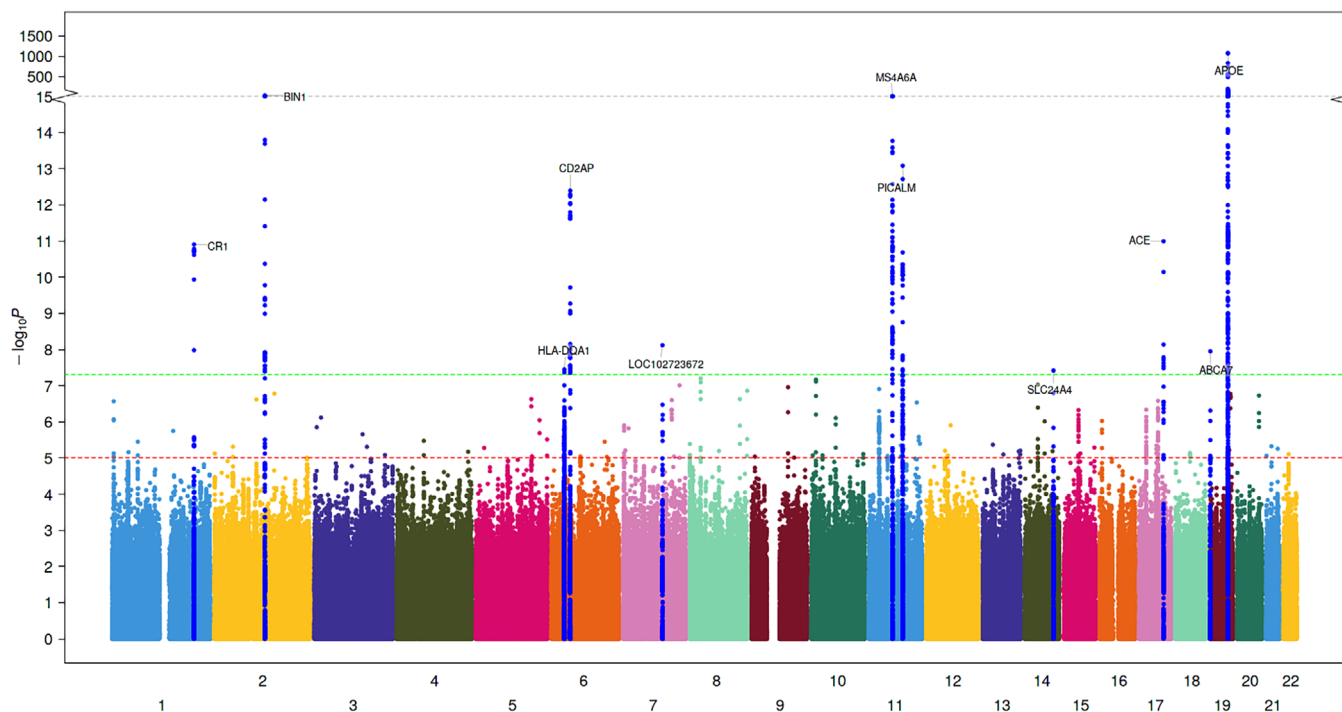
The meta-analyses of ACD and VaD GWAS in African, Asian, and Hispanic/Latino ancestries did not provide new GW significant variants.

We replicated our VaD signals using EADB data (Table 3). Overall, we replicated an association within the APOE region. The suggestive

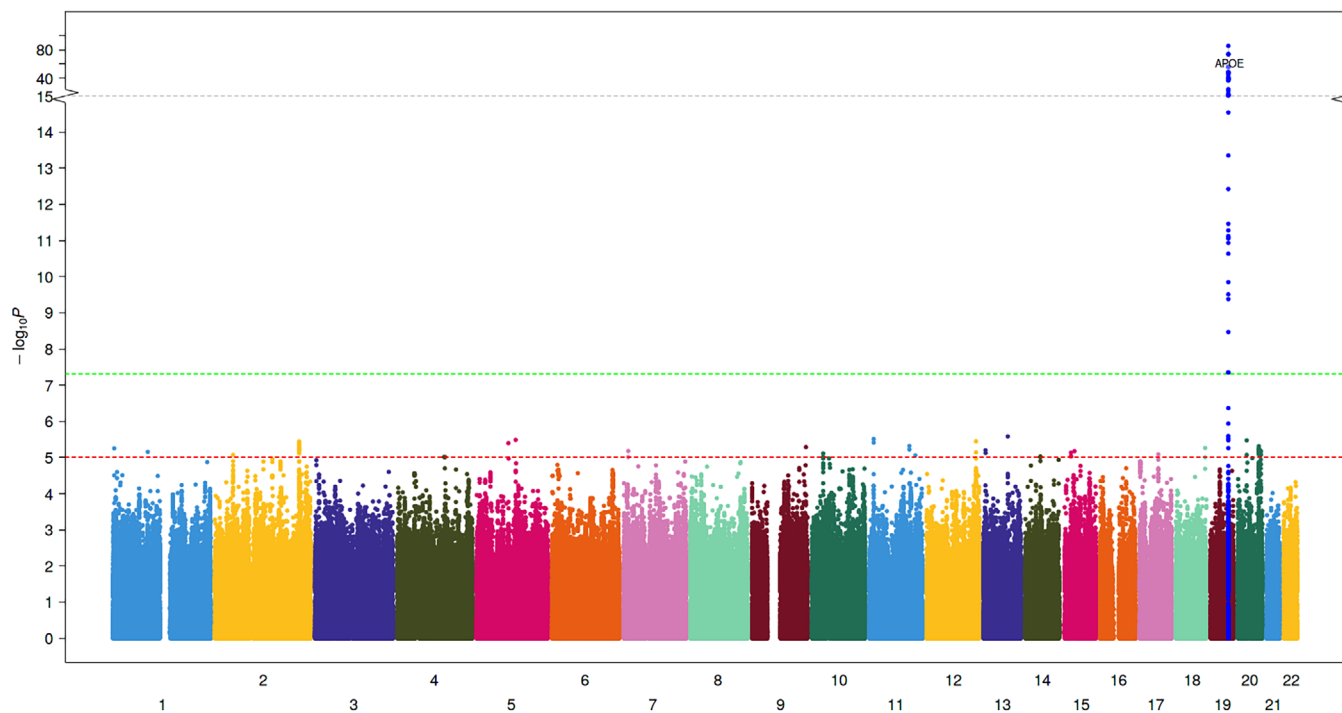
variant near SPRY2 also has the lowest  $p$  value in the EADB GWAS with the same direction of effect in both studies.

### 3.2 | Cross-ancestry meta-analysis of ACD and VaD GWAS

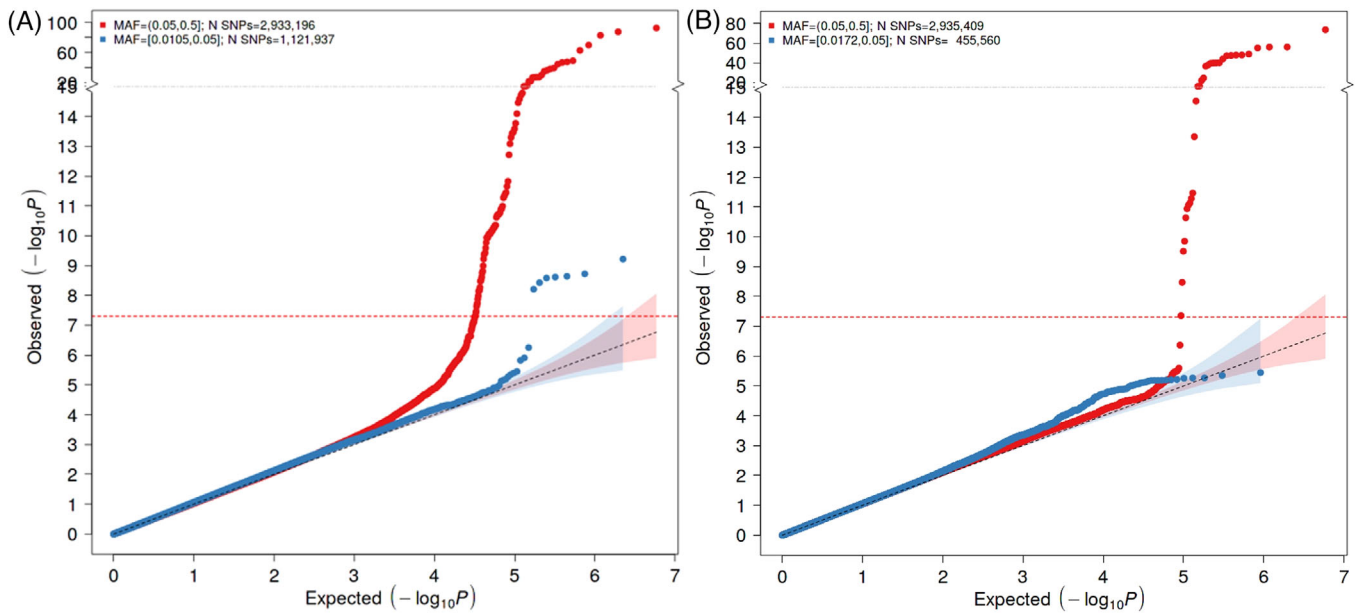
Next, we performed a cross-ancestry meta-analysis using MR-MEGA, first to assess whether the increased sample size could lead to the identification of additional loci associated with ACD and VaD and to identify loci that are relevant in other ancestries. Most of the cross-ancestry meta-analyses included individuals of European ancestry and smaller samples from African, Asian, and Hispanic/Latino ancestries. The total number of variants included was 17,054,226 and 11,595,061 for ACD and VaD, respectively. The Manhattan plots of the SNP-wide meta-analyses for both traits are provided in Figures S66 and S67. Significant and suggestive signals for ACD and VaD are presented in Tables 4 and 5, and the extended results are in Tables S4 and S5. We identified novel signals reaching GW significance at 20q11.21 (*CHD6*, an oxidative



**FIGURE 1** Manhattan plot of ACD GWAS. In addition to variants in APOE region, we identified five new genetic loci associated with VaD. Blue and red lines correspond to  $p$  value of  $5e^{-7}$  and  $5e^{-8}$  for genome-wide suggestive and significant SNPs, respectively. Manhattan plots for the cross-ancestry meta-analysis. Each dot represents a SNP, the x-axis shows the chromosomes where each SNP is located, and the y-axis shows  $-\log_{10} p$  value of the association of each SNP with ACD in the cross-ancestry meta-analysis. The red horizontal line shows the genome-wide significant threshold ( $p$  value =  $5e^{-8}$ ;  $-\log_{10} p$  value = 7.30). The nearest gene to the most significant SNP in each locus has been labeled.



**FIGURE 2** Manhattan plot of VaD GWAS. In addition to variants in the APOE region, we identified five new genetic loci associated with VaD. Blue and red lines correspond to a  $p$  value of  $5e^{-7}$  and  $5e^{-8}$  for genome-wide suggestive and significant SNPs, respectively. Manhattan plots for cross-ancestry meta-analysis. Each dot represents a SNP, the x-axis shows the chromosomes where each SNP is located, and the y-axis shows  $-\log_{10} p$  value of the association of each SNP with VaD in the cross-ancestry meta-analysis. The red horizontal line shows the genome-wide significant threshold ( $p$  value =  $5e^{-8}$ ;  $-\log_{10} p$  value = 7.30). The gene closest to the most significant SNP in each locus has been labeled.



**FIGURE 3** Q-Q plots of ACD (left) and VaD (right) GWASs. The expected  $p$  values (x-axis) are plotted against the observed  $p$  values (y-axis). The units of the axes are the  $-\log_{10}$  of the  $p$  value. The red and blue curves represent the plots with  $\text{MAF} \geq 0.05$  and  $0.01$ , respectively. The diagonal line of the null hypothesis and its 95% confidence interval are plotted in gray based on the  $p$  values without the previously reported SNPs. The red dotted line represents the cutoff for genome-wide significance. MAF, minor allele frequency.

**TABLE 4** Genome-wide significant ( $p < 5 \times 10^{-8}$ ) variants associated with all-cause dementia in cross-ancestry meta-analysis.

rsID	Nearest gene	Chr	Pos	EA/NEA	P value	MAF	Beta	SE
rs10402524	BCAM	19p11	45329344	T/C	1.21E-17	0.2336	-0.168	0.045
rs744373	BIN1	2q14.3	127894615	A/G	1.90E-17	0.358	-0.139	0.031
rs2278867	MS4A6A	11q13.1	59943109	A/T	1.72E-15	0.2897	0.113	0.020
rs10792832	PICALM	11q13.1	85867875	A/G	3.77E-12	0.3135	-0.074	0.036
rs10948367	CD2AP	6q14.3	47585615	A/G	1.67E-11	0.2328	-0.042	0.017
rs1408077	CR1	1q11.1	207804141	A/C	4.75E-10	0.1412	0.088	0.055
rs4295	ACE	17q21.1	61556298	C/G	1.60E-09	0.3666	-0.066	0.018
rs2208524	CHD6	20q11.21	40423299	T/C	1.66E-09	0.1268	-0.103	0.027
rs11691153	DAW1	2q14.1	228780072	T/C	1.83E-09	0.1536	0.099	0.025
rs6853262	LPHN3	4q22.1	61221892	C/T	6.22E-09	0.06989	0.208	0.112
rs2677386	PWRN2	15q15.1	24432053	T/C	7.18E-09	0.3612	-0.083	0.017
rs7006786	ARHGEF10	8q13.2	1792639	G/A	8.81E-09	0.08986	0.097	0.045
rs35483531	DEGS2	14q21.3	100653772	C/T	1.35E-08	0.2993	-0.004	0.024
rs170084	PMFBP1	16q11.2	72178483	T/A	2.79E-08	0.107	-0.068	0.029
rs10940421	SNX18	5q14.3	54036059	A/G	3.34E-08	0.372	0.040	0.017
rs138908633	EPB41L4A	5q14.3	111649017	G/A	3.76E-08	0.03095	-0.029	0.050
rs74435987	DUSP6	12q14.1	89152253	G/T	4.20E-08	0.08766	0.078	0.130
rs11225924	DDI1	11q13.1	103493165	C/T	4.27E-08	0.1034	0.152	0.105
rs113747850	MAPK9	5q14.3	179710663	T/C	4.93E-08	0.123	0.071	0.024

Note: The meta-analysis includes European, African, Asian, and Hispanic/Latino ancestries. Three new variants at 20q11.21, 2q14.1, and 15q15.1 reached genome-wide significance (highlighted in orange).

Abbreviation: MAF, minor allele frequency.

**TABLE 5** Genome-wide significant ( $p < 5 \times 10^{-8}$ ) and suggestive ( $p < 1 \times 10^{-6}$ ) variants associated with vascular dementia in cross-ancestry meta-analysis.

rsID	Nearest gene	Chr	Pos	EA/ NEA	p value	MAF	Beta	SE
rs10119	TOMM40	19	45406673	G/A	1.21E-17	0.2476	-0.327	0.054
rs4380108	MARCHF10	17	60893485	C/T	9.59E-09	0.3127	-0.172	0.031
rs55747619	ITSN2	2	24530447	C/G	8.05E-08	0.08706	-0.384	1.969
rs9379092	CAGE1	6	7344531	G/A	9.80E-08	0.1172	-0.336	0.077
rs3757193	RPS6KA2	6	166923463	C/T	1.09E-07	0.08347	2.151	0.636
rs3871399	CMTM7	3	32496413	C/G	2.61E-07	0.124	0.550	0.640
rs17315346	BRINP2	1	177282235	C/T	2.67E-07	0.01538	-2.412	5.17
rs1738249	DNAH8	6	38753960	C/T	2.86E-07	0.3013	-0.050	0.040
rs12095469	OSBPL9	1	52206082	G/A	3.60E-07	0.05292	3.654	3.513
rs4820650	ADRBK2	22	25925358	T/C	3.82E-07	0.2468	0.050	0.054
rs61859886	MGMT	10	131353192	T/G	4.45E-07	0.1528	-0.274	0.057
rs9857196	RYK	3	133830660	T/A	5.09E-07	0.01997	3.438	2.670
rs637924	PCDH7	4	31465610	T/C	6.77E-07	0.2564	-0.056	0.051
rs35810115	ZNF675	19	23780763	C/T	6.81E-07	0.04992	-1.169	2.339
rs115331896	CRBN	3	3204942	T/G	6.95E-07	0.01218	3.139	2.706
rs4401880	SLC18A1	8	19946066	C/T	7.20E-07	0.3249	0.019	0.051
rs4823298	FBLN1	22	45915987	T/C	7.96E-07	0.4581	0.029	0.0439
rs17335455	NXPH1	7	8853946	T/G	8.20E-07	0.1633	-0.096	0.042
rs517484	RP11-6N13.1	5	104490130	T/C	8.51E-07	0.1965	-0.120	0.046
rs12814413	RBMS2	12	56916614	T/C	8.77E-07	0.3514	0.050	0.051
rs4665372	CGREF1	2	27325837	T/A	9.19E-07	0.3948	-0.104	0.043

Note: The meta-analysis includes European, African, Asian, and Hispanic/Latino ancestries. Genome-wide significant variants are highlighted in orange. Abbreviation: MAF, minor allele frequency.

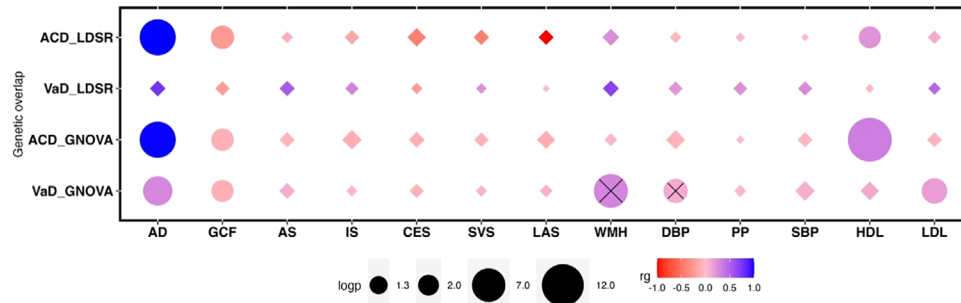
DNA damage response factor previously associated with neurological phenotype),<sup>41</sup> 2q14.1 (*DAW1*, involved in cerebrospinal fluid circulation and cilia motility during development),<sup>42</sup> and 15q15.1 (*PWRN2*, previously associated with tauopathy and Prader-Willi syndrome)<sup>43</sup> for ACD and 17q21.1 (*MARCHF10*) for VaD.

### 3.3 | Functional characterization of GW suggestive signals for ACD and VaD meta-analyses

#### 3.3.1 | Shared genetic susceptibility with complex disease traits

The substantial shared genetic susceptibility of ACD and VaD with risk factors and complex disease traits is evident across different genomic scales (single variant, regional, and the global level). ACD exhibits genetic pleiotropy with vascular risk factors (hypertension, WMH burden), hematological traits (neutrophil, lymphocyte count), and blood-based biomarkers indicative of inflammation (C-reactive protein levels), hemostasis (fibrinogen, factor-VII levels), and neurodegeneration (soluble *TREM2* levels) (Table S6). This shared genetic

susceptibility is primarily driven by the *MS4A* gene family (membrane-spanning 4A; *MS4A6A*, *MS4A4A*). The sharing of common genetic variation between ACD and vascular risk factors (blood pressure traits [DBP, SBP, PP], and T2D) at the *ACE* and *PILRB* locus (Figure S68, Table S6) is further supported by our regional Bayesian pairwise (GWAS-PW) analysis highlighting the high probability of harboring a shared causal variant (Table S7). Interestingly, the GWAS-PW approach additionally reveals the shared genetic susceptibility of VaD with IS and WMH at the *PRPF8* and *PRDM6* locus. In support, global-level genetic overlap analysis (excluding the *APOE* region) using GNOVA showed statistically robust evidence for the association of increased levels of WMH with increased risk of VaD (Table S26, Figure 4). Additionally, we observed an inverse association of high levels of HDL (protective) with ACD risk and high levels of DBP and LDL with VaD risk. As expected, a strong genetic correlation between poorer cognitive performance (GCF) and ACD was also observed. Our causal inference analysis, using MR-LAP, confirmed the putative causal association of increased DBP and WMH levels with VaD risk. However, the genetic correlation between AD and related risk factors using Kunkle 2019 GWAS did not show this causal association (Tables S26-S27, Figure 4).



**FIGURE 4** Shared genetic contribution between ACD/VaD and related risk factors. Contributions determined by LD score regression analysis (LDSR) (top), and Genetic Covariation Analyzer (GNOVA) (bottom). Effect sizes ( $r_g$ ) and significance levels ( $\log p$ ) are represented by color and symbol size. AD, Alzheimer's disease; GCF, general cognitive function; all stroke (AS) and its subtypes (ischemic, IS; cardioembolic, CES; small vessel, SVS; large artery, LAS); WMH, white matter hyperintensity burden; DBP, diastolic blood pressure; SBP, systolic blood pressure; PP, pulse pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein. Diamond shape: non-significant. Cross-significant causal effect estimates from MR-LAP analysis.

### 3.4 | Polygenicity and multi-trait analysis

To identify additional SNPs conferring susceptibility to ACD and acting through related risk factors, we jointly studied the GW distribution of genetic effects for ACD and its closely related traits. We first prioritized those traits that have a polygenic background similar to ACD using a Bayesian approach (*ashR*). The *ashR* analysis showed that certain traits (ACD, stroke and its subtypes, WMH, coronary artery disease [CAD]) had specific, possibly overlapping, pathophysiological processes compared to other ACD risk factors (SBP, smoking [SMK], body mass index) that involved multiple biological pathways (Figure S69, Table S9). Next, using multitrait GWAS analysis (MTAG, see Methods) on ACD and the prioritized traits (CAD, stroke, WMH), we identified intronic SNPs in *SMG6* and *ABCG8* to be GW significant ( $p_{MTAG} < 1.67E-08$ , for three phenotypes) for ACD (Table S10). Interestingly, *SMG6* may also have a role in tau biology.<sup>44</sup> Finally, we explored the genetic difference between ACD/VaD and related disorders using case–case GWAS (CC-GWAS, see Methods). Specifically, we compared (1) ACD/VaD with AD and (2) ACD with stroke. VaD was not compared with stroke because the two disorders are highly correlated. Here we report signals that were not GW significant in both respective case-control GWASs. For AD, we identified two loci associated with ACD-AD status, including the known *APOE* region and the *IQUB* gene ( $p < 2e-08$ ) on chr7 (Table S11). No GW significant loci were associated with VaD-AD status, although we observed some suggestive association (Table S12). For ACD-stroke, we identified 56 variants mapping to 10 genes on chromosomes 17, 8, 11, 15, 4, and 12, most of which are located at the *SREBF1/TOM1L2* locus ( $p < 1e-10$ ) on chr17 (Table S13).

### 3.5 | Functional prioritization using molecular profile (gene expression)

To functionally characterize and prioritize individual ACD and VaD genomic risk loci, we performed TWASs using TWAS-Fusion, ACD, and VaD association statistics and weights from 23 gene-expression refer-

ence panels from blood, arterial, and brain tissues (see Methods). We identified 29 trait-associated (ACD/VaD) SNPs functioning as eQTLs, regulating the expression of 22 genes (eGenes) in disease-relevant tissue types (Table S14). To explore whether the observed associations are real or merely reflect the random overlap between eQTLs and non-causal risk variants for the dementia traits, a colocalization analysis was performed at each significant locus estimating the posterior probability of a shared causal variant ( $PP4 \geq 75\%$ ) between the gene expression and trait association. Overall, 30% of the eQTL-eGene satisfied the colocalization threshold for a shared causal variant between the ACD or VaD and gene expression. In addition to fine mapping functional genes (*RP11-385F7.1*, *CR1*, *MS4A6A*, *ACE*, *APOC4*) in the loci exhibiting GW association with ACD/VaD, the TWASs identified putative novel (*CLU*-ACD, *PIKFYVE*-VaD, *SH3D21*-ACD) genes satisfying transcriptome-wide significance threshold ( $p_{TWAS} < 1.18E-05$ ) and the colocalization probability threshold. Most (91%) of the eGenes are supported by the positional overlap of corresponding eQTLs with regulatory marks (enhancer and promoter binding sites) for active transcription in relevant tissue types.

### 3.6 | Protein–protein interaction (PPI) evidenced SEMA4D, RBOFOX1, and SPRY2 as hub genes for ACD and VaD

To determine the functional interactome of genes near genome-wide significant (excluding *APOE* region) and suggestive loci ( $p < 1e-6$ ) associated with ACD and VaD, we performed a PPI analysis using the STRING database. The analysis comprised 82 ACD and 21 VaD GW significant and suggestive genes that were successfully mapped to the human genome. Evidence of interaction between proteins was based on “experiments,” “co-occurrence,” “database,” and “co-expression,” with a minimum score of 0.15. Non-connected proteins were removed from the network. To further determine how suggestive genes will fit in the network of known AD genes, we used *kmeans* to cluster the proteins based on validated interaction. ACD genes formed two

main clusters (Figure S70). The first cluster was enriched in known AD genes, including *BIN1*, *CLU*, *ABCA7*, and *CR1*, but also suggestive genes, including *SEMA4D*, *CHD18*, and *APH1B*, with more than two types of connection evidence. *RBFOX1* appears to be a major hub gene for the second cluster, which includes other suggestive genes like *AJAP1*, *ANO3*, and *TRIB1*. *RBFOX1* and *SEMA4D* strongly (>2 evidence of connection) interact with known AD genes, suggesting their potential role in ACD. The PPI network of VaD (Figure S71) genes highlights the potential role of *SPRY2* as it functionally connects other genes, including *ERBB4*, *RASGRP1*, and *FOXA2*.

### 3.7 | Pathway and functional enrichment analysis

We conducted several analyses (pathways, gene ontology, disease enrichment) to obtain functional and biological contexts of genes (near variants with  $p < 1e-6$ , excluding the APOE region) associated with ACD and VaD.

#### 3.7.1 | Pathway analysis

Pathway analyses (Tables S15 and S16) revealed enrichment in several pathways, including “SREBF and miR33 in cholesterol and lipid homeostasis,” “Hypertrophy model,” and “Cholesterol metabolism with Bloch and Kandutsch-Russell pathways” for ACD.

#### 3.7.2 | Gene Ontology (GO) analysis

GO analysis for ACD (Figure S72 and Table S17) focusing on the biological processes (GO-BP) were enriched in terms related to amyloid-beta, “amyloid-beta metabolic process,” “amyloid precursor protein catabolic process,” and “negative regulation of amyloid precursor protein catabolic process” for ACD. For VaD (Figure S73 and Table S18), GO-BP analysis was enriched in several terms, including “response to glucose,” “response to hexose,” “response to monosaccharide,” “mesenchymal cell differentiation,” and “response to carbohydrate.”

#### 3.7.3 | Disease enrichment and association analysis

(Figures S74 and S75, Tables S19–S25) revealed that ACD genes were previously connected to AD, tauopathy, nephritis, and central nervous system disease. It also highlighted previous associations of *SEMA4D* and *RBFOX1* with diseases of the central nervous system. Besides the AD connection, VaD genes were previously related to cancer, diabetes, and colorectal carcinoma. Finally, we used Framingham Heart Study data to estimate the heritability of VaD and the genetic correlation with ACD. We found the heritability of VaD to be 6.1%, with a 95% confidence interval of [3.2%, 21%]. The genetic correlation of VaD and ACD was 0.48 (SE = 0.84).

## 4 | DISCUSSION

Our findings expand the current knowledge base of dementia genetics by focusing on both ACD and VaD. Our GWAS of ACD replicated several genes previously associated with AD, and GWAS of VaD identified SNPs in the APOE region. Using functional PPI and TW analyses, we identified novel genes underlying ACD that have been implicated in recovery from vascular injury and in neurotrophin signaling. On the basis of LD score regression analysis, we suggest that certain vascular risk factors may not have a causal role not in both ACD and VaD pathogenesis.

In our ACD analysis of European ancestry, we identified 10 GW significant loci, including *APOE*, *BIN1*, *MS4A6A*, *PICALM*, *CR1*, *CD2AP*, *ABCA7*, *PILRB*, *SLC24A4*, and *ACE*, all of which have been linked with AD risk in prior studies.<sup>45</sup> In addition, our analyses highlighted 24 suggestive risk loci, of which 13 are novel. Among them are variants located near *ANO3*, a gene that encodes anoctamin-3, a transmembrane protein that belongs to a family of calcium-activated chloride channels and is implicated in focal dystonia, particularly craniocervical.<sup>46</sup> Another suggestive locus was located near *SEMA4D*, a gene that encodes Semaphorin 4D and is known to modulate various processes related to neuroinflammation and neurodegeneration, including the initiation of inflammatory microglial activation.<sup>47</sup> Indeed, *SEMA4D* is critical in regulating the transition between homeostatic and reactive states of various types of glial cells. Antibody blockade of *SEMA4D* is being explored as a potential disease-modifying strategy to slow cognitive decline in patients with early Huntington's disease<sup>48</sup> and may be beneficial in other ACD. We have also identified a prominent signal near *RBFOX1*, a gene that encodes the RNA binding fox-1, which has been shown to have a role in alternative splicing of the amyloid precursor protein. Genetic variation in this gene has been associated with brain amyloid burden in preclinical and early AD and with the risk of clinical AD in African Americans.<sup>49</sup> This gene may also impact dementia risk through non-amyloidogenic pathways as it additionally regulates neuron development and neuronal excitability, including brain-derived neurotrophic factor (BDNF)-dependent long-term potentiation in the hippocampus and has been implicated in brain development, essential tremor, and schizophrenia.<sup>50</sup>

Other suggestive loci are located in the *ZNF652* gene, a transcriptional repressor involved in nucleic acid binding that has diverse effects, including determining the risk of hypertension. Hypertension is the most important risk factor for stroke and WMH and may be the most important modifiable risk factor for population prevention of dementia.<sup>51</sup> We additionally identified a variant near Heparin Binding EGF like growth factor (*HBEGF*), a growth factor implicated in the pathobiology of cerebral autosomal dominant arteriopathy with sub-cortical infarcts and leukoencephalopathy (CADASIL),<sup>52</sup> the major Mendelian prototype of VaD. *HBEGF* also has an effect on angiogenesis, expression of vascular endothelial growth factor A (VEGF-A), inflammation, and oxidative stress and has been implicated in hydrocephalus.<sup>53</sup>

*APOE* was strongly associated with both ACD and VaD in our meta-analysis. While AD could drive the association of *APOE* with ACD, the

relationship with VaD is less established but has been demonstrated in some population studies and candidate-gene analyses<sup>54</sup> and in a recent GWAS among the GR@ACE project participants.<sup>16</sup> The link of APOE with VaD is in line with recent literature suggesting that the pathogenesis of APOE extends beyond A $\beta$  peptide aggregation and clearance.<sup>55</sup> Indeed, APOE also influences microglia and the blood-brain barrier (BBB)<sup>56</sup> and is associated with intracranial atherosclerosis,<sup>57</sup> WMH burden, and the presence of cerebral microbleeds,<sup>58</sup> as well as with cerebral hypertensive angiopathy, which is common in individuals with VaD.<sup>59</sup>

In addition to a significant association of APOE with VaD in our sample, we identified several suggestive variants also associated with VaD. These include variants near the *SPPRY2* protein-coding gene as well as *GALNT8*, *FOXA1*, *ERBB4*, *PSMA3*, and *SEMA6D* with consistency across samples in the direction of effect and many SNPs in LD with the lead SNP. Our downstream analyses supported a highly plausible causal link between variants, including *SEMA4D*, *HBEGF*, *PIKFYVE*, and *RBFOX1* with ACD and *SPRY2* with VaD. These genes collectively emphasize a possible role for novel pathological mechanisms in ACD and VaD. Our findings highlight a crucial mechanism underlying ACD: recovery after vascular injury. For example, *SEMA4D*, a member of the semaphorin family, is upregulated in the neurovascular unit after IS, where it exerts multiple neuroprotective effects.<sup>60</sup> Moreover, this gene has been additionally highlighted in our PPI analysis as strongly associated with known AD genes. Another example is *SPRY2*, highlighted in our study as a suggestive gene for VaD, with strong functional associations with known AD and related dementias genes.

In the replication analysis of VaD signals in the EADB dataset, *SPRY2* has the lowest *p* value and a consistent direction of association. This gene has also been suggested as a possible pharmacological target for stroke patients, as it promotes angiogenesis and glial scarring around the ischemic injury, preventing an increase in lesion size and secondary damage to brain tissue.<sup>61</sup> Also, *SPRY2* may exert neuroprotective effects as its expression regulates BDNF-induced signaling pathways.<sup>62</sup> Similarly, *PIKFYVE* is an essential regulator of platelet lysosome homeostasis, which in turn may promote recovery after IS.<sup>63</sup> Another hub gene in our analyses is *RBFOX1*, which, in addition to having a role in amyloid accumulation as discussed earlier, mediates ischemic damage by enhancing neuronal survival and BBB integrity after stroke.<sup>64</sup> This gene is a neuron-specific splicing factor implicated in intellectual disability, epilepsy, autism, and Parkinson's disease. Its downregulation has been associated with destabilizing mRNAs encoding for synaptic transmission proteins, which may contribute to the loss of synaptic function in AD.<sup>65</sup> Furthermore, *RBFOX1* upregulation was shown to influence neuronal expression levels of the BDNF receptor, TrkB, which in turn may affect the risk for ACD.<sup>66</sup>

We found that the MS4A gene cluster drove genetic pleiotropy that involves vascular risk factors, inflammation, hemostasis, and soluble TREM2 levels. These findings align with preclinical studies<sup>67</sup> and emphasize the critical role and multifactorial contribution of this gene cluster to ACD pathogenesis. Although previous literature pointed to an association of *ACE* with AD but not VaD,<sup>68</sup> we herein show that this gene underlies both ACD and vascular risk factors. A recent

study supports this finding by showing that overexpression of *ACE* on macrophages reduces vascular amyloid and GFAP+ astroglial reactivation, indicating its role in the protection of the neurovascular unit.<sup>69</sup> Moreover, our pairwise analysis highlighted a locus at the *PRDM6* that explained a shared genetic susceptibility of VaD with IS and WMH. Low levels of leukocyte DNA methylation of the *PRDM6* gene have been associated with an increased risk of IS and worse outcomes 3 months after an IS.<sup>70</sup> Moreover, *PRDM6* acts as an epigenetic regulator of vascular smooth muscle cell plasticity.<sup>71</sup>

Despite evidence showing an inverse relationship between plasma HDL levels and risk of incident AD, results are conflicting, with some studies pointing to higher dementia risk in individuals with high HDL levels, as was also the case in our study.<sup>72</sup> It should be acknowledged that HDL represents a class of lipoproteins that are heterogeneous in structure and function, which is not reflected by a simple measurement of HDL plasma levels. High HDL levels can be deleterious under certain conditions.<sup>73</sup> Vascular risk factors and the presence of cardiovascular disease can alter HDL functionality by changing the structure of HDLs and converting them into pro-inflammatory, pro-oxidant, pro-thrombotic, and proapoptotic compounds. Our observation aligns with recent Mendelian randomization data implicating an elevated HDL in risk of AD.<sup>74</sup>

The following limitations should be considered when interpreting the results of this study. First, the multifactorial nature and heterogeneous clinical manifestations of ACD and VaD have led to various attempts to develop diagnostic criteria, which were differentially applied across the participating cohorts. ACD has been ascertained using DSM-IV in some studies. In contrast, others have used ICD-9/10 codes alone or in combination with autopsy or death certificate information, which can result in a varying proportion of persons identified as having dementia. The various cohorts also used different diagnostic criteria to define VaD. In all cohorts, a key requirement for VaD diagnosis remains the demonstration of a cognitive deficit and the presence of cerebrovascular disease, consistent with the most recent consensus criteria for VCID.<sup>75</sup> Whereas these criteria differ in sensitivity and specificity, thereby introducing statistical noise, this heterogeneity does not diminish the importance of the loci identified despite the constraints. A second limitation is the limited power to identify associations with VaD in ancestries other than European.

Our study identified several putative genetic variants and biological pathways associated with ACD and VaD and added additional support for the involvement of vascular mechanisms in dementia pathogenesis.

## ACKNOWLEDGMENTS

We thank the many study participants, researchers, and staff for collecting and contributing to the data. This project was conducted within the neurology working group of the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium. The CHARGE cohorts are supported in part by the National Heart, Lung, and Blood Institute (NHLBI) infrastructure grants R01HL105756 (Psaty), RC2HL102419 (Boerwinkle) and the neurology working group is supported by the National Institute on Aging (NIA) R01 grant AG033193. Additional funding sources

include the UT Health San Antonio Center for Biomedical Neuroscience (CBN) and grants from the NIA (AG059421, AG054076, AG049607, AG033090, AG066524, P30AG066546, 5P30AG059305-03, RF1 AG061729A1, 5U01AG052409-04) and NINDS (NS017950, UF1NS125513, K01NS126489). Funding sources for each cohort are listed in Supplementary File 2.

### CONFLICT OF INTEREST STATEMENT

Agustin Ruiz and Itziar de Rojas acknowledge research support from Grifols SA (Spain), Fundacion Bacaria LaCaixa (Spain), Instituto de Salud Carlos III Ministry of Health (Spain), Roche, and Janssen. Agustin Ruiz received consulting fees and honoraria from Landsteiner Genmed SL, Grifols SA, and Janssen; support for attending meetings from Grifols SA; and stock options from Landsteiner Genmed SL. All authors report no conflicts of interest. Additional author disclosures are available in the supporting information (Supplementary File 2).

### DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions. [https://ctg.cncr.nl/software/summary\\_statistics](https://ctg.cncr.nl/software/summary_statistics), <https://pubmed.ncbi.nlm.nih.gov/36180795/>

### CONSENT STATEMENT

All participants provided written informed permission, or, for those with substantial cognitive impairment, consent was provided by a caregiver, legal guardian, or other proxy. Author disclosures are available in the [supporting information](#).

### SOFTWARE AVAILABILITY

CC-GWAS: <https://github.com/wouterpeyrot/CCGWAS>

Gene expression weights for TWAS: <http://gusevlab.org/projects/fusion/>

HESS: [https://huwenboshi.github.io/hess/local\\_hsqg/](https://huwenboshi.github.io/hess/local_hsqg/)

LDSR: <https://github.com/bulik/ldsc>

GWAS-PW: <https://github.com/joepickrell/gwas-pw>

Radial-MR: <https://github.com/WSpiller/RadialMR>

GREP: <https://github.com/saorisakaue/GREP>

EPIGWAS: <https://immunogenomics.hms.harvard.edu/code>

Magma.Celltyping: [https://github.com/NathanSkene/MAGMA\\_Celltyping](https://github.com/NathanSkene/MAGMA_Celltyping)

MR-MEGA: <https://www.geenivaramu.ee/en/tools/mr-mega>

### DEFINITIONS

GWAS: Genome-Wide Association Analysis Study

ACD: All-cause dementia

VaD: Vascular dementia

VCID: Vascular Cognitive Impairment and Dementia

CHARGE: Cohorts for Heart and Aging Research in Genomic Epidemiology

ADGC: Alzheimer's Disease Genetics Consortium

UKBB: UK Biobank

EADB: European Alzheimer Disease DNA BioBank

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## SUPPORTING INFORMATION

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

**How to cite this article:** The Mega Vascular Cognitive Impairment and Dementia (MEGAVCID) consortium. A genome-wide association meta-analysis of all-cause and vascular dementia. *Alzheimer's Dement.* 2024;20:5973–5995.  
<https://doi.org/10.1002/alz.14115>

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