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Shared genetic architecture between Alzheimer's disease and blood pressure implicates ACE and NBEAL1 in individuals of European ancestry

Nicholas Ray
Columbia University Irving Medical Center
Diya Yang
Case Western Reserve University School of Medicine
Yihe Yang
Case Western Reserve University School of Medicine
Ajneesh Kumar
Columbia University Irving Medical Center
Jiji Kurup
Columbia University Irving Medical Center
Balaji Kannappan
Columbia University Irving Medical Center
Jenny Loaiza
Columbia University Irving Medical Center
Pamela Del Rosario
Columbia University Irving Medical Center
William Bush
Case Western Reserve University School of Medicine
Gary Beecham
Wake Forest University School of Medicine
Christiane Reitz
cr2101@cumc.columbia.edu

Columbia University Irving Medical Center

Research Article

Keywords: Alzheimer's disease, blood pressure, genetic correlation

Posted Date: November 4th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-11269850/v1

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Additional Declarations: No competing interests reported.

Abstract

Background

Vascular dysfunction is increasingly recognized as a contributor to Alzheimer's disease (AD), yet the genetic mechanisms linking blood pressure (BP) and AD remain incompletely understood. We investigated shared genetic architecture between AD and systolic blood pressure (SBP), diastolic blood pressure (DBP), and pulse pressure (PP) to identify locus-specific mechanisms connecting vascular regulation and neurodegeneration.

Results

We analyzed genome-wide association study summary statistics from individuals of European ancestry using global and local genetic correlation and conjunctional false discovery rate (conjFDR), followed by cis-Mendelian randomization (cis-MR), functional annotation, expression quantitative trait locus associations, and AD-specific multi-omic evidence. AD showed modest negative global genetic correlations with BP but significant local genetic correlation at eight regions. ConjFDR identified 42 high-confidence variants across 22 independent LD regions, with *PRKD3*, *NBEAL1*, *NDUFAF6*, *SPI1*, and the *APOE* region supported by both local genetic correlation and conjFDR. Cis-MR provided evidence for effects of BP on AD at multiple regions, with *ACE* and the *APOE* region showing significant effects for all three BP traits. Integrative analysis most strongly prioritized the *APOE* region, with convergent evidence at *ACE* and *NBEAL1* and additional signals implicating immune and mitochondrial pathways.

Conclusions

The genetic relationship between AD and BP is characterized by heterogeneous, locus-specific overlap not fully captured by genome-wide genetic correlation. Convergent evidence implicates *APOE*, *ACE*, *NBEAL1*, and other loci involved in vascular, immune, and mitochondrial biology, supporting multiple, partially BP-trait-specific mechanisms linking vascular regulation to AD.

BACKGROUND

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive decline and memory loss that accounts for approximately 60% of dementia cases worldwide(1). Increasing evidence implicates vascular dysfunction in AD pathogenesis(2), with blood pressure (BP) emerging as a key contributor(3). Both hypertension and hypotension have been associated with cognitive decline, mild cognitive impairment, and dementia, suggesting that disruption of cerebral blood flow may accelerate neurodegenerative processes(4–12). However, the biological mechanisms underlying the association between BP and AD remain incompletely understood, and clarifying the mechanistic overlap between vascular dysfunction and neurodegeneration is critical for improving risk stratification, early screening, prevention strategies, and therapeutic target discovery.

Systolic blood pressure (SBP), diastolic blood pressure (DBP), and pulse pressure (PP) reflect distinct aspects of vascular function and have each been linked to cognitive outcomes across the lifespan(6, 13). Midlife hypertension is consistently associated with increased dementia risk and may contribute to AD through endothelial dysfunction, blood–brain barrier disruption, impaired amyloid-β clearance, tau pathology, microvascular injury, and cerebral hypoperfusion(4–6). Conversely, chronic and orthostatic hypotension have also been associated with cognitive impairment and dementia, potentially through chronic cerebral hypoperfusion, hypoxia, oxidative stress, and neuroinflammation(7–12). Together, these findings suggest that both elevated and reduced BP may contribute to AD through vascular and neurodegenerative pathways.

Recent genome-wide association studies (GWAS) have identified numerous loci associated with both AD(14, 15) and BP-related traits(16). However, despite strong epidemiologic evidence linking BP and AD, studies examining their shared genetic architecture have produced inconsistent findings. Genome-wide analyses using linkage disequilibrium score regression (LDSC) generally report weak global genetic correlations between AD and cardiovascular traits(17, 18), while Mendelian randomization (MR) studies have yielded conflicting evidence regarding the causal relationship between BP and AD risk(19–22). These inconsistencies suggest that shared genetic influences may be localized to specific genomic regions that are not captured by genome-wide approaches alone.

To address this gap, we investigated local genetic associations between AD and BP traits to identify specific genomic regions contributing to both vascular regulation and neurodegeneration. By focusing on locus-specific genetic overlap, this approach can uncover biological mechanisms linking cardiovascular dysfunction and AD. Clarifying these shared pathways could improve understanding of AD pathogenesis and inform risk prediction, prevention strategies, and therapeutic target development.

RESULTS

Global Genetic Correlation

Linkage disequilibrium score regression (LDSC)(23, 24) was used to estimate pairwise genetic correlations (r_g) between AD and each of the three BP traits. All three BP traits showed a weak, yet significant, negative genome-wide correlation with AD: SBP, r_g = -0.16, *SE* = 0.03, *P* = 3.94×10^{-7}; DBP, r_g = -0.14, *SE* = 0.03, *P* = 3.86×10^{-6}; PP, r_g = -0.12, *SE* = 0.03, *P* = .0002.

Local Genetic Correlation

To assess local correlation, LAVA(25) was used to estimate local r_g between AD and each BP trait at 2,495 semi-independent genomic regions. The full results for all three analyses are available in Supplementary Table 1. Eight loci showed r_g between AD and at least one BP trait with *P*-values less than the Bonferroni threshold of 2.004×10^{-5} and genetic signals in each trait significant at $P < 5\times10^{-5}$ (Table 1; Supplementary Figure 1). Local r_g is observed between AD and all three BP traits at three loci: chr2p22.2 (*PRKD3*), chr7p15.1 (*JAZF1*), and chr11p11.2 (*SPI1*); three loci show local r_g between AD and both SBP and PP: chr19q13.32 (*APOE*), chr8q22.1 (*NDUFAF6*), and chr2q33.2 (*NBEAL1*); and AD is correlated with both SBP and DBP at chr8p21.1 (*CLU*).

Table 1. Significant regions of genetic overlap between AD and at least one BP trait

Chromosomal Band	Nearest Gene	SBP		DBP		PP	
		r_g	*P*	r_g	*P*	r_g	*P*
chr19q13.32	*APOE*	.24	1.50×10^{-6}*	-.08	.12	.50	3.48×10^{-20}*
chr8q22.1	*NDUFAF6*	-.80	2.18×10^{-9}*	-.32	.06	-.71	1.63×10^{-10}*
chr2q33.2	*NBEAL1*	-.97	3.53×10^{-7}*	-.30	.15	-.87	1.07×10^{-7}*
chr11q24.3	*ADAMTS8*	.66	5.08×10^{-6}*	-.08	.60	.60	4.03×10^{-7}*
chr2p22.2	*PRKD3*	-.74	7.14×10^{-5}	-.45	.02	-.99	8.02×10^{-6}*
chr7p15.1	*JAZF1*	-.47	2.88×10^{-6}*	-.43	5.33×10^{-5}	-.29	3.92×10^{-3}
chr11p11.2	*SPI1*	.64	1.18×10^{-4}	.85	1.07×10^{-6}*	.50	5.10×10^{-3}
chr8p21.1	*CLU*	.38	.02	.81	4.12×10^{-6}*	-.03	.84

abbreviations: SBP = systolic blood pressure; DBP = diastolic blood pressure; PP = pulse pressure; r_g = genetic correlation coefficient

*Significant at Bonferroni threshold of $P < 2.004\times10^{-5}$

Conjunctional False Discovery Rate

While LDSC(23, 24) provides estimates of global r_g and LAVA(25) calculates local region-based r_g, conjunctional false discovery rate (conjFDR)(26, 27) leverages cross-trait enrichment to identify genetic overlap between two phenotypes at each individual genetic variant. 5,354 SNPs, located at 199 independent loci, were identified with conjFDR < .05 between AD and SBP (Supplementary Table 2 and Supplementary Figure 2); 5,645 SNPs at 94 independent loci overlapped between AD and DBP (Supplementary Table 3 and Supplementary Figure 3); and 5,785 SNPs at 126 independent loci were shared between AD and PP (Supplementary Table 4 and Supplementary Figure 4). 42 variants showed a conjFDR < .001 between AD and at least one BP trait and were deemed high-confidence variants and prioritized for subsequent downstream analyses. These variants were located across 22 independent LD regions (Table 2 and Supplementary Figure 5). Notably, Chr2p22.2 (*PRKD3*), chr2q33.2 (*NBEAL1*), chr8q22.1 (*NDUFAF6*), chr11p11.2 (*SPI1*), and chr19q13.32 (*APOE* locus) were identified as shared genetic loci between AD and BP in both the LAVA and conjFDR analyses.

Table 2. Loci with conjFDR < .001 between AD and at least one BP trait

Chromosomal Band	Nearest Gene(s)	AD and SBP		AD and DBP		AD and PP	
		SNP	conjFDR	SNP	conjFDR	SNP	conjFDR
chr1p34.2	*RIMKLA*	-	-	-	-	rs12403406	7.13×10^{-4}
chr2p22.2	*PRKD3*	rs2268987	2.60×10^{-4}	-	-	-	-
chr2q14.3	*BIN1*	rs11690153	1.27×10^{-4}	-	-	-	-
chr2q33.2	*NBEAL1*	rs10932008	5.27×10^{-4}	-	-	rs10932008	6.39×10^{-5}
chr3p22.2	*TRANK1*	-	-	-	-	rs7624498	2.61×10^{-4}
chr3q25.2	*MME*	rs61762319	2.00×10^{-4}	rs61762319	.03	rs61762319	.002
chr6p21.32	*HLA-DRB1, HLA-DQB1*	rs9271515	1.70×10^{-4}	rs2395516	2.41×10^{-6}	rs9271375	1.32×10^{-8}
chr7q22.1	*ZKSCAN1, ZSCAN21, AP4M1, TAF6, MCM7, LAMTOR4, RPL7P60*	rs4729578	8.61×10^{-4}	rs4424195 rs41280968	1.05×10^{-6} 4.65×10^{-4}	-	-
chr8q22.1	*NDUFAF6*	rs9297949	9.14×10^{-6}	rs481887	5.52×10^{-4}	rs4582532	2.21×10^{-5}
chr8q22.2	*SNX31*	rs1693551	1.60×10^{-5}	rs1693551	2.88×10^{-5}	-	-
chr8q24.3	*PLEC, SPATC1*	-	-	rs11784619 rs79832570	1.31×10^{-4} 3.61×10^{-4}	-	-
chr10q23.1	*ZNF519P1, TSPAN14*	rs2486304	4.17×10^{-7}	rs7098414	2.31×10^{-5}	rs7098414	4.03×10^{-5}
chr11p11.2	*SLC39A13-AS1*	rs10838702	1.61×10^{-8}	rs10838702	3.85×10^{-8}	rs10838702	1.07×10^{-8}
chr14q22.1	*FERMT2*	rs17125944	4.11×10^{-6}	-	-	rs74825460	1.59×10^{-6}
chr15q22.2	*RPS27L, LACTB*	rs11071733	1.10×10^{-5}	-	-	rs11071733	7.93×10^{-6}
chr16p11.2a	*TMEM219*	rs4788203	3.50×10^{-4}	-	-	rs4788203	7.04×10^{-4}
chr16p11.2b	*FBXL19-AS1, PRSS36*	-	-	rs78924645	2.27×10^{-6}	rs7185007	1.44×10^{-4}
chr17q21.31	*CRHR1, MAPT, KANSL1*	rs55938136 rs58879558	4.42×10^{-5} 3.59×10^{-6}	rs55938136 rs58879558	7.21×10^{-5} 1.84×10^{-5}	rs55938136 rs16940904	.008 3.10×10^{-4}
chr17q21.32	*FLJ40194*	rs7225606	6.64×10^{-5}	rs7225606	1.04×10^{-4}	-	-
chr17q23.3	*ACE*	rs4968783	3.23×10^{-12}	rs4292	3.82×10^{-12}	rs4968783	3.59×10^{-4}
chr19p13.3	*KLF16*	rs893541	9.03×10^{-4}	-	-	rs893541	7.51×10^{-4}

chr19q13.32	*BCAM*, *TOMM40*, *NECTIN2*, *CLPTM1*, *RELB*, *EXOC3L2*, *MARK4*, *BLOC1S3*	rs118147862 rs1160983 rs11668285 rs10417555 rs11667829	1.18×10^{-5} 5.59×10^{-5} 1.46×10^{-4} 2.49×10^{-4} 1.72×10^{-5}	rs11667829	3.06×10^{-5}	rs118147862 rs4239533 rs1160983 rs117261169 rs11668285 rs10417555 rs10415392 rs11667829	3.73×10^{-10} 5.28×10^{-4} 1.48×10^{-9} 1.84×10^{-4} .005 1.97×10^{-6} 5.33×10^{-4} .002

abbreviations: AD = Alzheimer's disease; SBP = systolic blood pressure; DBP = diastolic blood pressure; PP = pulse pressure; conjFDR = conjunctional false discovery rate.

note: "-" indicates no significant conjunctional false discovery rate (conjFDR < .05) between the two traits.

Two independent loci were identified within 16p11.2 and are therefore denoted 16p11.2a (rs4788203) and 16p11.2b (rs78924645 and rs7185007).

cis-Mendelian Randomization

A series of *cis*-Mendelian randomization (*cis*-MR) analyses were performed to evaluate the potential causal effects of the three BP traits on AD within a 1 Mb window centered on each of the 42 high-confidence variants identified by the conjFDR analyses. The causal effect estimates (θ) are reported in Supplementary Table 5, along with SuSiE fine-mapping results identifying the variants with the highest PIPs within each region. Of the 22 independent LD regions containing the 42 high-confidence variants (Table 2), the *cis*-MR results suggest that SBP exerts a significant causal effect ($P < .05$) on AD at 12 regions (chr2q14.3, chr2q33.2, chr3q25.2, chr7q22.1, chr8q22.2, chr8q24.3, chr10q23.1, chr14q22.1, chr16p11.2a, chr16p11.2b, chr17q23.3, and chr19q13.32), that DBP exerts an effect at 7 regions (chr3p22.2, chr7q22.1, chr8q22.2, chr15q22.2, chr17q21.32, chr17q23.3, and chr19q13.32), and that PP exerts an effect on AD at 8 regions (chr2q14.3, chr2q33.2, chr3q25.2, chr11p11.2, chr16p11.2a, chr16p11.2b, chr17q23.3, and chr19q13.32). Several regions showed evidence across multiple BP traits. Chr17q23.3 (*ACE*) and chr19q13.32 (APOE locus) demonstrated significant *cis*-MR effects of all three BP traits on AD. Significant effects were also shared between SBP and DBP at chr7q22.1 and chr8q22.2, and between SBP and PP at chr2q14.3, chr2q33.2, chr3q25.2, chr16p11.2a, and chr16p11.2b.

Functional Annotation

To further characterize the potential functional significance of the 42 high-confidence variants, we annotated each variant using Combined Annotation Dependent Depletion (CADD)(28, 29) (Supplementary Table 6), which identified two missense variants with PHRED-scaled CADD scores > 20: rs61762319 in *MME* (PHRED = 22.4) and rs41280968 in *AP4M1* (PHRED = 22.8), indicating high predicted functional impact. Several additional variants had PHRED scores > 10, including rs4292 near *ACE* (PHRED = 15.61), rs11784619 near *PLEC* (PHRED = 11.02), rs1693551 in *SNX31* (PHRED = 10.67), and rs17125944 in *FERMT2* (PHRED = 10.65). Five of these six variants were located in regions showing significant *cis*-MR effects of at least one BP trait on AD: rs61762319 for SBP and PP, rs41280968 and rs1693551 for SBP and DBP, rs17125944 for SBP, and rs4292 for all three BP traits.

Expression Quantitative Trait Loci (eQTL)

To investigate the potential regulatory effects of the 42 high-confidence variants, we queried significant single-tissue expression quantitative trait locus (eQTL) associations across blood, artery, cardiac, and brain tissues from the Genotype-Tissue Expression (GTEx) Project(30) (Supplementary Table 7). Several variants showed significant eQTL associations across multiple tissues. Variants within the HLA region on chromosome 6 were associated with expression of multiple HLA genes across vascular, cardiac, whole-blood, and brain tissues, while rs1693551 was consistently associated with *SNX31* expression across nearly all evaluated tissues. At chr8q22.1, rs481887, rs4582532, and rs9297949 were associated with *NDUFAF6* expression across several brain and cardiac tissues, with additional associations involving *INTS8* and *TP53INP1*. The chr16p11.2 variants also demonstrated extensive regulatory associations, including *INO80E* and *MAPK3* for rs4788203 and *KAT8* and *PRSS36* for rs7185007 and rs78924645. Variants in the chr17q21.31 region were associated with expression of *LINC02210*, *LRRC37A4P*, and related transcripts across multiple tissues. Notably, the chr17q23.3 variant rs4308 showed significant associations with *ACE* expression across multiple tissues, providing additional regulatory evidence implicating *ACE* at this shared AD-BP locus. Additional eQTL associations involved genes including *BIN1*, *PRKD3*, and *LACTB*.

Integrative Variant Prioritization

Integrative variant prioritization identified several variants with strong convergent evidence across genetic, causal, functional, and regulatory analyses (Supplementary Table 8). The prioritization framework incorporated evidence from GWAS association statistics, local genetic correlation, conjFDR, *cis*-MR, CADD functional annotation, GTEx eQTL associations, and Agora AD risk scores. Based on the overall composite score, which integrated evidence across all three BP traits, chr19q13.32 was the most prominently prioritized region, with rs1160983 (*TOMM40*/*NECTIN2*) and rs118147862 (*BCAM*) ranking first and third overall, respectively. Rs1160983 also ranked in the top 10% for all three trait-specific composite scores, while rs118147862 ranked in the top 10% for SBP and PP and rs4239533 ranked in the top 10% for PP. Together, these findings identified chr19q13.32 as the region with the most consistent integrative evidence across AD and the three BP traits. The second-highest ranked variant overall, rs10838702, was located at chr11p11.2 (*SLC39A13-AS1*), with additional highly ranked variants implicating chr7q22.1 (*ZKSCAN1*/*ZSCAN21* and *AP4M1*/*TAF6*/*MCM7*), chr2q33.2 (*NBEAL1*), and chr17q23.3 (*ACE*).

Several additional regions showed high trait-specific composite scores for more than one BP trait. At chr11p11.2, rs10838702 (*SLC39A13-AS1*) ranked in the top 10% for both SBP and DBP. At chr17q23.3, rs4968783 ranked in the top 10% for SBP and rs4292 ranked in the top 10% for DBP. These two variants are in strong LD (r^2 = .95)(31), suggesting that their trait-specific prioritization reflects a shared underlying signal within the *ACE* region. At chr7q22.1, rs41280968 (*AP4M1*/*TAF6*/*MCM7*) was prioritized for SBP, whereas rs4424195 (*ZKSCAN1*/*ZSCAN21*) was prioritized for DBP. In contrast to the *ACE* variants, rs41280968 and rs4424195 are not in LD (r^2 = .04)(31), suggesting distinct signals within the same genomic region. At chr17q21.31, rs16940904 (*KANSL1*) ranked in the top 10% for DBP, while rs58879558 (*MAPT*) ranked in the top 10% for PP.

After accounting for prioritized variants occurring within the same genomic regions, chr2q33.2 represented the primary trait-specific signal, with rs10932008 (*NBEAL1*) ranking in the top 10% for PP but not SBP or DBP. For SBP or DBP no regions were uniquely prioritized after grouping nearby variants within their corresponding loci.

DISCUSSION

In this study, we integrated complementary genetic and functional approaches to characterize the shared architecture between AD and BP traits. Although genome-wide genetic correlations were modest and negative, analyses at the locus level revealed substantially greater heterogeneity, with a smaller set of regions showing convergence across local genetic correlation, cross-trait enrichment, *cis*-MR, functional annotation, gene expression, and AD-specific multi-omic evidence. The findings indicate that the relationship between BP and AD is unlikely to reflect a single genome-wide mechanism but instead involves multiple locus-specific pathways, some shared across BP traits and others more trait-specific. The

analysis reinforced signals at established AD-BP loci while identifying additional loci that may provide new insight into the biological connections between vascular regulation and neurodegeneration.

The chr19q13.32 APOE region and the chr17q23.3 loci near *ACE* emerged as two of the strongest regions of convergence, consistent with the established roles of these loci in AD and vascular biology. Chr19q13.32 showed the strongest overall convergence across the integrative analyses, with multiple variants and genes within the region consistently prioritized, including *TOMM40*, *NECTIN2*, and *BCAM*. The prominence of this region is expected given the established role of *APOE* in AD susceptibility and its extensive involvement in lipid and vascular biology(32). However, the prioritization of multiple genes and variants suggests that the shared AD-BP signal at this locus may extend beyond the canonical *APOE* effect and reflect a broader regulatory and vascular architecture. Similarly, chr17q23.3 near *ACE* showed particularly strong convergence across BP traits, including *cis*-MR, regulatory associations with *ACE* expression, and functional annotation. Because *ACE* is already established in BP regulation(33) and has been implicated in AD(34), these findings do not represent a novel association at the locus. Rather, the convergence of independent genetic, causal, and regulatory evidence strengthens the biological link between renin-angiotensin signaling, vascular homeostasis, and AD. Effects of this pathway on cerebral blood flow, blood–brain barrier integrity, oxidative stress, and neuroinflammation provide plausible mechanisms through which altered vascular regulation could contribute to neurodegeneration.

Beyond these established loci, several regions emerged as potentially novel contributors to the shared AD-BP architecture. The chr2q33.2 region near *NBEAL1* was particularly notable because it showed convergence across local genetic correlation, cross-trait enrichment, and *cis*-MR, with evidence involving both SBP and PP and stronger representation in the PP-specific prioritization. This locus is biologically compelling because *NBEAL1* has been implicated in arterial lipid biology, coronary artery disease, and white matter hyperintensity burden(35, 36), while recent multi-omic evidence has linked *NBEAL1* to AD-related vascular phenotypes(37). The convergence observed here therefore strengthens the possibility that *NBEAL1* represents a molecular connection between lipid handling, cerebrovascular dysfunction, and neurodegeneration. Its stronger association with PP may be particularly informative, as PP captures aspects of arterial stiffness and vascular aging that are not fully represented by SBP or DBP.

Additional novel loci further broaden the biological interpretation of the shared architecture. The chr11p11.2 region near *SPI1* showed local genetic correlation across all three BP traits and was independently supported by cross-trait enrichment and variant prioritization. *SPI1*, which encodes the transcription factor PU.1, plays a central role in myeloid-cell differentiation and immune regulation(38). Lower *SPI1* expression has been associated with delayed AD onset, while the PU.1 cistrome is enriched for AD heritability and experimental modulation of PU.1 alters AD-related gene expression and microglial phagocytic activity(39). Its identification in the AD-BP analysis raises the possibility that immune and vascular processes intersect in AD susceptibility, potentially through neuroinflammatory or vascular inflammatory pathways. The chr8q22.1 region near *NDUFAF6* provides a complementary signal implicating mitochondrial biology. *NDUFAF6* encodes an assembly factor required for mitochondrial complex I function(40), and mitochondrial has been implicated in both impaired vascular homeostasis(41) and neurodegenerative processes, including AD(42). The convergence of genetic and regulatory evidence at this locus therefore raises the possibility that altered cellular energy metabolism may contribute to the interface between vascular dysfunction and AD. Together, these loci extend the shared AD-BP architecture beyond established lipid and vascular pathways to include immune and mitochondrial mechanisms.

Collectively, the pattern of findings suggests that AD-BP genetic overlap is distributed across multiple biologically distinct pathways rather than driven by a single vascular mechanism. The established *APOE* and *ACE* loci provide important anchors and demonstrate that the integrative framework captures biologically credible AD-BP signals. In contrast, the convergence observed at *NBEAL1*, *SPI1*, and *NDUFAF6* provides potentially new mechanistic insight and identifies loci that may be particularly informative for future functional studies. The differences in loci prioritized across SBP, DBP, and PP further suggest that these traits should not be considered interchangeable measures of vascular biology in relation to AD, but rather may capture partially distinct pathways contributing to neurodegenerative risk.

This study has several strengths, including the use of large GWAS datasets and integration of complementary approaches that capture distinct aspects of genetic overlap. This multilevel framework enabled us to identify loci supported by convergent genetic, causal, functional, regulatory, and AD-specific evidence rather than relying on any single analytic approach. However, several limitations warrant consideration. The *cis*-MR findings provide supportive but not definitive evidence for causality, as estimates may be influenced by horizontal pleiotropy, complex LD, weak-instrument behavior, or reverse causality. Similarly, functional annotation and eQTL analyses provide biological context but do not establish the causal variant, gene, or cell type. Analyses were restricted to European-ancestry individuals, limiting generalizability to other populations, and the use of summary statistics precluded evaluation of individual-level interactions and non-additive effects. Functional analyses were further constrained by available tissues and bulk-tissue resolution. Finally, the composite score was designed to capture convergence across evidence types rather than provide a formal probability of causality; prioritized variants and loci should therefore be regarded as candidates for further investigation and hypothesis generation rather than definitive causal mechanisms.

CONCLUSIONS

Our findings reveal a heterogeneous genetic architecture linking AD and BP, with established loci such as *APOE* and *ACE* providing biological anchors and less-established loci including *NBEAL1*, *SPI1*, and *NDUFAF6* identifying potentially actionable pathways at the vascular-neurodegenerative interface. By resolving shared genetic effects into locus- and BP-trait-specific mechanisms, this framework provides a foundation for prioritizing therapeutic targets, developing vascular biomarkers, and identifying genetically defined patient subsets most likely to benefit from vascular or pathway-specific interventions. Ultimately, integrating vascular and AD genetic architecture may advance precision approaches to AD prevention and treatment by linking molecular mechanisms to biomarker development and targeted therapeutic strategies.

METHODS

Utilized Genomic Data

Summary statistics were obtained from the largest and most recent publicly available GWAS on AD(14) and BP(16) that have been conducted on individuals of European ancestry. The AD GWAS meta-analyzed results from 39,106 clinically diagnosed AD cases, 46,828 proxy AD and related dementia cases, and 401,577 cognitively normal controls across 10 cohorts (Supplementary Table 9): the European Alzheimer & Dementia Biobank (EADB), the GR@ACE study, the European Alzheimer's Disease Initiative (EADI), the Genetic and Environmental Risk in AD (GERAD) study, DemGene, Bonn, the Rotterdam study, the Copenhagen City Heart Study (CCHS), the Neocodex–Murcia (NxC) study, and the UK Biobank (UKB). The BP meta-analysis included 1,028,751 individuals from four cohorts: the Million Veteran Program (MVP), Vanderbilt University's BioVU, the UK Biobank (UKB), and the International Consortium for Blood Pressure (ICBP) (Supplementary Table 10). Genome-wide association analyses were performed for SBP, DBP, and PP.

Global Genetic Correlation Analyses

LDSC was used to estimate pairwise global genetic correlation between AD and each of the three BP traits using the GWAS summary statistics. Alleles from all four summary statistics were first aligned to the 1000 Genomes Phase 3 European reference panel(43). The summary statistics were then harmonized and reformatted (using the same reference panel(43)) with the *munge_sumstats.py* utility included in the LDSC software package(23, 24), which converts GWAS summary statistics into a standardized format, filters out non-SNP variants and strand-ambiguous SNPs, and removes SNPs with duplicated RSIDs, invalid/missing p-values, low imputation quality, and/or minor allele frequency less than or equal to .01. The '--rg' function in LDSC estimates the genetic correlation between two traits by calculating the cross-product of Z-scores from both traits at each SNP and regressing this value from the SNP's LD score. The slope of this regression (which

captures the genome-wide covariance structure) is then standardized by the heritabilities of each trait to estimate the genetic correlation (r_g)(23).

Local Genetic Correlation Analyses

Local genetic correlation analyses between Alzheimer's disease (AD) and each blood pressure (BP) trait were performed using LAVA (Local Analysis of [co]Variant Association)(25). LAVA partitions the genome into 2,495 semi-independent loci based on linkage disequilibrium and estimates locus-specific bivariate genetic correlations while accounting for sampling covariance and sample overlap. Statistical significance was determined using a Bonferroni-corrected threshold of P < 2.004×10^-5.

Conjunctional False Discovery Rate

To evaluate genetic overlap between AD and BP at the variant level, we applied the conjFDR framework implemented in the pleioFDR toolbox(26, 27), which leverages cross-trait enrichment between two phenotypes. First, conditional quantile-quantile (Q-Q) plots were constructed by stratifying SNPs according to their level of association with a secondary phenotype (BP) and plotting observed versus expected -log10(p) values for the primary phenotype (AD). Progressive leftward deflection of these curves with increasing levels of association in the secondary phenotype is interpreted as evidence of cross-trait enrichment. Fold-enrichment plots were additionally generated to quantify enrichment as the ratio of the cumulative -log10(p) distribution within each stratum relative to all SNPs. To minimize confounding from population stratification and relatedness, test statistics were corrected for genomic inflation using intergenic SNPs. SNPs were further pruned to approximate independence by randomly selecting one SNP per linkage disequilibrium block ($r^2 > 0.1$) across 500 iterations. The conditional false discovery rate (condFDR) for each SNP was then estimated using a two-dimensional lookup table, computing the FDR for the primary phenotype conditional on the *P*-values of the secondary phenotype.

conjFDR was applied to identify loci jointly associated with both phenotypes. This was calculated as the maximum of the two condFDR values obtained by alternating the roles of the primary and secondary phenotypes, providing a conservative estimate of shared association. This combined approach improves power for SNP discovery and enables identification of shared genetic loci, independent of effect direction. Three conjFDR analyses were performed with a conjFDR threshold of 0.05 using the summary statistics for AD and the three BP traits that were aligned and QCed with *munge_sumstats.py*(24) and the 1000 Genomes Phase 3 European reference panel(43) as described above. Variants in the major histocompatibility complex region (chr6: 25119106-33854733) were excluded.

AD was always the primary phenotype, and each of the three BP traits (SBP, DBP, and PP) was entered as the secondary phenotype. Cross-trait enrichment was visualized using conditional quantile-quantile (Q-Q) plots, which display the distribution of *P*-values for a primary phenotype across all SNPs and for SNP strata defined by their association strength with the secondary phenotype. Significant variants were grouped into genomic loci using the locus-definition procedure implemented in pleioFDR, which clusters associated variants according to local LD structure and identifies a single lead SNP to represent each locus(26). To focus subsequent analyses on variants with the strongest evidence of shared association, variants with a conjFDR < 0.001 between AD and at least one BP trait were designated as high-confidence variants and selected for downstream cis-MR, functional annotation, eQTL, and integrative prioritization analyses.

***cis*-Mendelian Randomization Analyses**

cis-MR is an instrumental variable (IV) method that utilizes genetic variants (in proximity to a target gene or SNP) as IVs to estimate the causal effects of exposures (e.g., BP) on outcomes (e.g., AD)(44). *Cis*-MRBEE(45) estimates causal effects using a penalized regression framework applied to predicted GWAS effects. Sparse exposure effects are identified using the Sum of Single Effects (SuSiE)(46), which selects nonzero instruments and defines 95% credible sets. To reduce bias from weak instruments, *Cis*-MRBEE incorporates an unbiased estimating equation. At each iteration, causal effect estimates are updated by solving a bias-corrected score equation, ensuring consistency even when standard estimating

equations would otherwise yield biased estimates. Because SuSiE-based predictions can produce highly correlated or identical exposures, particularly in regions with limited genetic resolution, *Cis*-MRBEE introduces an additional discrete differential penalty. This penalty operates within SuSiE-defined credible sets, constraining exposure-specific effects to be similar and effectively treating variants within a credible set as a single signal. This approach mitigates collinearity and stabilizes estimation.

Three analyses were performed with cis-MRBEE: AD was always the outcome and each of the three BP traits (SBP, DBP, and PP) were entered as exposures. For each locus identified with conjFDR, we created a 1 Mb window (500 kb up and down from the lead SNP) and then applied the *CisMRBEE_UV* function from the 'MRBEEX' R package to this region. All variants in these regions were extracted from the summary statistics for AD(14) and BP(16), which were previously aligned to the 1000 Genomes Phase 3 European reference panel(43) as described above. Sample overlap between AD and each BP trait was estimated with LDSC(23, 24) and the Principal Orthogonal complEment Thresholding (POET) method(47) was used to shrink the 1000 Genomes reference panel. Genetic variants were clumped using PLINK(48) with $r^2 < 0.64$ and $p < .001$ to remove highly correlated variants while preserving informative proxies for causal variants and the correlation matrix between exposure and outcome estimation errors (Rxy) was set to account for potential sample overlap, with minimal correlation (0.01) used between AD and BP. Maximum causal signals for fine-mapping (xQTL.max.L) was set to 5, posterior inclusion probability (PIP) threshold (xQTL.pip.thres) was set to 0.5, minimum PIP for credible set purification (xQTL.pip.min) was set to 0.2, the ADMM penalty parameter (admm.rho) was set to 1, and the tuning parameter vector for direct causal effect penalization was entered as such: 'tauvec = seq(1.5, 4, by =0.2)'.

Functional Annotation

Functional annotation was performed for the 42 high-confidence variants identified by the conjFDR analyses using CADD v1.7 (https://cadd.bihealth.org/info)(28, 29). CADD integrates diverse genomic annotations, including conservation metrics, regulatory information, and protein-level predictions, using a machine learning framework that contrasts observed human variants with simulated mutations. PHRED-scaled CADD scores were obtained for each variant, with higher scores indicating greater predicted deleteriousness (e.g., scores ≥20 correspond to the top 1% of predicted deleterious variants).

CADD also annotates variants using existing gene models to identify overlapping genes and predicted functional consequences (e.g., intronic, synonymous, or missense). Variants may be assigned to multiple genes or transcripts when they overlap more than one genomic feature. For noncoding variants, these annotations reflect genomic overlap and do not necessarily identify the gene through which the variant exerts a regulatory effect.

Expression Quantitative Trait Loci

eQTL data were obtained using the gtexr R package(49), which queries the GTEx API V2 to retrieve data from GTEx(30). The get_significant_single_tissue_eqtls function was used to extract the most significant eQTL association reported by GTEx for each high-confidence variant within each evaluated tissue. Associations were queried across tissues relevant to vascular and neurological function, including whole blood, artery (aorta, coronary, and tibial); heart (atrial appendage and left ventricle), and brain (amygdala, anterior cingulate cortex, caudate [basal ganglia], cortex, frontal cortex, hippocampus, hypothalamus, nucleus accumbens [basal ganglia], putamen [basal ganglia], and substantia nigra).

Agora AD Risk Scores

The Agora AD Knowledge Portal (https://agora.adknowledgeportal.org/) summarizes a variety of genetic and epigenetic evidence to calculate scores that represent the association between a gene and AD risk(50). The Genetic Risk Score ranges from 0–3 and incorporates evidence from 24 GWAS, including GWAS-by-proxy analyses, three quantitative trait locus studies, supporting phenotypic data from human and/or animal models, and information regarding gene modeling within the MODEL-AD consortium. The Multi-omic Risk Score ranges from 0–2 and incorporates transcriptomic and proteomic evidence, including RNA-sequencing and protein-abundance data across multiple neocortical tissues. The Target Risk

Score is calculated as the sum of the Genetic and Multi-omic Risk Scores and was used as the gene-level Agora metric in the present study.

Integrative Variant Prioritization

To integrate evidence across complementary genetic, causal, functional, and regulatory analyses, we developed a composite scoring framework to prioritize the high-confidence variants identified by conjFDR. An overall composite score incorporating evidence across all three BP traits was calculated, along with trait-specific composite scores for SBP, DBP, and PP.

The prioritization framework incorporated evidence from GWAS association statistics, local genetic correlation, conjFDR, *cis*-MR, CADD functional annotation, GTEx eQTL associations, and Agora AD risk scores. Statistical significance measures were -log10 transformed such that larger values represented stronger evidence of association. This transformation was applied to GWAS *P*-values, LAVA local genetic correlation *P*-values, *cis*-MR *P*-values, and conjFDR values. Although conjFDR is not a *P*-value, smaller conjFDR values indicate stronger evidence of shared association and were therefore transformed in the same manner for incorporation into the composite score. For the eQTL component, tissue-specific *P*-values were -log10 transformed, and the transformed values were averaged across tissues with available eQTL data to generate a single mean eQTL score for each variant. This approach ensured that eQTL evidence contributed a single component to the composite score rather than weighting each tissue-specific association independently. For the Agora component, the Target Risk Score was obtained for the gene annotated to each high-confidence variant by CADD. When a variant was annotated to multiple genes, the mean of the available Target Risk Scores across those genes was calculated to generate a single Agora score for that variant. Variants for which no Target Risk Score was available were treated as missing for this component of the composite score. All continuous components were subsequently standardized as z-scores to place the different sources of evidence on a common scale. The CADD PHRED score, mean eQTL score, and mean Agora Target Risk Score each contributed a single standardized component. Missing values were excluded from calculation of the composite scores rather than assigned a value. For the overall composite score, the standardized components included the AD, SBP, DBP, and PP GWAS association statistics; AD-SBP, AD-DBP, and AD-PP conjFDR values; AD-SBP, AD-DBP, and AD-PP local genetic correlation *P*-values; AD-SBP, AD-DBP, and AD-PP *cis*-MR *P*-values; and the CADD PHRED, mean eQTL, and mean Agora Target Risk Scores. The overall composite score was calculated as the mean of all available standardized components for each variant. For the trait-specific composite scores, components were restricted to evidence relevant to the corresponding BP trait. The SBP composite score incorporated the AD and SBP GWAS association statistics, AD-SBP conjFDR value, AD-SBP local genetic correlation *P*-value, AD-SBP *cis*-MR *P*-value, CADD PHRED score, mean eQTL score, and mean Agora Target Risk Score. Corresponding components were used for the DBP and PP composite scores. Higher composite scores indicated stronger convergent evidence across the incorporated genetic, causal, functional, and regulatory measures. Variants were ranked according to their overall and trait-specific composite scores, and percentile ranks were calculated to facilitate comparison across variants.

Declarations

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study used publicly available summary-level data from previously published genome-wide association studies and did not involve the collection of new individual-level data or biological samples. Ethical approval and informed consent were obtained by the investigators of the original studies in accordance with their respective institutional and study-specific requirements. Details regarding ethical approval and participant consent procedures are provided in the original publications for each contributing study.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

All data analyzed in this study were obtained from publicly available genome-wide association study summary statistics and publicly available genomic resources. The datasets used in the analyses are described and cited in the Methods section and can be accessed through the repositories and resources specified in the original publications. No new individual-level data were generated as part of this study.

COMPETING INTERESTS

The authors have no competing interests to report related to this publication.

FUNDING

This work was supported by grants from the National Institute on Aging (NIA), National Institutes of Health (NIH): P30AG066462, U01AG079850, U01AG084545, U19AG074865, R01AG072547, U24AG056270, and R01AG064614.

AUTHORS' CONTRIBUTIONS

NRR and CR conceived and designed the study. NRR performed the primary analyses, interpreted the results, and drafted the manuscript. DY, YY, and WSB developed the analytical pipeline used in the study. DY provided substantial methodological and analytical support for the conjunctional false discovery rate and cis-Mendelian randomization analyses, and YY provided methodological and analytical support for the cis-Mendelian randomization analyses. AK, JK, BK, JL, and PDR contributed to data analysis, interpretation of findings, and manuscript review. WSB and GWB contributed expertise in statistical genetics, interpretation of the genetic analyses, and critical review of the manuscript. CR supervised the study, contributed to interpretation of the findings, and critically revised the manuscript. All authors reviewed and approved the final manuscript.

ACKNOWLEDGEMENTS

The authors acknowledge the Genotype-Tissue Expression (GTEx) Project for providing the gene expression and expression quantitative trait locus data used in this study. The GTEx Project was supported by the Common Fund of the Office of the Director of the National Institutes of Health and by the National Cancer Institute, National Human Genome Research Institute, National Heart, Lung, and Blood Institute, National Institute on Drug Abuse, National Institute of Mental Health, and National Institute of Neurological Disorders and Stroke.

The authors also acknowledge the Agora Alzheimer's Disease Gene Evidence Portal and the AD Knowledge Portal for providing the genetic and multi-omic evidence used for AD gene prioritization. Agora and the AD Knowledge Portal are developed and maintained by Sage Bionetworks with support from the National Institute on Aging and include data and analytical resources generated through the Accelerating Medicines Partnership–Alzheimer's Disease (AMP-AD), TREAT-AD, and other NIA-supported research programs.

The authors additionally acknowledge the investigators and participants of the genome-wide association studies whose summary statistics made these analyses possible, as well as the 1000 Genomes Project for providing the reference data used for genetic harmonization and linkage disequilibrium analyses.

References

1. Major D, Dósa N, Balázs P, Fekete M, Pártos K, Árva D et al (2026) Global trends in the incidence and prevalence of Alzheimer's disease. Advances in Translational Research. :1661.2025. 00106

2. Sweeney MD, Kisler K, Montagne A, Toga AW, Zlokovic BV (2018) The role of brain vasculature in neurodegenerative disorders. Nat Neurosci 21(10):1318–1331
3. Sheikh AM, Yano S, Tabassum S, Nagai A (2024) The Role of the Vascular System in Degenerative Diseases: Mechanisms and Implications. Int J Mol Sci. ;25(4)
4. Canavan M, O'Donnell MJ (2022) Hypertension and Cognitive Impairment: A Review of Mechanisms and Key Concepts. Front Neurol 13:821135
5. Gabin JM, Tambs K, Saltvedt I, Sund E, Holmen J (2017) Association between blood pressure and Alzheimer disease measured up to 27 years prior to diagnosis: the HUNT Study. Alzheimers Res Ther 9(1):37
6. Jiang E, Ullah S, Waheed I, Han J, Zhang X (2026) Hypertension as a Major Risk Factor in Alzheimer's Disease: Mechanisms, Interactions and Therapeutic Perspectives. Clin Interv Aging. :585864
7. Momtaz YA, Hamid TA, Haron SA, Bagat MF, Mohammadi F (2018) Prevalence of hypotension and its association with cognitive function among older adults. Aging Ment Health 22(4):447–452
8. Min M, Shi T, Sun C, Liang M, Zhang Y, Tian S et al (2020) The association between orthostatic hypotension and cognition and stroke: a meta-analysis of prospective cohort studies. Blood Press 29(1):3–12
9. Cansino S, Torres-Trejo F, Estrada-Manilla C, Mercado-Canales A, Medina-Velázquez D, Esquivel-García R et al (2022) Effects of hypotension and hypertension on source memory and working memory. Aging Ment Health 26(9):1738–1746
10. Kleipool EEF, Trappenburg MC, Rhodius-Meester HFM, Lemstra AW, van der Flier WM, Peters MJL et al (2019) Orthostatic Hypotension: An Important Risk Factor for Clinical Progression to Mild Cognitive Impairment or Dementia. The Amsterdam Dementia Cohort. J Alzheimers Dis 71(1):317–325
11. den Brok M, Eggink E, Hoevenaar-Blom MP, van Gool WA, van Moll EP, Richard E et al (2022) Low Values for Blood Pressure, BMI, and Non-HDL Cholesterol and the Risk of Late-Life Dementia. Neurology 99(15):e1630–e9
12. Cheng Y, Lin L, Huang P, Zhang J, Wang Y, Pan X (2025) Hypotension with neurovascular changes and cognitive dysfunction: An epidemiological, pathobiological, and treatment review. Chin Med J (Engl) 138(4):405–418
13. Adesuyan M, Jani YH, Alsugeir D, Cheung ECL, Chui CSL, Howard R et al (2022) Antihypertensive Agents and Incident Alzheimer's Disease: A Systematic Review and Meta-Analysis of Observational Studies. J Prev Alzheimers Dis 9(4):715–724
14. Bellenguez C, Küçükali F, Jansen IE, Kleineidam L, Moreno-Grau S, Amin N et al (2022) New insights into the genetic etiology of Alzheimer's disease and related dementias. Nat Genet 54(4):412–436
15. Kunkle BW, Grenier-Boley B, Sims R, Bis JC, Damotte V, Naj AC et al (2019) Genetic meta-analysis of diagnosed Alzheimer's disease identifies new risk loci and implicates Aβ, tau, immunity and lipid processing. Nat Genet 51(3):414–430
16. Keaton JM, Kamali Z, Xie T, Vaez A, Williams A, Goleva SB et al (2024) Genome-wide analysis in over 1 million individuals of European ancestry yields improved polygenic risk scores for blood pressure traits. Nat Genet 56(5):778–791
17. Bellou E, Escott-Price V (2022) Are Alzheimer's and coronary artery diseases genetically related to longevity? Front Psychiatry 13:1102347
18. Zhu Z, Lin Y, Li X, Driver JA, Liang L (2019) Shared genetic architecture between metabolic traits and Alzheimer's disease: a large-scale genome-wide cross-trait analysis. Hum Genet 138(3):271–285
19. Østergaard SD, Mukherjee S, Sharp SJ, Proitsi P, Lotta LA, Day F et al (2015) Associations between Potentially Modifiable Risk Factors and Alzheimer Disease: A Mendelian Randomization Study. PLoS Med 12(6):e1001841 discussion e
20. Sargurupremraj M, Soumaré A, Bis JC, Surakka I, Jürgenson T, Joly P et al (2024) Genetic Complexities of Cerebral Small Vessel Disease, Blood Pressure, and Dementia. JAMA Netw Open 7(5):e2412824

21. Larsson SC, Traylor M, Malik R, Dichgans M, Burgess S, Markus HS (2017) Modifiable pathways in Alzheimer's disease: Mendelian randomisation analysis. BMJ 359:j5375
22. Ou YN, Yang YX, Shen XN, Ma YH, Chen SD, Dong Q et al (2021) Genetically determined blood pressure, antihypertensive medications, and risk of Alzheimer's disease: a Mendelian randomization study. Alzheimers Res Ther 13(1):41
23. Bulik-Sullivan B, Finucane HK, Anttila V, Gusev A, Day FR, Loh PR et al (2015) An atlas of genetic correlations across human diseases and traits. Nat Genet 47(11):1236–1241
24. Bulik-Sullivan BK, Loh PR, Finucane HK, Ripke S, Yang J, Patterson N et al (2015) LD Score regression distinguishes confounding from polygenicity in genome-wide association studies. Nat Genet 47(3):291–295
25. Werme J, van der Sluis S, Posthuma D, de Leeuw CA (2022) An integrated framework for local genetic correlation analysis. Nat Genet 54(3):274–282
26. Andreassen OA, Thompson WK, Schork AJ, Ripke S, Mattingsdal M, Kelsoe JR et al (2013) Improved detection of common variants associated with schizophrenia and bipolar disorder using pleiotropy-informed conditional false discovery rate. PLoS Genet 9(4):e1003455
27. Smeland OB, Frei O, Shadrin A, O'Connell K, Fan CC, Bahrami S et al (2020) Discovery of shared genomic loci using the conditional false discovery rate approach. Hum Genet 139(1):85–94
28. Kircher M, Witten DM, Jain P, O'Roak BJ, Cooper GM, Shendure J (2014) A general framework for estimating the relative pathogenicity of human genetic variants. Nat Genet 46(3):310–315
29. Schubach M, Maass T, Nazaretyan L, Röner S, Kircher M (2024) CADD v1.7: using protein language models, regulatory CNNs and other nucleotide-level scores to improve genome-wide variant predictions. Nucleic Acids Res 52(D1):D1143–d54
30. Lonsdale J, Thomas J, Salvatore M, Phillips R, Lo E, Shad S et al (2013) Nat Genet 45(6):580–585The Genotype-Tissue Expression (GTEx) project
31. Machiela MJ, Chanock SJ (2015) LDlink: a web-based application for exploring population-specific haplotype structure and linking correlated alleles of possible functional variants. Bioinformatics 31(21):3555–3557
32. Yamazaki Y, Zhao N, Caulfield TR, Liu CC, Bu G (2019) Apolipoprotein E and Alzheimer disease: pathobiology and targeting strategies. Nat Rev Neurol 15(9):501–518
33. Bernstein KE, Giani JF, Shen XZ, Gonzalez-Villalobos RA (2014) Renal angiotensin-converting enzyme and blood pressure control. Curr Opin Nephrol Hypertens 23(2):106–112
34. Xin XY, Lai ZH, Ding KQ, Zeng LL, Ma JF (2021) Angiotensin-converting enzyme polymorphisms AND Alzheimer's disease susceptibility: An updated meta-analysis. PLoS ONE 16(11):e0260498
35. Bindesbøll C, Aas A, Ogmundsdottir MH, Pankiv S, Reine T, Zoncu R et al (2020) NBEAL1 controls SREBP2 processing and cholesterol metabolism and is a susceptibility locus for coronary artery disease. Sci Rep 10(1):4528
36. Traylor M, Zhang CR, Adib-Samii P, Devan WJ, Parsons OE, Lanfranconi S et al (2016) Genome-wide meta-analysis of cerebral white matter hyperintensities in patients with stroke. Neurology 86(2):146–153
37. Li R, Feng R, Liu A, Cao X, De Jager PL, Bennett D et al (2025) Neuroimaging-derived brain endophenotypes link molecular mechanisms to Alzheimer's disease and aging. medRxiv
38. Li G, Hao W, Hu W (2020) Transcription factor PU.1 and immune cell differentiation (Review). Int J Mol Med 46(6):1943–1950
39. Huang KL, Marcora E, Pimenova AA, Di Narzo AF, Kapoor M, Jin SC et al (2017) A common haplotype lowers PU.1 expression in myeloid cells and delays onset of Alzheimer's disease. Nat Neurosci 20(8):1052–1061
40. Sung AY, Guerra RM, Steenberge LH, Alston CL, Murayama K, Okazaki Y et al (2024) Systematic analysis of NDUFAF6 in complex I assembly and mitochondrial disease. Nat Metab 6(6):1128–1142

41. Kirkman DL, Robinson AT, Rossman MJ, Seals DR, Edwards DG (2021) Mitochondrial contributions to vascular endothelial dysfunction, arterial stiffness, and cardiovascular diseases. Am J Physiol Heart Circ Physiol 320(5):H2080–h100
42. Monzio Compagnoni G, Di Fonzo A, Corti S, Comi GP, Bresolin N, Masliah E (2020) The Role of Mitochondria in Neurodegenerative Diseases: the Lesson from Alzheimer's Disease and Parkinson's Disease. Mol Neurobiol 57(7):2959–2980
43. Auton A, Brooks LD, Durbin RM, Garrison EP, Kang HM, Korbel JO et al (2015) A global reference for human genetic variation. Nature 526(7571):68–74
44. Smith GD, Ebrahim S (2003) Mendelian randomization': can genetic epidemiology contribute to understanding environmental determinants of disease? Int J Epidemiol 32(1):1–22
45. Yang Y, Lorincz-Comi N, Li M, Zhu X (2025) A multivariable cis-Mendelian randomization method robust to weak instrument bias and horizontal pleiotropy bias. Brief Bioinform. ;26(3)
46. Zou Y, Carbonetto P, Wang G, Stephens M (2022) Fine-mapping from summary data with the Sum of Single Effects model. PLoS Genet 18(7):e1010299
47. Fan J, Liao Y, Mincheva M (2013) Large Covariance Estimation by Thresholding Principal Orthogonal Complements. J R Stat Soc Ser B Stat Methodol. ;75(4)
48. Purcell S, Neale B, Todd-Brown K, Thomas L, Ferreira MA, Bender D et al (2007) PLINK: a tool set for whole-genome association and population-based linkage analyses. Am J Hum Genet 81(3):559–575
49. Warwick AN, Zuckerman B, Ung CY, Luben R, Olvera-Barrios A (2025) gtexr: A convenient R interface to the Genotype-Tissue Expression (GTEx) Portal API. J Open Source Softw 10(109):8249
50. Cary GA, Wiley JC, Gockley J, Keegan S, Amirtha Ganesh SS, Heath L et al (2024) Genetic and multi-omic risk assessment of Alzheimer's disease implicates core associated biological domains. Alzheimers Dement (N Y) 10(2):e12461

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