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ORIGINAL PAPER

Dissecting the genetic relationship between cardiovascular risk factors and Alzheimer's disease

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Abstract

Cardiovascular (CV)- and lifestyle-associated risk factors (RFs) are increasingly recognized as important for Alzheimer's disease (AD) pathogenesis. Beyond the ε4 allele of apolipoprotein E (*APOE*), comparatively little is known about whether CV-associated genes also increase risk for AD. Using large genome-wide association studies and validated tools to quantify genetic overlap, we systematically identified single nucleotide polymorphisms (SNPs) *jointly* associated with AD and one or more CV-associated RFs, namely body mass index (BMI), type 2 diabetes (T2D), coronary artery disease (CAD), waist hip ratio (WHR), total cholesterol (TC), triglycerides (TG), low-density (LDL) and high-density lipoprotein (HDL). In fold enrichment plots, we observed robust genetic enrichment in AD as a function of plasma lipids (TG, TC, LDL, and HDL); we found minimal AD genetic enrichment conditional on BMI, T2D, CAD, and WHR. Beyond *APOE*, at conjunction FDR < 0.05 we identified 90 SNPs on 19 different chromosomes that were jointly associated with AD and CV-associated outcomes. In meta-analyses across three independent cohorts, we found four novel loci within *MBLAC1* (chromosome 7, meta-$p = 1.44 \times 10^{-9}$), *MINK1* (chromosome 17, meta-$p = 1.98 \times 10^{-7}$) and two chromosome 11 SNPs within the *MTCH2/SPI1* region (closest gene = *DDB2*, meta-$p = 7.01 \times 10^{-7}$ and closest gene = *MYBPC3*, meta-$p = 5.62 \times 10^{-8}$). In a large 'AD-by-proxy' cohort from the UK Biobank, we replicated three of the four novel AD/CV pleiotropic SNPs, namely variants within *MINK1*, *MBLAC1,* and *DDB2*. Expression of *MBLAC1, SPI1, MINK1* and *DDB2* was differentially altered within postmortem AD brains. Beyond *APOE*, we show that the polygenic component of AD is enriched for lipid-associated RFs. We pinpoint a subset of cardiovascular-associated genes that strongly increase the risk for AD. Our collective findings support a disease model in which cardiovascular biology is integral to the development of clinical AD in a subset of individuals.

Keywords Lipids · Polygenic enrichment · Cardiovascular · Alzheimer's disease · Genetic pleiotropy

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Introduction

There is mounting evidence that cardiovascular (CV) disease impacts Alzheimer's disease (AD) pathogenesis. Co-occurrence of CV and AD pathology is the most common cause of dementia among the elderly [6] and imaging manifestations of vascular pathology are routinely observed in the brain on MRI scans of AD patients [41]. Observational epidemiology studies have found that cardiovascular-/lifestyle-related risk factors (RFs) are associated with dementia risk and targeting these modifiable RFs may represent a viable dementia

prevention strategy [7, 32]. Recently, the *National Academy of Medicine* [30] and the *Lancet* [26] commissioned independent reports on strategies for dementia prevention. Both reports found encouraging evidence for targeting cardiovascular RFs with the *Lancet* commission concluding that 35% of dementia could be prevented by modifying several RFs including diabetes, hypertension, obesity, and physical inactivity.

Genetic studies have found CV-associated loci that also increase risk for late-onset AD. The ε4 allele of apolipoprotein E (*APOE*) is the biggest genetic risk factor for AD and encodes a lipid transport protein involved in cholesterol metabolism [29]. Genome-wide association studies (GWAS) in late-onset AD have identified single nucleotide polymorphisms (SNPs) implicated in lipid processes, such as *CLU* and *ABCA7* [24, 37], and enrichment in cholesterol metabolism pathways [9]. Considered together, these findings suggest 'pleiotropy', where variations in a single gene can affect multiple, seemingly unrelated phenotypes [42].

We have previously shown that genetic enrichment in cardiovascular-/lifestyle-associated RFs and diseases (hereafter referred to as CV-associated RFs) results in improved statistical power for discovery of novel AD genes [13]. Building on this work, in the present study, we systematically evaluated shared genetic risk between AD and cardiovascular-/lifestyle-associated RFs and diseases. We focused on publicly available genetic data from cardiovascular outcomes and a combination of traits and diseases that have been epidemiologically associated with increased AD risk. Using large GWAS and validated tools to estimate pleiotropy, we sought to identify SNPs *jointly* associated with AD and one or more CV-associated RF, namely body mass index (BMI), type 2 diabetes (T2D), coronary artery disease (CAD), waist hip ratio (WHR), total cholesterol (TC), triglycerides (TG), low-density (LDL) and high-density lipoprotein (HDL). We additionally assessed whether the AD/CV genes showed independent replication within a large 'AD-by-proxy' phenotype sample that relies upon parental AD status to identify proxy cases and proxy controls [52]. Finally, we examined whether the AD/CV pleiotropic genes are differentially expressed within AD brains.

Methods

Participant samples

We evaluated complete GWAS results in the form of summary statistics (*p* values and odds ratios) for clinically diagnosed AD dementia [24] and eight CV-associated RFs, including BMI [47], T2D [28], CAD [31], WHR [18], and plasma lipid levels (TC, TG, LDL, and HDL [44]). We obtained publicly available AD GWAS summary statistic data from the International Genomics of Alzheimer's Disease Project (IGAP Stages 1 and 2; for additional details, see Supplemental Information and [24]; Table 1). As our primary cohort, we used IGAP Stage 1 which consists of 17,008 AD cases (mean age = 74.7 ± 7.7 years; 59.4% female) and 37,154 controls (mean age = 76.3 ± 8.1 years; 58.6% female) drawn from four different consortia across North America and Europe with genotyped or imputed data at 7,055,881 SNPs (for a description of the AD dementia cases and controls within the IGAP Stage 1 sub-studies, please see Ref. [24]). To confirm our findings from IGAP Stage 1, we assessed the *p* values of pleiotropic SNPs (conjunction FDR < 0.05; see statistical analysis below) from two independent AD cohorts, namely the IGAP Stage 2 [24] sample, and a cohort of AD cases and controls drawn from the population of the United States and part of phase 2 of the Alzheimer's Disease Genetics Consortium (ADGC2). The IGAP Stage 2 sample consisted of 8,572 AD cases (mean age = 72.5 ± 8.1 years; 61% female) and 11,312 controls (mean age = 65.5 ± 8.0 years; 43.3% female) of European ancestry with genotyped data at 11,632 SNPs (for additional details, see Ref. [24]). The ADGC2 sample consisted of 2,122 AD cases and 3,213 controls of European ancestry (for additional details, see Ref. [21]).

We further assessed the *p* values of our AD/CV pleiotropic SNPs in an AD-by-proxy cohort that is based on individuals of European ancestry in the UK Biobank (UKB) for whom parental AD status was available (*N* proxy cases = 47,793; *N* proxy controls = 328,320) (for additional details, see Ref. [52]). Individuals with one or two parents with AD were defined as proxy cases, while putting more weight on the proxy cases with two parents. Similarly, individuals with two parents without AD were defined as proxy controls, where older cognitively normal parents were upweighted as proxy controls to account for the higher likelihood that younger parents may still develop AD. As the proxy phenotype is not equivalent to a clinical diagnosis of AD and may include individuals that never develop AD, we evaluated the UKB by-proxy sample separately from the IGAP and ADGC2 case control samples.

Details of the summary data and available URLs from all GWAS used in the current study are listed in Table 1. The relevant institutional review boards or ethics committees approved the research protocol of all individual GWAS used in the current analysis, and all human participants gave written informed consent.

Genetic enrichment and conjunction false discovery rates (FDR)

A brief summary of these methods follows. For details, see Supplementary methods and previous publications [2, 3, 5, 8, 12, 13, 19, 48].

Table 1 Summary data from all GWAS used in the current study

Disease/trait	Abbr	Sample size	Cases	Controls	References	URL	Ethnicities included	SNPs	Covariate adjustments
Alzheimer's disease	AD		17,008	37,154	[24]	http://web.pasteur-lille.fr/en/recherche/u744/igap/igap_download.php	EUR	7,055,881	Adjusted for age, sex and principal components
High-density lipoprotein	HDL	62,166			[44]	http://diagram-consortium.org/2015_ENGAGE_1KG/ file: HDL-C	EUR	9,549,055	Adjusted for age, age^2, and first 3 principal components
Low-density lipoprotein	LDL	62,166			[44]	http://diagram-consortium.org/2015_ENGAGE_1KG/ file: LDL-C	EUR	9,545,543	Adjusted for age, age^2, and first 3 principal components
Total triglycerides	TG	62,166			[44]	http://diagram-consortium.org/2015_ENGAGE_1KG/ file: TG	EUR	9,544,499	Adjusted for age, age^2, and first 3 principal components
Total cholesterol	TC	62,166			[44]	http://diagram-consortium.org/2015_ENGAGE_1KG/ file: TC	EUR	9,553,380	Adjusted for age, age^2, and first 3 principal components
Body-mass index	BMI	681,275			[47]	https://portals.broadinstitute.org/collaboration/giant/index.php/GIANT_consortium_data_files file: Download Updated Meta-analysis Locke et al. + UK Biobank 2018 GZIP	EUR	2,336,270	Adjusted for age, sex, recruitment center, genotyping batches, and ten principle components calculated from SNPs pre-selected by the UKB quality control team for PC analysis
Type 2 diabetes	T2D		48,286	250,671	[28]	http://diagram-consortium.org/downloads.html file: T2D GWAS meta-analysis—European Summary Statistics	EUR	133,587	Adjusted for age, sex, six axes of genetic variation, genotyping array, and body mass index
Coronary artery disease	CAD		17,283	137,914	[31]	http://www.cardiogramplusc4d.org/data-downloads/ file: UKBB.GWAS1KG.EXOME.CAD.SOFT.META.PublicRelease.300517.txt.gz	EUR	9,026,568	Adjusted for array (UK Biobank versus UK BiLEVE) and the first five principal components
Waist-to-hip ratio	WHR	180,423			[18]	https://zenodo.org/record/1251813#.W9I1Ay-ZOjQ file: whradjbmi.giant-ukbb.meta-analysis.combined.23May2018.txt.gz	EUR	27,375,637	Adjusted for age, age^2, sex, BMI, sex, first 5 principal components

Abbr abbreviation, *EUR* European, *SNPs* single nucleotide polymorphisms

We evaluated whether there is pleiotropic genetic enrichment in AD as a function of each of the eight CV-associated RFs. To do this, we compare the association with a primary trait (e.g., AD) across all SNPs and within SNP strata determined by their association with a secondary trait (e.g., BMI), and provide a visual pattern of overlap in SNP associations. For given associated phenotypes A (e.g., AD) and B (e.g., BMI), pleiotropic 'enrichment' of phenotype A with phenotype B exists if the proportion of SNPs or genes associated with phenotype A increases as a function of increased association with phenotype B (see Supplementary Methods). To assess for enrichment, we constructed fold-enrichment plots of nominal $-\log_{10}(p)$ values for all AD SNPs and for subsets of SNPs determined by the significance of their association with each of the eight CV-associated RFs (e.g., $-\log_{10}(p) > 1, > 2$, and > 3 in CV-associated RFs). In fold-enrichment plots, the presence of enrichment is reflected as an upward deflection of the curve for phenotype A if the degree of deflection from the expected null line is dependent on the degree of association with phenotype B. More specifically, fold enrichment is computed as follows: first, we compute the empirical cumulative distribution of $-\log_{10}(p)$ values for SNP association with a given phenotype (e.g., AD) for all SNPs, and then the cumulative $-\log_{10}(p)$ values for each SNP stratum, which is determined by the p value of these SNPs in the conditioning phenotype (e.g., BMI). We then calculate the fold enrichment of each stratum as the ratio between the $-\log_{10}(p)$ cumulative distribution for that stratum and the cumulative distribution for all SNPs. The x-axis shows nominal p values ($-\log_{10}(p)$); the y-axis shows fold enrichment. To assess for polygenic effects below the standard GWAS significance threshold, we focused the fold-enrichment plots on SNPs with nominal $-\log_{10}(p) < 7.3$ (corresponding to $p > 5 \times 10^{-8}$). The enrichment seen can be directly interpreted in terms of true discovery rate [TDR = 1 − false discovery rate (FDR)] (for additional details, see Supplemental Information).

To account for large blocks of linkage disequilibrium (LD) that may result in spurious genetic enrichment, we applied a random pruning approach, where one random SNP per LD block (defined by an r^2 of 0.8) was used and averaged over 200 random pruning runs. Given prior evidence that several genetic variants within the human leukocyte antigen (*HLA*) region on chromosome 6 [43, 49], microtubule-associated tau protein (*MAPT*) region on chromosome 17 [12] and the *APOE* region on chromosome 19 [13] are associated with increased AD risk, one concern is that random pruning may not sufficiently account for these large LD blocks, resulting in artificially inflated genetic enrichment [8]. To better account for these large LD blocks, in our genetic enrichment analyses, we removed all SNPs in LD with $r^2 > 0.2$ within 1 Mb of *HLA, MAPT* and *APOE* variants (based on 1000 Genomes Project LD structure).

To identify specific loci jointly involved with AD and the eight CV-associated risk factors, we computed conjunction false discovery rates (FDRs), a statistical framework that is well suited to a genetic epidemiology approach to investigate genetic pleiotropy. The standard FDR framework is based on Bayesian statistics and follows the assumption that SNPs are either associated with the phenotype (non-null) or are not associated with the phenotype (null SNPs). Within a Bayesian statistical framework, the FDR is then the probability of the SNP being null given its p value is as small as or smaller than the observed one. An extension of the standard FDR is the conjunction FDR, defined as the probability that a SNP is null for either phenotype or for both phenotypes simultaneously given its p value in both phenotypes are as small or smaller as the observed ones. The conjunction is a conservative approach requiring that loci exceed a conjunction FDR significance threshold for two traits jointly. *Conjunction* FDR, therefore, is more conservative and specifically pinpoints pleiotropic loci between the traits of interest. We used an overall FDR threshold of < 0.05, which means five expected false discoveries per hundred reported. Manhattan plots were constructed based on the ranking of conjunction FDR to illustrate the genomic location of the pleiotropic loci. In all analyses, we controlled for the effects of genomic inflation using intergenic SNPs (see Supplemental and previous reports for additional details [2, 5, 8, 12, 13, 19]).

For loci with conjunction FDR < 0.05, we performed a fixed-effect, inverse variance-weighted meta-analysis [46] using independent AD cohorts: IGAP Stages 1 and 2 (cases = 25,580, controls = 48,466) and ADGC2 (cases = 2122, controls = 3213). As the separate IGAP Stage 2 summary statistics are not publically available, in our meta-analysis, we used the combined IGAP Stage 1 and 2 sample which was available publically. The meta-analyses were conducted using the R package meta (http://CRAN.R-project.org/package=meta). Briefly, the fixed effects, inverse variance-weighted meta-analysis summarizes the combined statistical support across independent studies under the assumption of homogeneity of effects. Individual study estimates (log odds ratios) are averaged, weighted by the estimated standard error [23].

Functional evaluation of shared risk loci

To assess whether SNPs that are shared between AD and CV-associated RFs modify gene expression, we identified *cis*-expression quantitative loci (eQTLs, defined as variants within 1 Mb of a gene's transcription start site) and regional brain expression of AD/CV SNPs in a publicly available dataset of normal control brains (UKBEC, http://braineac.org [36]). Given the evaluation of CV-associated RFs, we also evaluated eQTLs using a blood-based dataset [45].

Gene expression alterations in AD brains

To determine whether the AD/CV pleiotropic genes are differentially expressed in AD brains, we analyzed gene expression of overlapping genes in a publicly available dataset. We accessed the Mayo Clinic Brain Bank (Mayo) RNAseq study from the Accelerating Medicines Partnership-Alzheimer's Disease (AMP-AD) portal (syn3163039; accessed April 2017). We examined gene expression in the temporal cortex of brains with neuropathologic diagnosis of AD dementia ($N=82$) and elderly control brains that lacked a diagnosis of neurodegenerative disease ($N=80$) [1]. Multi-variable linear regression analyses were conducted using CQN normalized gene expression measures and including age at death, gender, RNA integrity number (RIN), brain tissue source, and flow cell as biological and technical covariates.

Results

Pleiotropic enrichment in AD conditional on plasma lipid levels

For progressively stringent p value thresholds for AD SNPs [i.e., increasing values of nominal $-\log_{10}(p)$], we found approximately 100-fold enrichment using LDL, 75-fold enrichment using TC, 65-fold enrichment using TG, and 25-fold enrichment using HDL (Fig. 1). In comparison, we found minimal to no enrichment with BMI, T2D, CAD, and WHR. Together, these findings suggest selective genetic overlap between plasma lipids and AD. We note that these results reflect genetic enrichment in AD as a function of CV-associated RFs after the exclusion of SNPs in LD with *HLA, MAPT,* and *APOE* (see "Methods").

Given the long-range LD associated with the *APOE/TOMM40* region [49], we focused our pleiotropy analyses on genetic variants outside chromosome 19. At a conjunction FDR < 0.05, we identified 90 SNPs, in total, across 19 chromosomes jointly associated with AD and the CV-associated RFs (Fig. 2; Table 2). After accounting for LD, we

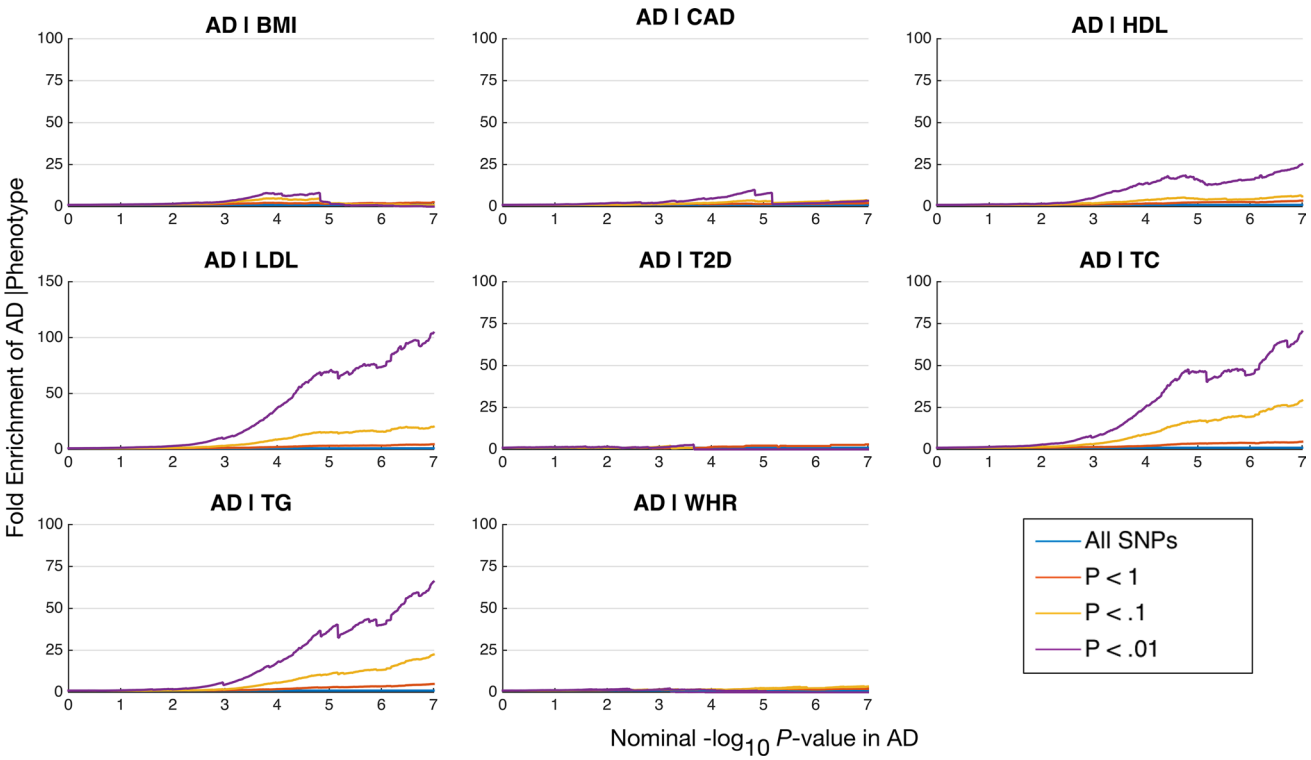

Fig. 1 Fold enrichment plots of nominal $-\log_{10}$ p values (corrected for inflation and excluding *APOE, MAPT,* and *HLA* regions) in Alzheimer's disease (AD) below the standard GWAS threshold of $p<5\times10^{-8}$ as a function of significance of association with body mass index (BMI), type 2 diabetes (T2D), coronary artery disease (CAD), waist hip ratio (WHR), total cholesterol (TC), triglycerides (TG), low-density lipoprotein (LDL), and high-density lipoprotein (HDL) at the level of $p\leq1$, $p\leq0.1$, $p\leq0.01$, respectively. Blue line indicates all SNPs

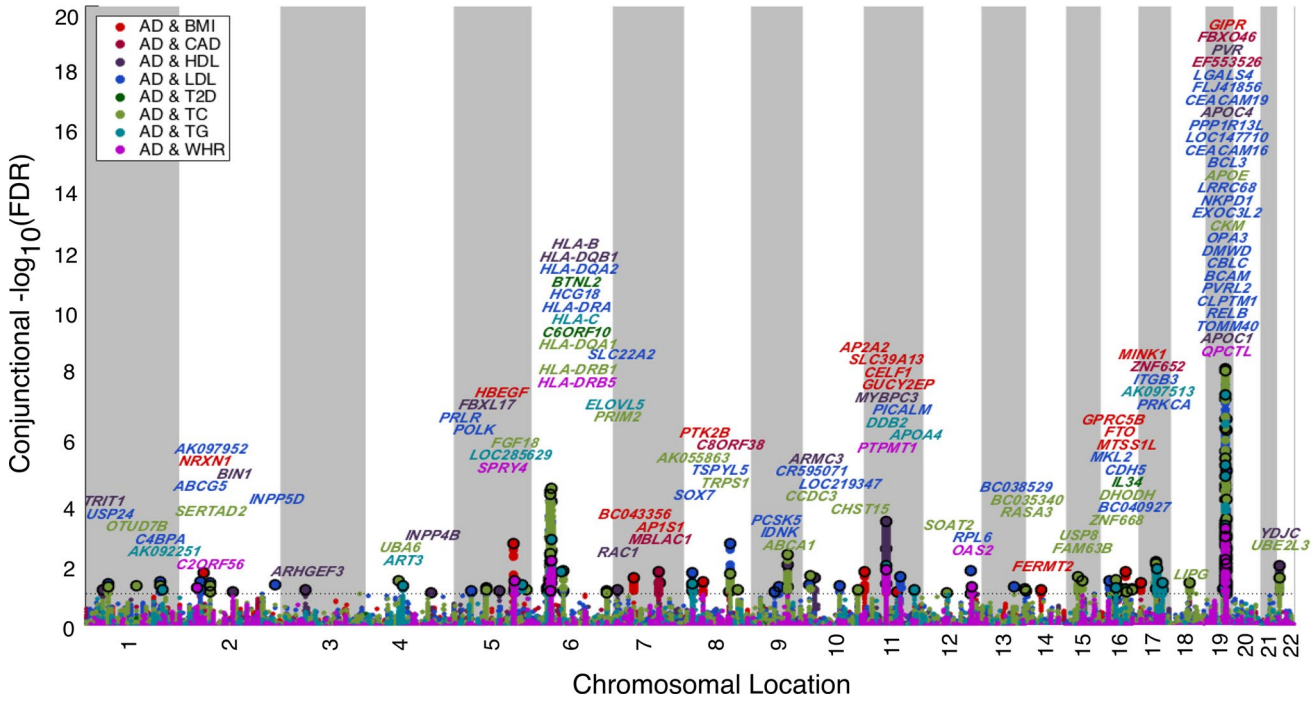

Fig. 2 Conjunction Manhattan plot of conjunction $-\log_{10}$ (FDR) values for Alzheimer's disease (AD) alone (black) and AD given body mass index (BMI; AD&BMI, red), type 2 diabetes (T2D; AD&T2D, blue), coronary artery disease (CAD; AD&CAD, pink), waist hip ratio (WHR; AD&WHR, magenta), total cholesterol (TC; AD&TC, green), triglycerides (TG; AD&TG, teal), low-density lipoprotein (LDL; &LDL, purple) and high-density lipoprotein (HDL, AD|HDL, maroon). SNPs with conjunction $-\log_{10}$ FDR > 1.3 (i.e., FDR < 0.05) are shown with large points. A black line around the large points indicates the most significant SNP in each LD block and this SNP was annotated with the closest gene, which is listed above

identified several AD-/CV-associated loci involved in cholesterol/lipid function including variants within *ABCG5, ABCA1,* and *APOA4*.

For the 90 pleiotropic SNPs, we conducted a meta-analysis across IGAP Stages 1 and 2 and ADGC2. We focused on SNPs found in all three cohorts and identified six variants with $p < 5.0 \times 10^{-8}$ (Table 3; Fig. 3a–f): (1) rs6733839 (chromosome 2, closest gene = *BIN1*, conditioning trait = HDL, reference allele = T, OR = 1.210, 95% CI 1.18–1.1.25, $p = 1.44 \times 10^{-45}$), (2) rs1534576 (chromosome 11, closest gene = *SLC39A13*, conditioning trait = BMI, reference allele = T, OR = 1.080, 95% CI 1.05–1.11, $p = 1.49 \times 10^{-9}$), (3) rs3844143 (chromosome 11, closest gene = *PICALM*, conditioning trait = LDL, reference allele = T, OR = 0.899, 95% CI 0.877–0.922, $p = 6.52 \times 10^{-17}$), (4) rs17125924 (chromosome 14, closest gene = *FERMT2*, conditioning trait = BMI, reference allele = G, OR = 1.130, 95% CI 1.08–1.18, $p = 2.62 \times 10^{-8}$), (5) rs35991721 (chromosome 7, closest gene = *MBLAC1/GATS*, conditioning trait = CAD, reference allele = T, OR = 0.921, 95% CI 0.896–0.947, $p = 1.44 \times 10^{-9}$), (6) rs536810 (chromosome 6, closest gene = *HLA-DRB5*, conditioning trait = WHR, reference allele = T, OR = 0.924, 95% CI 0.899–0.95, $p = 1.14 \times 10^{-8}$).

We also identified three AD susceptibility loci at $p < 1.0 \times 10^{-6}$ (Table 3; Supplemental Figure 1): (1) rs11039131 (chromosome 11, closest gene = *DDB2*, conditioning trait = TG, reference allele = T, OR = 0.934, 95% CI 0.91–0.96, $p = 7.01 \times 10^{-7}$), 2) rs8070572 (chromosome 17, closest gene = *MINK1*, conditioning trait = BMI, reference allele = C, OR = 1.120, 95% CI 1.07–1.17, $p = 1.98 \times 10^{-7}$), and (3) rs2071305 (chromosome 11, closest gene = *MYBPC3*, conditioning trait = HDL, reference allele = C, OR = 0.928, 95% CI 0.903–0.953, $p = 5.62 \times 10^{-8}$).

These meta-analyses point to novel AD-associated susceptibility loci. On chromosome 7, we found that the genome-wide significant rs35991721 was not in LD with the previously reported SNP rs1476679 ([24], $r^2 = 0.28$, $D' = 0.56$) and may be tagging genetic signal within *GATS, STAG3* or *PVRIG* (Fig. 4). On chromosome 11 within the *CELF1* region, we detected independent signal within rs1534576, rs11039131 and rs2071305 (Fig. 5). The genome-wide significant rs1534576 was in LD with the previously reported rs10838725 ($r^2 = 0.64$, $D' = 0.99$) indicating that these two SNPs may be tagging signal within *CELF1* [24]. In contrast, rs11039131 and rs2071305 were not in LD with rs10838725 suggesting independent signal from

Table 2 Overlapping loci between AD and CV RFs at a conjunction FDR < 0.05

	SNP	Chr	Closest gene	A1	Reference trait	Min ConjFDR	AD *p* value	Reference trait *p* value
1	rs61779841	1	TRIT1	A	HDL	3.75E−02	5.44E−04	7.37E−04
2	rs78363635	1	C4BPA	C	LDL	2.02E−02	8.30E−04	5.46E−05
3	rs1759499	1	USP24	G	LDL	2.50E−02	1.05E−03	1.57E−09
4	rs6587723	1	OTUD7B	C	TC	2.89E−02	3.26E−04	1.50E−03
5	rs1431985	1	AK092251	A	TG	3.78E−02	6.63E−04	4.20E−04
6	rs858952	2	NRXN1	C	BMI	1.11E−02	9.45E−06	2.22E−04
7	rs6733839	2	BIN1	T	HDL	4.38E−02	7.11E−26	8.94E−04
8	rs72796734	2	ABCG5	T	LDL	2.02E−02	8.29E−04	2.33E−05
9	rs55819441	2	AK097952	T	LDL	2.30E−02	9.56E−04	1.40E−04
10	rs7421448	2	INPP5D	T	LDL	2.58E−02	5.84E−04	1.45E−03
11	rs12994639	2	SERTAD2	G	TC	4.35E−02	1.60E−03	9.53E−05
12	rs61208496	2	C2ORF56	T	WHR	3.22E−02	5.73E−05	1.88E−04
13	rs6805910	3	ARHGEF3	C	HDL	3.78E−02	6.10E−04	6.93E−04
14	rs28670348	4	INPP4B	G	HDL	4.79E−02	1.81E−04	1.01E−03
15	rs13114818	4	UBA6	C	TC	1.88E−02	6.28E−04	8.96E−04
16	rs6852075	4	ART3	G	TG	2.80E−02	4.02E−04	5.17E−04
17	rs2074613	5	HBEGF	C	BMI	1.30E−03	9.29E−07	1.36E−05
18	rs4912851	5	SPRY4	G	WHR	1.99E−02	3.39E−05	2.32E−05
19	rs12188460	5	FBXL17	G	HDL	4.20E−02	6.23E−04	8.49E−04
20	rs5744712	5	POLK	C	LDL	3.15E−02	1.35E−03	1.29E−17
21	rs6883056	5	PRLR	C	LDL	3.96E−02	8.48E−05	2.30E−03
22	rs62383992	5	FGF18	A	TC	3.64E−02	1.30E−03	9.12E−04
23	rs2176298	5	LOC285629	T	TG	2.52E−02	1.50E−04	4.56E−04
24	rs141129230	6	HLA-B	G	HDL	4.15E−02	6.73E−04	1.75E−04
25	rs145749015	6	HLA-DQB1	T	HDL	2.11E−03	2.71E−05	6.54E−06
26	rs115785781	6	HCG18	C	LDL	3.17E−02	1.35E−03	1.81E−05
27	rs9272561	6	HLA-DQA1	G	TC	2.17E−05	5.37E−09	7.23E−07
28	rs115795926	6	HLA-DQA2	C	LDL	5.84E−05	1.94E−06	1.28E−06
29	rs115674098	6	HLA-DRA	T	LDL	2.85E−05	9.28E−07	2.21E−08
30	rs116715716	6	HLA-DRB1	T	TC	2.57E−03	7.87E−05	2.25E−05
31	rs7774782	6	PRIM2	C	TC	9.25E−03	2.93E−04	1.83E−04
32	rs3103351	6	SLC22A2	G	LDL	4.06E−02	1.78E−03	4.04E−06
33	rs115802139	6	BTNL2	G	T2D	8.23E−04	4.39E−06	2.35E−07
34	rs114465688	6	C6ORF10	G	T2D	1.66E−02	9.45E−05	1.23E−04
35	rs536810	6	HLA-DRB5	T	WHR	4.51E−03	7.18E−06	4.33E−14
36	rs12194027	6	ELOVL5	C	TG	1.03E−02	1.39E−04	1.53E−04
37	rs115813375	6	HLA-C	A	TG	3.27E−02	5.67E−04	1.05E−06
38	rs1048365	7	AP1S1	T	BMI	2.18E−02	7.84E−05	2.22E−04
39	rs2597283	7	BC043356	C	BMI	1.53E−02	4.20E−05	3.46E−04
40	rs35991721	7	MBLAC1	T	CAD	1.03E−02	5.77E−05	3.22E−06
41	rs702483	7	RAC1	T	HDL	3.82E−02	6.18E−04	3.11E−04
42	rs12056620	8	PTK2B	T	BMI	2.12E−02	7.56E−05	3.35E−04
43	rs2011566	8	C8ORF38	G	CAD	4.47E−02	2.78E−04	3.83E−04
44	rs7014168	8	SOX7	A	LDL	1.09E−02	4.28E−04	4.01E−04
45	rs16895579	8	TSPYL5	A	LDL	1.27E−03	8.90E−06	5.77E−05
46	rs117922969	8	AK055863	T	TC	3.97E−02	1.43E−03	5.31E−04
47	rs13277568	8	TRPS1	G	TC	3.67E−02	1.19E−03	1.17E−03
48	rs10991386	9	ABCA1	G	TC	2.80E−03	8.54E−05	6.19E−07
49	rs12339683	9	IDNK	T	LDL	3.08E−02	1.31E−03	3.11E−04
50	rs11144711	9	PCSK5	G	LDL	4.23E−02	5.65E−04	2.49E−03

Table 2 (continued)

	SNP	Chr	Closest gene	A1	Reference trait	Min ConjFDR	AD *p* value	Reference trait *p* value
51	rs145301439	10	ARMC3	A	HDL	1.61E−02	2.42E−04	1.57E−04
52	rs12784561	10	CR595071	A	LDL	2.55E−02	3.80E−04	1.43E−03
53	rs12783314	10	LOC219347	A	LDL	2.72E−02	2.60E−04	1.53E−03
54	rs10906257	10	CCDC3	G	TC	1.36E−02	4.39E−04	4.72E−04
55	rs7098392	10	CHST15	A	TC	3.81E−02	1.37E−03	9.00E−04
56	rs6597951	11	AP2A2	C	BMI	1.03E−02	2.94E−05	1.38E−04
57	rs7928842	11	CELF1	C	BMI	2.37E−02	8.75E−05	3.19E−24
58	rs1893306	11	GUCY2EP	G	BMI	4.26E−02	4.25E−05	1.46E−03
59	rs1534576	11	SLC39A13	T	BMI	1.79E−03	3.21E−06	6.62E−08
60	rs11039131	11	DDB2	T	TG	6.47E−03	4.08E−05	8.55E−05
61	rs2071305	11	MYBPC3	C	HDL	2.58E−04	3.01E−06	2.53E−07
62	rs3844143	11	PICALM	T	LDL	1.44E−02	1.94E−08	7.79E−04
63	rs1263170	11	APOA4	T	TG	3.73E−02	6.55E−04	4.33E−09
64	rs11039297	11	PTPMT1	A	WHR	8.51E−03	1.24E−05	5.15E−05
65	rs7972529	12	RPL6	G	LDL	9.05E−03	3.52E−04	4.49E−04
66	rs77451327	12	SOAT2	C	TC	4.58E−02	9.06E−04	2.56E−03
67	rs1635142	12	OAS2	A	WHR	3.01E−02	5.32E−05	2.28E−04
68	rs7331792	13	BC038529	A	LDL	2.93E−02	1.25E−03	4.69E−04
69	rs61963560	13	BC035340	A	TC	3.61E−02	5.92E−04	1.94E−03
70	rs7981577	13	RASA3	C	TC	4.16E−02	1.37E−04	2.28E−03
71	rs17125924	14	FERMT2	G	BMI	3.65E−02	1.48E−05	1.17E−03
72	rs650366	15	FAM63B	G	TC	1.96E−02	6.54E−04	6.86E−04
73	rs3131575	15	USP8	G	TC	1.42E−02	4.59E−04	4.34E−04
74	rs16953089	16	FTO	C	BMI	3.32E−02	1.36E−04	8.62E−04
75	rs9941245	16	GPRC5B	G	BMI	4.96E−02	2.29E−04	5.27E−16
76	rs4985557	16	MTSS1L	T	BMI	1.02E−02	2.87E−05	1.19E−04
77	rs9931998	16	BC040927	A	LDL	3.45E−02	5.23E−04	1.99E−03
78	rs12595955	16	CDH5	G	LDL	3.98E−02	1.74E−03	4.69E−04
79	rs246174	16	MKL2	T	LDL	1.93E−02	7.89E−04	5.91E−04
80	rs79161472	16	ZNF668	A	TC	1.78E−02	5.87E−04	6.23E−04
81	rs4985556	16	IL34	A	T2D	3.42E−02	2.11E−04	4.10E−04
82	rs8062895	16	DHODH	G	TC	4.27E−02	1.56E−03	4.12E−04
83	rs8070572	17	MINK1	C	BMI	2.33E−02	4.92E−06	6.24E−04
84	rs2960171	17	ZNF652	C	CAD	2.33E−02	1.37E−04	8.72E−05
85	rs7221196	17	ITGB3	G	LDL	4.67E−03	1.78E−04	1.57E−07
86	rs8071250	17	PRKCA	C	LDL	2.18E−02	7.56E−04	1.21E−03
87	rs850520	17	AK097513	A	TG	7.79E−03	1.25E−04	1.08E−04
88	rs9954848	18	LIPG	A	TC	2.19E−02	4.58E−04	1.09E−03
89	rs2298428	22	YDJC	T	HDL	6.45E−03	9.00E−05	1.58E−08
90	rs4821116	22	UBE2L3	T	TC	1.50E−02	4.02E−04	7.10E−04

Chromosome 19 SNPs are excluded

SNP single nucleotide polymorphism, *Chr* chromosome, *Min ConjFDR* minimum conjunction false discovery rate, *AD* Alzheimer's disease

CELF1 (Fig. 5). Of interest, rs2071305 (but not rs11039131) was in LD with rs1057233 ($r^2 = 0.65$, $D' = 0.99$), a SNP that has been associated with AD age of onset in a survival analysis [20]. Collectively, these results suggest several different AD-associated genetic variants within chromosome 11.

We also assessed whether the AD/CV pleiotropic SNPs listed in Table 2 replicated in an AD-by-proxy cohort. Of the 90 IGAP pleiotropic SNPs, 68 SNPs were available in the UKB AD-by-proxy cohort. We identified 20 significant SNPs at $p < 0.05$ (Table 4). The replicated variants include

Table 3 Meta-analysis using ADGC Phase 2 and IGAP stages 1 and 2 cohorts

	SNP	Chr	Closest gene	A1	Ref trait	ADGC 2 *p* value	ADGC 2 OR	ADGC 2 95% CI	IGAP 1 and 2 *p* value	IGAP 1 and 2 OR	IGAP 1 and 2 95% CI	Meta-*p* value	Meta-OR	Meta-95% CI
1	rs1431985	1	AK092251	A	TG	6.55E−01	0.9779	0.887–1.08	2.40E−03	1.04	1.01–1.07	4.84E−03	1.04	1.01–1.06
2	rs78363635	1	C4BPA	C	LDL	7.42E−01	0.9625	0.767–1.21	6.22E−03	1.09	1.02–1.16	1.03E−02	1.08	1.02–1.14
3	rs55819441	2	AK097952	T	LDL	6.35E−01	1.049	0.861–1.28	7.55E−02	0.962	0.922–1	1.01E−01	0.966	0.927–1.01
4	rs6733839	2	BIN1	T	HDL	8.05E−03	1.165	1.04–1.3	**6.94E−44**	1.22	1.22–1.22	**1.44E−45**	1.21	1.18–1.25
5	rs72796734	2	ABCG5	T	LDL	1.15E−01	0.8402	0.677–1.04	3.26E−02	0.937	0.883–0.995	1.32E−02	0.93	0.878–0.985
6	rs7421448	2	INPP5D	T	LDL	5.75E−01	1.06	0.865–1.3	2.23E−04	0.911	0.867–0.957	5.59E−04	0.918	0.875–0.964
7	rs858952	2	NRXN1	C	BMI	4.67E−01	0.9602	0.861–1.07	3.08E−03	1.05	1.02–1.08	7.69E−03	1.04	1.01–1.07
8	rs13114818	4	UBA6	C	TC	4.08E−01	0.9441	0.824–1.08	3.03E−03	1.05	1.02–1.08	7.50E−03	1.05	1.01–1.08
9	rs28670348	4	INPP4B	G	HDL	9.30E−01	0.9918	0.826–1.19	7.76E−03	1.07	1.02–1.12	1.10E−02	1.06	1.01–1.12
10	rs6852075	4	ART3	G	TG	6.23E−01	0.9767	0.889–1.07	1.96E−02	0.969	0.944–0.995	1.77E−02	0.97	0.945–0.995
11	rs12188460	5	FBXL17	G	HDL	2.50E−01	1.057	0.962–1.16	4.85E−03	1.04	1.01–1.07	2.64E−03	1.04	1.01–1.06
12	rs2176298	5	LOC285629	T	TG	4.52E−01	0.9628	0.872–1.06	1.47E−02	1.03	1.01–1.05	3.07E−02	1.03	1–1.06
13	rs4912851	5	SPRY4	G	WHR	2.32E−01	1.06	0.963–1.17	7.07E−03	1.04	1.01–1.07	3.58E−03	1.04	1.01–1.06
14	rs536810	6	HLA-DRB5	T	WHR	1.53E−01	0.9311	0.844–1.03	**3.48E−08**	0.923	0.897–0.95	**1.14E−08**	0.924	0.899–0.949
15	rs2597283	7	BC043356	C	BMI	3.53E−01	1.048	0.949–1.16	**1.67E−07**	0.932	0.908–0.957	1.65E−06	0.939	0.915–0.963
16	rs35991721	7	MBLAC1	T	CAD	7.17E−04	0.8255	0.739–0.923	**2.62E−07**	0.928	0.902–0.955	**5.32E−09**	0.921	0.896–0.947
17	rs702483	7	RAC1	T	HDL	5.60E−01	1.029	0.935–1.13	1.75E−02	0.97	0.946–0.995	3.17E−02	0.973	0.95–0.998
18	rs12056620	8	PTK2B	T	BMI	5.50E−01	1.029	0.937–1.13	2.66E−03	1.04	1.01–1.07	2.23E−03	1.04	1.01–1.07
19	rs7014168	8	SOX7	A	LDL	6.74E−01	1.024	0.917–1.14	1.39E−04	0.942	0.913–0.971	3.57E−04	0.948	0.92–0.976
20	rs10906257	10	CCDC3	G	TC	7.75E−01	1.022	0.88–1.19	5.37E−03	1.06	1.02–1.1	5.80E−03	1.06	1.02–1.1
21	rs12784561	10	CR595071	A	LDL	3.50E−01	0.9262	0.789–1.09	1.31E−04	0.918	0.879–0.959	8.51E−05	0.918	0.88–0.958
22	rs11039131	11	DDB2	T	TG	2.18E−02	0.8803	0.789–0.982	5.18E−06	0.938	0.913–0.964	**7.01E−07**	0.934	0.91–0.96
23	rs1263170	11	APOA4	T	TG	8.95E−01	1.007	0.908–1.12	3.37E−03	1.05	1.02–1.08	4.22E−03	1.04	1.01–1.07
24	rs1534576	11	SLC39A13	T	BMI	7.03E−03	1.139	1.04–1.25	**2.97E−08**	1.08	1.05–1.11	**1.49E−09**	1.08	1.05–1.11
25	rs1893306	11	GUCY2EP	G	BMI	6.68E−01	1.023	0.922–1.13	1.09E−03	0.953	0.926–0.981	2.35E−03	0.958	0.932–0.985
26	rs2071305	11	MYBPC3	C	HDL	1.12E−03	0.8264	0.737–0.927	1.54E−06	0.934	0.908–0.96	**5.62E−08**	0.928	0.903–0.953
27	rs3844143	11	PICALM	T	LDL	1.62E−01	0.9349	0.851–1.03	**1.33E−16**	0.896	0.873–0.92	**6.52E−17**	0.899	0.877–0.922
28	rs1635142	12	OAS2	A	WHR	4.61E−01	1.04	0.937–1.15	1.50E−04	0.947	0.921–0.974	5.00E−04	0.953	0.927–0.979
29	rs61963560	13	BC035340	A	TC	7.43E−02	1.126	0.988–1.28	7.58E−04	0.939	0.905–0.974	5.79E−03	0.952	0.919–0.986
30	rs7981577	13	RASA3	C	TC	8.34E−01	0.9898	0.899–1.09	9.56E−02	0.976	0.949–1	9.76E−02	0.977	0.95–1
31	rs17125924	14	FERMT2	G	BMI	7.69E−01	1.026	0.864–1.22	**1.55E−08**	1.13	1.08–1.18	**2.62E−08**	1.13	1.08–1.18
32	rs3131575	15	USP8	G	TC	3.52E−01	1.055	0.943–1.18	3.74E−05	0.933	0.903–0.964	2.13E−04	0.942	0.913–0.972
33	rs16953089	16	FTO	C	BMI	1.84E−01	1.071	0.968–1.19	9.85E−04	0.954	0.928–0.981	4.63E−03	0.962	0.937–0.988
34	rs246174	16	MKL2	T	LDL	7.04E−01	0.981	0.889–1.08	4.41E−03	1.04	1.01–1.07	8.23E−03	1.04	1.01–1.06
35	rs4985556	16	IL34	A	T2D	7.48E−01	1.025	0.882–1.19	1.41E−06	1.11	1.06–1.16	2.06E−06	1.1	1.06–1.14

Table 3 (continued)

	SNP	Chr	Closest gene	A1	Ref trait	ADGC 2 *p* value	ADGC 2 OR	ADGC 2 95% CI	IGAP 1 and 2 *p* value	IGAP 1 and 2 OR	IGAP 1 and 2 95% CI	Meta-*p* value	Meta-OR	Meta-95% CI
36	rs4985557	16	MTSS1L	T	BMI	1.39E−01	1.077	0.976–1.19	9.28E−05	1.05	1.02–1.08	3.34E−05	1.06	1.03–1.08
37	rs9931998	16	BC040927	A	LDL	5.89E−01	1.038	0.907–1.19	4.59E−04	0.94	0.908–0.973	1.12E−03	0.946	0.915–0.978
38	rs9941245	16	GPRC5B	G	BMI	9.04E−02	0.9022	0.801–1.02	9.42E−05	0.937	0.907–0.968	2.58E−05	0.934	0.905–0.964
39	rs8070572	17	MINK1	C	BMI	3.05E−02	1.195	1.02–1.4	1.49E−06	1.11	1.06–1.16	**1.98E−07**	1.12	1.07–1.17
40	rs8071250	17	PRKCA	C	LDL	8.83E−01	0.9929	0.903–1.09	4.27E−04	0.955	0.931–0.98	5.96E−04	0.958	0.935–0.982
41	rs9954848	18	LIPG	A	TC	4.22E−01	0.9605	0.87–1.06	1.61E−03	0.959	0.934–0.984	1.12E−03	0.959	0.935–0.983
42	rs2298428	22	YDJC	T	HDL	6.47E−01	1.028	0.914–1.16	5.04E−04	0.942	0.911–0.974	1.34E−03	0.948	0.918–0.979

Bold values indicate $p < 1 \times 10^{-6}$

SNP single nucleotide polymorphism, *Chr* chromosome, *Ref* reference, *OR* odds ratio, *CI* confidence interval

three of the four novel AD/CV pleiotropic SNPs, namely variants within *MINK1*, *MBLAC1,* and *DDB2*.

Shared genetic risk between CV-associated RFs

To evaluate whether the AD susceptibility loci listed in Table 2 are associated with a single CV-associated RF or with multiple associated RFs, we constructed a matrix plot. For each of the eight CV-associated RFs, we plotted the minimum conjunction FDR for all AD/CV closest genes (Fig. 6; Supplemental Table 1). We found that some common genetic variants influencing AD risk are associated with multiple CV-associated RFs. For minimum conjunction FDR < 0.05, variants within (1) *ABCA1* were associated with CAD, lipid fractions, and WHR, (2) *C6ORF10* with T2D and lipid fractions and (3) *SPRY4* with BMI, lipid fractions, and WHR (Fig. 6).

cis-eQTLs

We focused on the four novel genetic variants (one genome-wide significant and three suggestive SNPs, see above) and found significant *cis*-associations in either brain or blood tissue types (Supplemental Table 2). None of the associations replicated in *both* tissue types. Within blood, rs8070572 showed a significant *cis*-eQTLs with *PLD2* (Supplemental Table 2).

Gene expression in brains from AD patients and healthy controls

To investigate whether the AD/CV pleiotropic genes are differentially expressed in AD brains, we compared gene expression in AD brains with neuropathologically normal control brains. We focused on differential expression of the closest genes from the four novel genetic variants (one genome-wide significant and three suggestive SNPs, see above) and *SPI1* based on LD within chromosome 11 (see above). We used a Bonferroni-corrected *p* value of < 0.01 and found significant effects for differential expression of *MINK1, SPI1, DDB2* and *MBLAC1* (Supplemental Table 3).

Discussion

Beyond *APOE*, we identified 90 SNPs on 19 different chromosomes that jointly conferred increased risk for AD and cardiovascular outcomes. In meta-analyses across three independent cohorts, we found four novel genetic variants that increased risk for AD. Three of these new susceptibility loci independently replicated in an AD-by-proxy cohort. Expression of three of these AD/CV pleiotropic genes was differentially altered within AD brains. Collectively, our

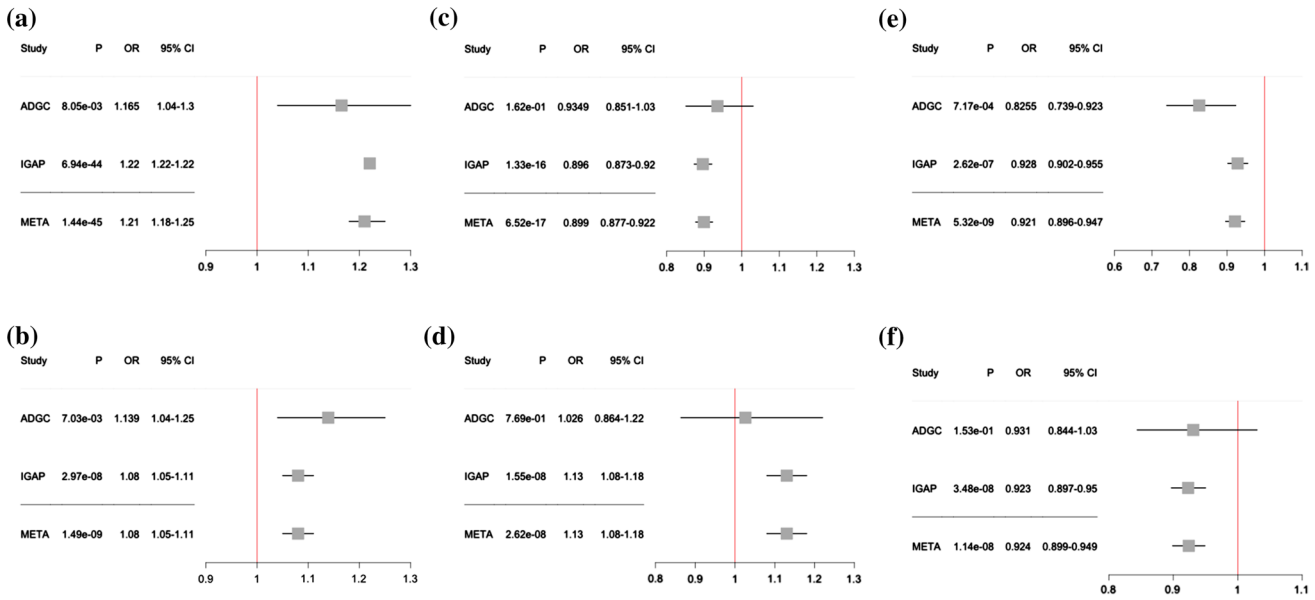

Fig. 3 Forest plots for **a** rs6733839 on chromosome 2, **b** rs1534576 on chromosome 11, **c** rs3844143 on chromosome 11, **d** rs17125924 on chromosome 14, **e** rs35991721 on chromosome 7, and **f** rs536810 on chromosome 6

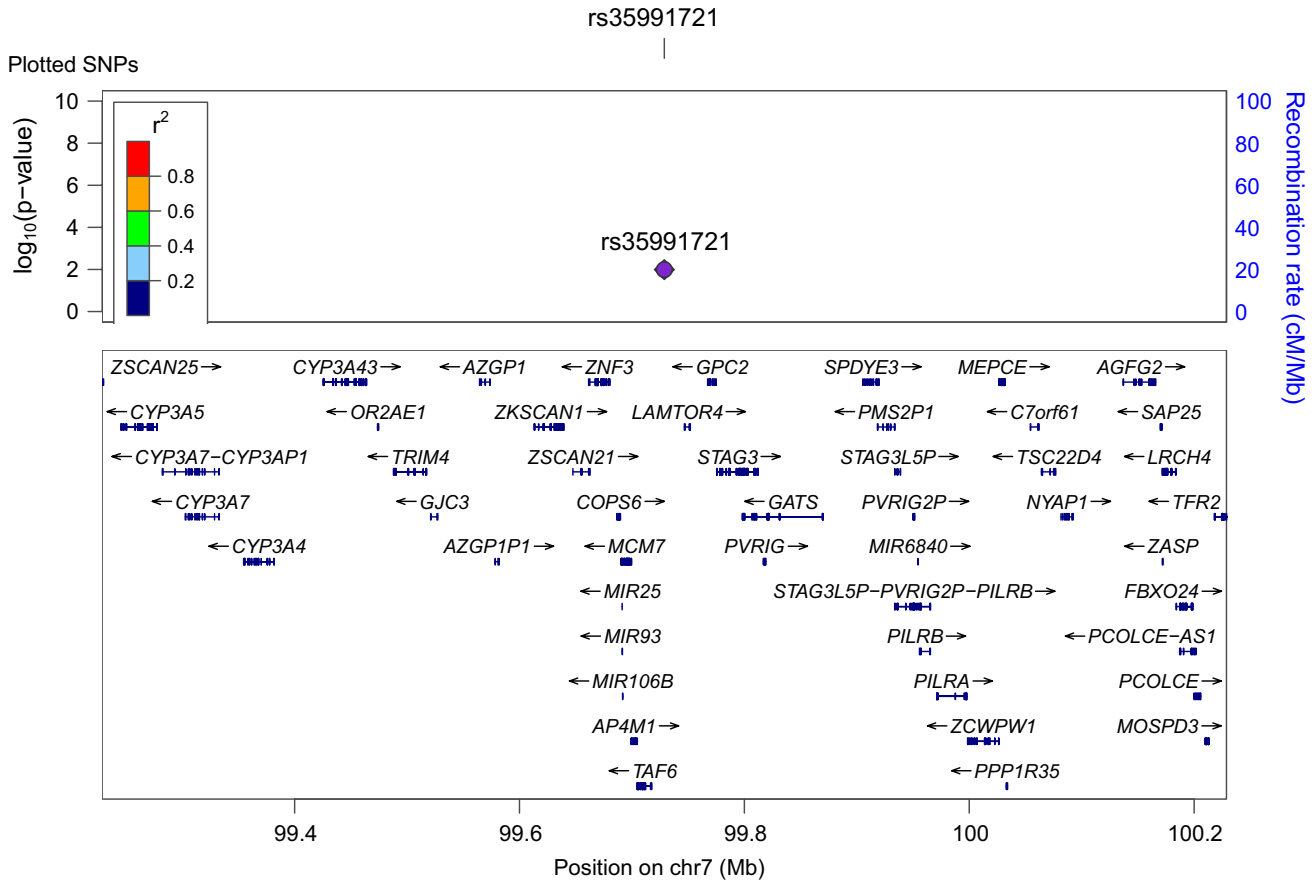

Fig. 4 Regional association plots for rs35991721 on chromosome 7. Linkage disequilibrium measured in the 1000 genomes European populations

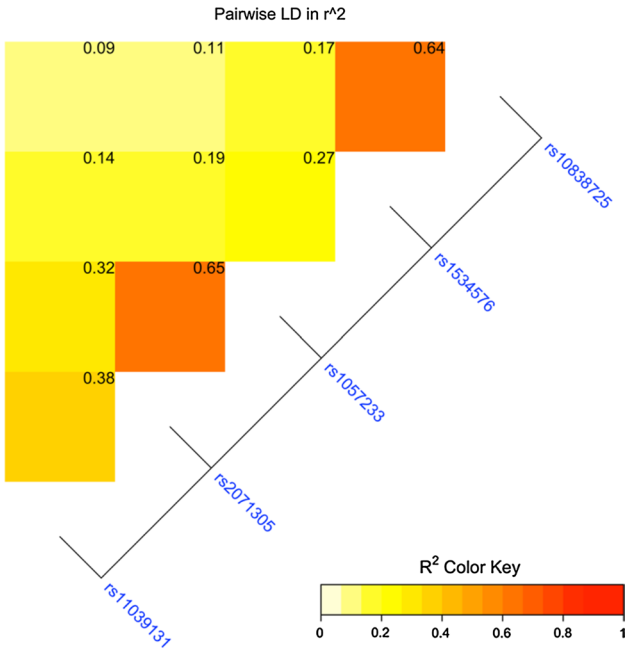

Fig. 5 The pair-wise linkage disequilibrium patterns between rs1534576, rs11039131 rs2071305, rs10838725, and rs1057233 on chromosome 11

findings suggest that the polygenic component of AD is highly enriched for cardiovascular RFs.

In their genetic association with AD, not all cardiovascular RFs are created equal. We found minimal genetic enrichment in AD as a function of T2D, BMI, WHR, and CAD suggesting that the known comorbidity [27, 34, 40] between these CV-associated RFs and Alzheimer's etiology are likely not genetic. In contrast, genetic enrichment in AD was predominantly localized to plasma lipids. Each of the four plasma lipid RFs resulted in a comparable level of enrichment suggesting a tight correlation between the lipid fractions. Building on our prior work leveraging statistical power from large CV GWASs for AD gene discovery [13], we found genetic variants jointly associated with AD and CV-associated RFs, many with known cholesterol/lipid function. By conditioning on plasma TC, TG, LDL, and HDL levels, we identified AD susceptibility loci within genes encoding apolipoproteins, such as *APOA4*, ATP-binding cassette transporters, such as *ABCA1* and *ABCG5*, and phospholipases, such as *ATP8B4* and *LIPG* (for a discussion on lipid genes and AD, see Ref. [14]).

Cholesterol in the brain involves metabolic pathways that work independently from those in peripheral tissue. The blood–brain barrier (BBB) prevents peripheral cholesterol from entering and leaving the brain. In the adult brain, cholesterol is synthesized predominately in astrocytes and oligodendrocytes; minimal cholesterol is synthesized in neurons. Within glial cells, cholesterol is transported by apoE and secreted into the extracellular matrix via *ABCA1*- and *ABCG1*-associated mechanisms [50]. The cholesterol then binds to the low-density receptors (LDLR) on neuronal cells. This cholesterol is critical for synapse development, synapse formation, dendrite differentiation, and synaptic transmission [50]. In the periphery, cholesterol is produced in the liver or obtained through diet. Mounting epidemiological, clinical, and animal research indicates that high plasma lipid levels (i.e., hypercholesterolemia) act as a risk factor for AD [51]. Hypercholesterolemia is thought to possibly damage the BBB, resulting in pathological cholesterol metabolism in the brain [51]. Collectively, our findings demonstrate a shared genetic basis for plasma lipids and AD. Further, we pinpoint specific genes that may be driving this genetic association.

By combining several GWASs, our results provide important insights into shared genetic risk. Conceptually similar to stepwise gatekeeper hypothesis testing [12] and a proxy phenotype approach [38], conjunction FDR identifies loci associated with two traits. These two-stage methods do not lower the statistical 'bar' for gene detection and maintain a constant Type I error rate. Unlike stepwise gatekeeper hypothesis testing [12] and proxy phenotype [38], which have predominantly been used in a genome-wide framework, conjunction FDR focuses on 'hidden' SNPs with $p < 5 \times 10^{-8}$, which directly translates into an effective increase in sample size [4]. Here, we used independent samples to confirm our conjunction FDR results, thereby pinpointing a subset of cardiovascular-associated genes strongly associated with AD. Our findings reinforce that specific Alzheimer's genes, such as *BIN1* and *PICALM*, also increase risk for cardiovascular outcomes. Importantly, using this pleiotropy informed approach, and across three independent cohorts, we found four new susceptibility loci associated with elevated Alzheimer's risk.

In meta-analyses, we identified novel AD-associated genetic signal in one genome-wide SNP and three SNPs at $p < 1 \times 10^{-6}$. By conditioning on cardiovascular RFs, we detected a genetic variant within the *MBLAC1/GATS/STAG3* region on chromosome 7 and with a meta-*p* value of 1.44×10^{-9}. *MBLAC1* encodes a metallo-β-lactamase domain-containing protein and shows ubiquitous expression in the brain [16]. Building on this, we found that expression of *MBLAC1* was differentially altered in AD brains. We also identified a variant within *MINK1* on chromosome 17. Interestingly, *MINK1* expression was altered in AD brains supporting the hypothesis that phosphorylated kinases, like *MINK1*, are abnormal in AD [10].

On chromosome 11, our results point to AD-associated genetic signal within the *MTCH2/SPI1* region that is independent of *CELF1/CUGB1*. We identified rs2071305 and rs11039131 that were tagging variants within *MYBPC3* and *DDB2,* within the *MTCH2* and *SPI1*

Table 4 Replication of AD/CVD pleiotropic SNPs in a UKB AD-by-proxy cohort

	SNP	Chr	Closest Gene	BP	A1	NMISS	P	OR	CIs
1	rs1431985	1	AK092251	214148246	A	362011	8.04E−01	1	1–1
2	rs61779841	1	TRIT1	40324666	A	364772	8.12E−01	1	1–1
3	rs78363635	1	C4BPA	207324781	C	364859	2.05E−01	1.002	0.999–1.01
4	rs12994639	2	SERTAD2	64959331	G	364859	2.34E−01	1.002	0.999–1.01
5	rs55819441	2	AK097952	65082415	T	364859	6.27E−01	0.9992	0.996–1
6	rs61208496	2	C2ORF56	37464230	T	363628	**8.04E−03**	1.004	1–1.01
7	rs72796734	2	ABCG5	44063731	T	364005	6.24E−01	1.001	0.997–1.01
8	rs7421448	2	INPP5D	233982205	T	364859	**1.52E−05**	0.9929	0.99–0.996
9	rs858952	2	NRXN1	50875879	C	353852	2.34E−01	1.002	0.999–1.01
10	rs6805910	3	ARHGEF3	56739923	C	364232	7.18E−01	0.9994	0.996–1
11	rs13114818	4	UBA6	68550295	C	361934	4.40E−01	0.9987	0.995–1
12	rs28670348	4	INPP4B	143625388	G	362077	9.18E−01	1	1–1
13	rs12188460	5	FBXL17	107172269	G	357888	4.58E−01	0.9988	0.996–1
14	rs2074613	5	HBEGF	139714564	C	364859	1.57E−01	1.002	0.999–1
15	rs2176298	5	LOC285629	160388643	T	364192	1.86E−01	1.002	0.999–1
16	rs4912851	5	SPRY4	141815488	G	359562	9.38E−01	1	1–1
17	rs5744712	5	POLK	74892002	C	364232	9.67E−01	0.9999	0.995–1
18	rs62383992	5	FGF18	170866296	A	356784	1.50E−01	0.9976	0.994–1
19	rs6883056	5	PRLR	35080145	C	363845	4.71E−01	1.001	0.998–1
20	rs12194027	6	ELOVL5	53255776	C	364000	1.47E−01	0.9976	0.994–1
21	rs3103351	6	SLC22A2	160716066	G	363577	**4.52E−02**	0.9967	0.993–1
22	rs536810	6	HLA-DRB5	32577497	T	363853	**2.03E−04**	0.9939	0.991–0.997
23	rs7774782	6	PRIM2	57618491	C	362322	5.06E−01	1.001	0.998–1
24	rs1048365	7	AP1S1	100804430	T	363555	9.45E−01	0.9999	0.997–1
25	rs2597283	7	BC043356	37690507	C	363815	6.48E−02	0.997	0.994–1
26	rs35991721	7	MBLAC1	99728790	T	364144	**2.34E−04**	0.9939	0.991–0.997
27	rs702483	7	RAC1	6426941	T	362242	1.05E−01	0.9973	0.994–1
28	rs117922969	8	AK055863	9257853	T	364639	5.98E−01	0.9991	0.996–1
29	rs12056620	8	PTK2B	27291749	T	364405	1.27E−01	1.003	0.999–1.01
30	rs13277568	8	TRPS1	116679547	G	364859	2.61E−01	1.002	0.999–1.01
31	rs16895579	8	TSPYL5	98364076	A	363783	1.08E−01	1.003	0.999–1.01
32	rs2011566	8	C8ORF38	95971921	G	363930	**3.35E−03**	0.9952	0.992–0.998
33	rs7014168	8	SOX7	10641965	A	363086	5.65E−02	0.9968	0.994–1
34	rs10991386	9	ABCA1	107630433	G	348514	**2.33E−02**	1.004	1–1.01
35	rs11144711	9	PCSK5	78614020	G	362976	8.55E−01	1	1–1
36	rs12339683	9	IDNK	86214149	T	358092	**3.06E−03**	1.005	1–1.01
37	rs12784561	10	CR595071	11712965	A	364859	1.82E−01	0.9978	0.995–1
38	rs145301439	10	ARMC3	23146430	A	357876	1.27E−01	0.9975	0.994–1
39	rs11039131	11	DDB2	47232038	T	360088	**3.34E−02**	0.9965	0.993–1
40	rs11039297	11	PTPMT1	47581443	A	364264	**2.80E−02**	1.004	1–1.01
41	rs1263170	11	APOA4	116678413	T	359973	4.42E−01	1.001	0.998–1
42	rs1534576	11	SLC39A13	47419663	T	363313	**7.46E−04**	1.006	1–1.01
43	rs1893306	11	GUCY2EP	76434820	G	361099	5.58E−01	0.999	0.996–1
44	rs3844143	11	PICALM	85850243	C	364859	**5.31E−11**	0.9892	0.986–0.992
45	rs6597951	11	AP2A2	991530	C	363427	1.70E−01	0.9977	0.994–1
46	rs7928842	11	CELF1	47566352	C	364616	8.25E−01	0.9996	0.996–1
47	rs1635142	12	OAS2	113434518	A	360076	3.06E−01	0.9983	0.995–1
48	rs77451327	12	SOAT2	53524259	C	364824	7.26E−01	1.001	0.995–1.01
49	rs61963560	13	BC035340	113605534	A	359151	8.67E−01	0.9997	0.996–1
50	rs7981577	13	RASA3	114835802	C	364119	3.44E−01	0.9984	0.995–1
51	rs17125924	14	FERMT2	53391680	G	363118	**1.47E−03**	1.005	1–1.01

Table 4 (continued)

	SNP	Chr	Closest Gene	BP	A1	NMISS	P	OR	CIs
52	rs3131575	15	USP8	50731154	G	364208	**3.79E−02**	0.9966	0.993–1
53	rs650366	15	FAM63B	59061142	G	361213	**4.48E−07**	0.9917	0.988–0.995
54	rs12595955	16	CDH5	66144173	G	364594	9.66E−01	0.9999	0.995–1
55	rs16953089	16	FTO	54155742	C	353751	6.54E−01	0.9992	0.996–1
56	rs246174	16	MKL2	14379931	T	357267	8.80E−01	0.9997	0.996–1
57	rs4985556	16	IL34	70694000	A	364859	**3.55E−03**	1.005	1–1.01
58	rs4985557	16	MTSS1L	70704974	T	347131	6.93E−01	1.001	0.996–1.01
59	rs8062895	16	DHODH	72048632	G	361194	1.81E−01	0.9978	0.995–1
60	rs9941245	16	GPRC5B	19916895	G	360821	8.54E−01	0.9997	0.997–1
61	rs2960171	17	ZNF652	47378771	C	364076	**9.80E−05**	1.006	1–1.01
62	rs7221196	17	ITGB3	45374994	G	359882	3.70E−01	1.001	0.999–1
63	rs8070572	17	MINK1	4766937	C	364784	**6.38E−03**	1.005	1–1.01
64	rs8071250	17	PRKCA	64321567	C	364511	**2.11E−02**	0.9962	0.993–0.999
65	rs850520	17	AK097513	47333067	A	364105	**2.40E−04**	1.006	1–1.01
66	rs9954848	18	LIPG	47131781	A	364682	1.23E−01	0.9975	0.994–1
67	rs2298428	22	YDJC	21982892	T	364859	1.90E−01	0.9978	0.995–1
68	rs4821116	22	UBE2L3	21973319	T	364630	1.10E−01	0.9974	0.994–1

Bold values indicate $p < 0.05$

SNP single nucleotide polymorphism, *Chr* chromosome

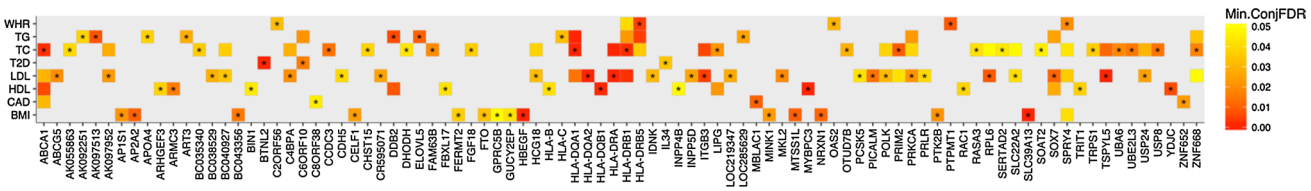

Fig. 6 Matrix plot mapping minimum conjunction FDR for the non-*APOE* AD/CV pleiotropic genes for each CV-associated RF. Asterisk indicates the conditioning RF used to identify the most significant SNP (see Table 2 and Fig. 2)

regions. Furthermore, rs2071305 was in LD with an AD age of onset SNP that was associated with lower expression of *SPI1* in monocytes and macrophages [20, 22]. We found that SPI1 expression was altered in AD brains. *SPI1* encodes a transcription factor, PU.1, that is essential for myeloid cell development and a major regulator of cellular communication in the immune system [29]. Coupled with our *HLA* findings, these results implicate genes expressed in microglia, astrocytes or other myeloid cell types in AD pathogenesis [39].

We identified enrichment for our novel AD/CV genetic variants within an AD-by-proxy cohort. Of the four new SNPs that strongly influenced Alzheimer's risk, we found that *MBLAC, DDB2* and *MINK1* were associated with proxy AD status in the UKB sample. Importantly, five of the six IGAP/ADGC2 SNPs replicated in UKB consistent with prior work highlighting the usefulness of the by-proxy phenotype approach for AD [52]. Although a proxy phenotype is not equivalent to a clinical diagnosis of dementia, our findings illustrate that a subset of cardiovascular genes influences disease risk even in people with a genetic predisposition for developing AD.

Our pleiotropy findings suggest that complex diseases and traits have a complex genetic architecture. Although we did not evaluate causal associations using a Mendelian Randomization (MR) framework, our results have implications for the relationship between common genetic variants, CV-associated RFs and AD as an outcome. To date, MR studies have typically evaluated a single CV risk factor at a time, which is valid only if the genetic variants used for the MR influence AD exclusively via the selected CV-associated risk factor [25, 33]. For some variants, we found pleiotropy challenging the conventional MR approach for genes such as *ABCA1* [17]. Instead of a single causal link [15], these results suggest two possible scenarios for genetic variants associated with multiple traits: (1) genetic variants influence cardiovascular RFs and AD independently, or (2) genetic variants influence AD through multiple cardiovascular RFs.

Several studies have explored the overall genetic relationship between CV-associated risk factors and Alzheimer's

disease. In line with our results, studies have reported significant genetic overlap between AD and plasma lipids [13, 53]. However, others have found weak casual evidence for plasma lipids and AD using MR [54] or no association between these traits using LD score regression [55]. The methods used in these studies may help explain differences from our results to some extent. As discussed above, MR analyses do not account for pleiotropic effects, which we specifically focus on in the current manuscript. Further, our pleiotropic approach allows for allelic heterogeneity and might consequently find shared genetic effects missed by the LD score regression method. Moreover, similar to our findings, others have shown minimal to no genetic overlap between CAD and T2D and AD [53]. Using MR, some have explored the causal relationship between CAD and AD risk [56] and found a lack of causal relevance of CAD for risk of late-onset AD after exclusion of *APOE*. Also, although CAD and AD show minimal genetic overlap, a genetic risk score for CAD has been shown to modify the association between CVD and AD [53]. Further, our understanding of the genetic relationship between BMI and AD is not well understood. We found minimal genetic overlap between BMI and AD. Others have found strong genetic overlap between BMI and AD [53], and yet others found no casual evidence between these traits [57]. These findings suggest that the genetic relationship between AD and BMI and CAD is complex and other factors may be influencing the relationship.

Our findings have clinical implications. First, given the common co-occurrence of vascular and Alzheimer's pathology, it is highly likely that the clinically diagnosed AD individuals from our cohort have concomitant vascular brain disease, which may further contribute to their cognitive decline and dementia. As such, a plausible interpretation of our findings is that the susceptibility loci identified in this study may increase brain vulnerability to vascular and/or inflammatory insults, which in turn may exacerbate the clinical consequences of AD pathological changes. Second, no single common variant detected in this study will be clinically informative. Rather, integration of these pleiotropic variants into a cardiovascular pathway-specific, polygenic 'hazard' framework for predicting AD age of onset may help identify older individuals jointly at risk for cardiovascular and Alzheimer's disease [11]. Therapeutically targeting cardiovascular RFs in these individuals may impact the Alzheimer's disease trajectory.

This study has limitations. First, our AD patients were diagnosed largely using clinical criteria without neuropathology confirmation and this may result in misclassification of case status. However, such misclassification should reduce statistical power and bias results toward the null. Second, we focused on the closest genes as the eQTL analyses did not replicate in both brain and blood. Additional work will be required to determine the causal genes responsible for the association between these novel loci and AD. Finally, given evidence that phospholipids are proinflammatory [35], future work should evaluate whether LDL, HDL TG, or TC influence AD risk through inflammation or other mediator variables.

In summary, we show cardiovascular-associated polygenic enrichment in AD. Beyond *APOE*, our findings support a disease model in which lipid biology is integral to the development of clinical AD in a subset of individuals. Lastly, considerable clinical, pathological and epidemiological evidence has shown overlap between Alzheimer's and cardiovascular risk factors. Here, we provide genetic support for this association.

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Compliance with ethical standards

Conflict of interest JBB served on advisory boards for Elan, Bristol-Myers Squibb, Avanir, Novartis, Genentech, and Eli Lilly and holds stock options in CorTechs Labs, Inc. and Human Longevity, Inc. AMD is a founder of and holds equity in CorTechs Labs, Inc., and serves on its Scientific Advisory Board. He is also a member of the Scientific Advisory Board of Human Longevity, Inc. (HLI), and receives research funding from General Electric Healthcare (GEHC). The terms of these arrangements have been reviewed and approved by the University of California, San Diego, in accordance with its conflict of interest policies.

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