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Genetic risk for coronary heart disease alters the influence of Alzheimer's genetic risk on mild cognitive impairment

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DECLARATION OF INTEREST

Dr. Dale is a Founder of and holds equity in CorTechs Labs, Inc, and serves on its Scientific Advisory Board. He is a member of the Scientific Advisory Board of Human Longevity, Inc. and receives funding through research agreements with General Electric Healthcare and Medtronic, Inc. The terms of these arrangements have been reviewed and approved by UCSD in accordance with its conflict of interest policies. The remaining authors declare no competing interests.

The data contained in the manuscript being submitted have not been previously published, have not been submitted elsewhere and will not be submitted elsewhere while under consideration at Neurobiology of Aging.

All participants provided informed consent and the study was approved by local Institutional Review Boards at the University of California, San Diego and Boston University.

All authors have reviewed the contents of the manuscript being submitted, approve of its contents and validate the accuracy of the data.

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Abstract

Understanding genetic influences on Alzheimer's disease (AD) may improve early identification. AD polygenic risk scores (AD-PRSs) are associated with increased odds of AD and mild cognitive impairment (MCI). Additional sources of genetic risk may also contribute to disease outcomes. Coronary artery disease (CAD) is a risk factor for AD, interacts with AD pathology, and is also heritable. We showed that incidence-based and prevalence-based CAD-PRSs moderate the association between the AD-PRS and MCI, but in opposing directions. Higher incidence-based CAD-PRSs interacted with the AD-PRS to further increase MCI risk. Conversely, the AD-PRS was predictive of MCI when prevalence-based CAD-PRSs were low. The latter finding is likely due to prevalent CAD cases being biased toward longer post-event survival times, perhaps selecting for protective loci that offset AD risk. These results demonstrate: i) the importance of examining multiple PRSs and their interactions; ii) how genetic risk for one disease can modify the impact of genetic risk for another; and iii) the importance of considering ascertainment procedures of GWAS used for genetic risk prediction.

Keywords

Alzheimer's disease; coronary artery disease; polygenic risk scores; incidence-prevalence bias; Neyman bias; cognitive impairment

INTRODUCTION

Alzheimer's disease (AD) is highly heritable (Gatz et al., 2006), with the *APOE*-ε4 allele having by far the greatest impact of any genetic locus. Large-scale genome-wide association studies (GWAS) of AD have identified 19 additional susceptibility loci (Lambert et al., 2013), yet common variants identified by GWAS tend to account for only a small proportion of the variance in most complex diseases (Visscher et al., 2012). The variance explained in AD risk can be increased using polygenetic risk score (PRS) approaches, which sum across many variants with small effect sizes (Escott-Price et al., 2015). Our group further found that a validated AD-PRS is also associated with significantly higher odds of mild cognitive impairment (MCI) (Logue et al., 2018). These results lend support to the idea that MCI is an aging-related disorder that represents an early stage of AD, and demonstrate the utility of PRSs in early identification.

Typically, associations between a phenotype and a single PRS are tested. However, a study using a multiple polygenic risk score approach (including PRSs associated with multiple traits in a model) increased the proportion of explained variance in complex traits such as general cognitive ability (Krapohl et al., 2018), but this analysis did not examine the potential interactive effects of genetic risk factors or examine AD or MCI as an outcome. Previous studies have looked at interactions at the SNP or gene level (Gusareva et al., 2014; Hohman et al., 2016), but thus far none have examined interactions of PRSs, which captures a larger proportion of the genetic risk for complex diseases (Escott-Price et al., 2017b;

Escott-Price et al., 2015; Khera et al., 2018). Additional genetic risk factors may exert their effect by conferring additional susceptibility or resilience to the effects of primary AD risk genes.

Poorer cardiovascular health has been shown to be a significant risk factor for cognitive decline and progression to dementia (Jefferson et al., 2015; Kaffashian et al., 2013; Skoog, 2000; Viticchi et al., 2015), and vascular dementia is a common source of non-AD cognitive impairment in older age groups. However, many patients demonstrate both AD and vascular lesions, and the presence of both greatly increases the odds of dementia (Azarpazhooh et al., 2018; Jellinger, 2008). Although some findings suggest that vascular and coronary risk are independent of Aβ pathology (Esiri et al., 2014; Marchant et al., 2013; Vemuri et al., 2015), others have found direct effects (Reed et al., 2012; van Norden et al., 2012). Whether amyloidogenic or not, vascular risk factors do appear to moderate the deleterious effects of AD pathology on cognitive and brain outcomes (Brickman et al., 2008; Snowdon et al., 1997; Villeneuve et al., 2014). Critically, results from the SPRINT-MIND study find that intensive control of blood pressure can significantly reduce risk of MCI (Sprint Mind Investigators for the SPRINT Research Group et al., 2019). Improved understanding of how vascular risk influences risk for MCI will therefore facilitate one of the few intervention strategies that has, to this point, demonstrated clear effects.

Like AD and MCI, coronary artery disease (CAD) is also under considerable genetic influence (Zdravkovic et al., 2002). Previous studies have found that the *APOE* and lipoprotein lipase genes are risk factors for both AD and CAD (Eichner et al., 2002; Song et al., 2004; Xie et al., 2010), suggesting some common biological basis. Genetic risk also appears to moderate the link between these diseases. For example, vascular risk factors increase the odds of cognitive decline or conversion to AD much more strongly in carriers of the *APOE*-ε4 allele (Helzner et al., 2009; Hofman et al., 1997). However, the extent to which additional susceptibility loci identified by GWAS interact is less clear. AD is a complex, polygenic disease. Thus, a model that incorporates PRSs for AD and CAD presents an opportunity to better characterize the potentially heterogenous genetic etiology of disease outcomes. Findings of synergistic effects at the phenotypic level between AD pathology and vascular risk further underscore the need to examine interactions of genetic risk for these factors in the context of multiple PRS models.

When generating a PRS, it is important to consider how the corresponding trait or disease status is defined in the original GWAS. The most common design for GWAS is case-control, which often depends on identifying prevalent cases. For conditions that may have a relatively high case-fatality rate, this may induce incidence-prevalence bias, also known as Neyman's bias (Hill et al., 2003; Neyman, 1955). A GWAS of prevalent cases may be biased toward including individuals with lower mortality rates because individuals with shorter survival times after disease onset are less likely to be available for inclusion. Therefore, putative risk loci may actually be associated with increased survival time after disease onset in addition to those associated with disease onset itself. Incident cases of CAD include individuals with both brief and extended post-event survival times, decreasing such bias. In fact, a GWAS of incident CAD cases (Dehghan et al., 2016) did find that variants in the 9p21 locus, identified as risk alleles in a prior GWAS of prevalent CAD (The

CARDIoGRAMplusC4D Consortium et al., 2012), were associated with increased risk of initial myocardial infarction, but also longer post-event survival times. While failing to replicate associations of known SNPs identified by prior GWAS of prevalent CAD, this GWAS of incident cases did identify a novel risk gene (*QKI*) despite a much smaller sample size. Thus, the loci detected in incidence-based versus prevalence-based analyses may represent somewhat different genetic influences, and may differently affect risk for AD or MCI.

In the present study, we examined how genetic risks for AD and CAD associate with MCI status in late middle-aged men. Better characterizing the genetic influences on this early disease stage may improve our ability to identify those individuals most appropriate for intervention. Based on evidence of phenotypic interactions between AD pathology and CAD risk factors, we focused on the interaction of genetic risk for AD and CAD. Importantly, to determine if the way in which cases were identified alters the association, we assessed one PRS based on prevalent cases of CAD and a second based on incident cases of CAD. Given that case-control designs of incident cases are less biased towards individuals with longer survival times, we predicted that an incident-based CAD-PRS would more strongly exacerbate the effect of AD genetic risk on cognitive status.

METHODS & MATERIALS

Participants

There were 1,329 men in the Vietnam Era Twin Study of Aging (VETSA) (Kremen et al., 2013; Kremen et al., 2006) who were determined to be of white, non-Hispanic European ancestry (WNH). As PRSs are primarily ancestry specific, and large scale GWASs have been performed in WNH subjects, we excluded subjects of other ancestry from the analysis. We then excluded those with missing data that would preclude a possible MCI diagnosis, and with conditions that could cause cognitive deficits unrelated to MCI including seizure disorder, multiple sclerosis, stroke, HIV/AIDS, schizophrenia, substance dependence, or brain cancer (Kremen et al., 2014). Additionally, in the present study the MCI group was limited to participants with amnestic MCI (aMCI). The final sample comprised 1,208 participants (mean age = 56.7, sd = 3.27).

Sample characteristics are shown in Table 1. VETSA constitutes a national sample comparable to American men in their age range with respect to health and lifestyle characteristics (Schoeneborn and Heyman, 2009). All were in some branch of military service sometime between 1965 and 1975. Nearly 80% report no combat exposure. VETSA participants had to be 51-59 years old at the time of recruitment in wave 1, and both twins in a pair had to be willing to participate (Kremen et al., 2013; Kremen et al., 2006). Here we included wave 1 and new wave 2 participants, so that all were undergoing their initial assessment. In sum, VETSA constitutes a reasonably representative sample of community-dwelling men in their age range who were not selected for any health or diagnostic characteristic. All participants provided informed consent and the study was approved by local Institutional Review Boards at the University of California, San Diego and Boston University.

Health/medical measures

A comprehensive medical history was collected for all participants (Kremen et al., 2006). A summary measure of ischemic heart disease was created based on diagnosis or self-report of myocardial infarction, cardiac procedure (e.g. stent, balloon angioplasty, coronary artery bypass) or angina (Xian et al., 2010). Depressive symptoms were assessed with the Center for Epidemiological Studies Depression Scale (Radloff, 1977). Diabetes was assessed if a participant reported being told by a physician that he had diabetes or if he was taking medication for diabetes. Type 1 diabetes would have ruled out entry into the military.

Definition of mild cognitive impairment

MCI was diagnosed using the Jak-Bondi actuarial/neuropsychological approach (Bondi et al., 2014; Jak et al., 2009). Participants completed a comprehensive neuropsychological test battery comprising 18 tests covering 6 cognitive domains, as described elsewhere (Kremen et al., 2014). To account for change from “premorbid” levels, we adjusted neuropsychological scores for a measure of young adult general cognitive ability (Lyons et al., 2017; Lyons et al., 2009). Impairment in a cognitive domain was defined as having at least two tests that were >1.5 SDs below age- and education-adjusted normative means. The MCI group was restricted to individuals classified as amnestic MCI (aMCI; e.g., impaired memory domain). With this criterion, 1,119 (92.6%) individuals were cognitively normal (CN), and 89 (7.4%) individuals had aMCI. Individuals with non-amnestic MCI were not included in the analysis. Support for the validity of these criteria comes from our finding that higher AD-PRSs were associated with significantly increased odds of aMCI in these individuals (Logue et al., 2018), based on an AD-PRS that has been validated against autopsy-confirmed AD (Escott-Price et al., 2017a; Escott-Price et al., 2015).

Genotyping methods

Genotyping and SNP cleaning methods have been described previously in detail (Logue et al., 2018), but are summarized here in brief. Whole genome genetic variation was assessed at deCODE Genetics (Reykjavik, Iceland). Genotyping was performed on Illumina HumanOmniExpress-24 v1.0A (Illumina, San Diego, CA). Beadchips were imaged using the Illumina iScan System and analyzed with Illumina GenomeStudio v2011.1 software containing Genotyping v1.9.4 module.

Cleaning and quality control of genome-wide genotype data was performed using PLINK v1.9 (Chang et al., 2015). SNPs with more than 5% missing data or SNPs with Hardy-Weinberg equilibrium P-values $<10^{-6}$ were excluded. Self-reported ancestry was confirmed using both SNPweights (Chen et al., 2013) and a principal components (PCs) analysis performed in PLINK v1.9 in conjunction with 1000 Genomes Phase 3 reference data (The 1000 Genomes Project Consortium, 2015). Analyses were restricted to participants of primarily European ancestry. PCs for use as covariates to control for population substructure were recomputed among this WNH set. Imputation was performed using MiniMac (Fuchsberger et al., 2015; Howie et al., 2012) computed at the Michigan Imputation Server (https://imputationserver.sph.umich.edu). The 1,000 genomes phase 3 EUR data were used as a haplotype reference panel. Due to concerns about potential distortion in the haplotype-phasing step of imputation, only one randomly chosen participant’s data per genotyped

monozygotic (MZ) twin pair was submitted for imputation, and that participant's resulting imputed data were applied to his MZ co-twin.

Polygenic risk score calculation

The AD polygenic risk scores (AD-PRSs) were computed using summary data from the AD GWAS as presented in Lambert et al. (Lambert et al., 2013). Individual SNP effect estimates and *P*-values were downloaded from http://web.pasteur-lille.fr/en/recherche/u744/igap/igap_download.php. Summary statistics from the coronary artery disease GWAS (Nikpay et al., 2015) used for the prevalent CAD-PRS have been contributed by CARDIoGRAMplusC4D investigators and have been downloaded from http://www.CARDIOGRAMPLUSC4D.ORG. The incident CAD-PRSs were computed using data from a GWAS on incident coronary heart disease (Dehghan et al., 2016) downloaded from the dbGaP web site, under phs000930.v6.p1 (https://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs000930.v6.p1). The incident CAD GWAS included five prospective studies that form the Cohorts for Heart and Aging Research in Genome Epidemiology (CHARGE) Consortium (Psaty et al., 2009). These studies also contribute to the CARDIoGRAMplusC4D Consortium along with additional cohorts of prevalent CAD cases. Participants in these studies were primarily middle-age and older adults of European ancestry.

Each PRS is a weighted average of VETSA sample additive imputed SNP dosages with the log-odds ratios (ORs) for each SNP estimated in the GWAS used as the weights. Rare SNPs (MAF<1%) and SNPs with poor imputation quality (R^2<0.5) were excluded from PRS calculation. The remaining SNPs were trimmed for LD using PLINK's clumping procedure (r^2 threshold of 0.2 in a 500 kb window) based on LD patterns in the 1000 Genomes EUR cohort. PRSs were computed by PLINK v1.9 using a *P*-value threshold of $P<0.50$ for the AD-PRS because that threshold best differentiated AD or MCI cases from cognitively normal adults in 3 studies, including our own (Escott-Price et al., 2017a; Escott-Price et al., 2015; Logue et al., 2018). CAD-PRSs were calculated for a range of p-value thresholds (0.001, 0.05, 0.1, 0.2, 0.3, 0.4, 0.5, 1.0). However, we selected the threshold most strongly related to the corresponding phenotype of heart disease for inclusion in the primary analyses using independent samples t-tests. Risk scores at each threshold were compared between VETSA participants with and without heart disease. These tests were not meant as rigorous analyses of the association between genetic risk and disease outcome as our prior study of the AD-PRS and MCI status was (Logue et al., 2018), but rather a procedure to select a single score to be carried forward to the main interaction analysis with a separate outcome phenotype (i.e., MCI). The prevalence-based and incidence-based CAD-PRSs were both calculated with a threshold of $P<0.05$ because they showed the strongest association with the heart disease phenotype [incident CAD-PRS: $t(1206)=2.513$, $p=0.01$; prevalent CAD-PRS: $t(1206)=3.032$; $p<0.001$]. The AD-PRS included 238,065 SNPs, the AD-PRS excluding *APOE* regions included 237,823 SNPs, the prevalent CAD-PRS included 39,055 SNPs, and the incident CAD-PRS included 20,817 SNPs. Genetic correlations between the 3 PRSs (AD, prevalent CAD, and incident CAD) were tested with LD Score regression software (Bulik-Sullivan et al., 2015a; Bulik-Sullivan et al., 2015b) using the base summary statistics as input.

To determine whether interactions with the AD-PRS were being driven by the *APOE* locus or were independent of *APOE*, a second version of the AD-PRS was computed that excluded the region of LD surrounding the *APOE* gene (44,409,039 to 46,412,650 bp according to GRch37/Feb 2009). In models using this version of the AD-PRS, we additionally examined the influence of *APOE*-ε4 measured by direct genotyping (Schultz et al., 2008) separately from the AD-PRS.

Statistical analysis

Differences in demographic variables were examined with chi-square tests and t-tests. We performed mixed effects logistic regression analyses using the glmer function from the *lme4* package (Bates et al., 2015) in R v3.2.1 (R Core Team, 2017) to examine interactions between the AD-PRS and each CAD-PRS (i.e., incidence- and prevalence-based) on aMCI status. Although differentiating effects of *APOE* from other genes that contribute to the AD-PRS was not a primary focus of this study, we conducted secondary analyses to determine whether interaction effects were driven by the *APOE* gene. These analyses included two interactions: 1) the interaction between a given CAD-PRS and *APOE*-ε4 carrier status, and 2) the interaction between a given CAD-PRS and the AD-PRS excluding the *APOE* region. All analyses adjusted for the first 3 PCs in order to account for any cryptic population substructure (Sadeh et al., 2016a; Sadeh et al., 2016b; Wolf et al., 2016). We also adjusted for the following factors that may affect cognitive function: age, diabetes, and depressive symptoms (from the CESD), and history of head injury. Pair ID was included as a random effect to account for the nonindependence within twin pairs.

RESULTS

CN and aMCI groups did not differ with respect to age, *APOE*-ε4 status, depressive symptoms, or diabetes (Table 1). There was a significantly greater proportion of individuals with ischemic heart disease in the CN group compared with the aMCI group [χ^2 (1)=5.99, p=0.014]. There was a moderate genetic correlation between the incident CAD-PRS and prevalent CAD-PRS [r_g=0.55; p=0.01]. However, the AD-PRS was not genetically correlated with either CAD-PRS [incident CAD-PRS: r_g=0.04, p=0.89; prevalent CAD-PRS: r_g=−0.06, p=0.55].

The model based on the AD-PRS and incident CAD-PRS showed main effects of both the AD-PRS [OR=1.57, 95% CI = 1.17 – 2.10, p=0.002] and the incident CAD-PRS [OR=0.70, 95% CI = 0.53 – 0.93, p=0.015]. There was also a significant *positive* interaction between the AD-PRS and the incident CAD-PRS [OR=1.39, 95% CI = 1.06 – 1.82, p=0.017], with the association between the AD-PRS and aMCI status becoming stronger as incident CAD-PRSs increased. That is, as shown to the right of the dashed red line in Figure 1A, individuals at high genetic risk for AD were much more likely to have aMCI if they also had high genetic risk for incident CAD. See Supplemental Table S1 for full regression results.

There was a very different result in the model based on the AD-PRS and the prevalent CAD-PRS. There was a significant main effect of the AD-PRS [OR=1.44, 95% CI = 1.10 – 1.90, p=0.009] such that individuals with a higher score had greater odds of being in the aMCI group. There was no main effect of the prevalent CAD-PRS. However, there was a

significant *negative* interaction between the AD-PRS and the prevalent CAD-PRS [OR=0.73, 95% CI = 0.56 – 0.95, p=0.020], with the association between the AD-PRS and aMCI status weakening as prevalent CAD-PRSs increased. In other words, as shown to the left of the dashed red line in Figure 1B, the AD-PRS was significantly predictive of aMCI status when prevalent CAD-PRS scores were low, but no longer predictive when prevalent CAD-PRS scored were high. See Supplemental Table S2 for full regression results.

Follow-up tests were conducted to determine the extent to which these effects were driven by the *APOE*-ε4 risk allele. We tested models including separate interactions of the CAD-PRSs with both directly genotyped *APOE*-ε4 status and the AD-PRS with *APOE* regions excluded (AD-PRS$_{\text{no } APOE}$). As before, in the model based on the incident CAD-PRS, both the main effect of the AD-PRS$_{\text{no } APOE}$ [OR=1.50, 95% CI = 1.12 – 2.01, p=0.007] and the incident CAD-PRS [OR=0.65, 95% CI = 0.47 – 0.90, p=0.010] remained significant. The interaction between the AD-PRS$_{\text{no } APOE}$ and the incident CAD-PRS [OR=1.26, 95% CI = 0.95 – 1.66, p=0.108] was reduced to trend level significance, although the interaction effect was in the positive direction (i.e., the AD-PRS$_{\text{no } APOE}$ showed a trend for being more strongly associated with increased risk of aMCI when the incident CAD-PRS was also high). The interaction between the incident CAD-PRS and directly genotyped *APOE*-ε4 status was not significant [OR=1.19, 95% CI = 0.64 – 2.21, p=0.580]. See Supplemental Table S3 for full regression results.

The model based on the prevalent CAD-PRS showed a significant main effect of the AD-PRS$_{\text{no } APOE}$ [OR=1.38, 95% CI = 1.05 – 1.83, p=0.023]. However, the interaction between the prevalent CAD-PRS and AD-PRS$_{\text{no } APOE}$ was reduced to a trend [OR=0.76, 95% CI = 0.58 – 1.01, p=0.055] when the *APOE* region was excluded, and the effect remained in the negative direction. The interaction between the prevalent CAD-PRS and directly genotypes *APOE*-ε4 status was not significant [OR=0.62, 95% CI = 0.34 – 1.11, p=0.108]. See Supplemental Table S4 for full regression results.

DISCUSSION

Here, we chose to examine PRSs for CAD in addition to an AD-PRS because CAD is an important risk factor for AD (Jefferson et al., 2015; Kaffashian et al., 2013; Skoog, 2000; Viticchi et al., 2015). More importantly, we examined whether there were interactive effects of genetic risk that mirror findings at the phenotypic level (Brickman et al., 2008; Snowdon et al., 1997; Villeneuve et al., 2014). Additionally, because conditions with high case-fatality rates such as CAD may result in incidence-prevalence bias (Hill et al., 2003; Neyman, 1955), we separately tested interactions between an AD-PRS with incidence-based and prevalence-based CAD-PRSs.

We found that PRSs for CAD – a risk factor for AD – significantly moderated the association between genetic risk for AD and MCI status. Moreover, the interaction of the AD-PRS with the CAD-PRS went in opposite directions depending on whether the CAD-PRS was based on incident or prevalent cases. The association between the AD-PRS and an incidence-based CAD-PRS was positive, such that individuals at elevated genetic risk for AD (i.e., high AD-PRS) were even more likely to have MCI when they also had a high

incident CAD-PRS. In contrast, there was a somewhat counterintuitive interaction between the AD-PRS and a prevalence-based CAD-PRS. This interaction was negative, such that the AD-PRS was predictive of MCI when scores on the prevalent CAD-PRS were low, but no longer predictive of MCI when score on the CAD-PRS were high.

These results illustrate the value of testing interactions between PRSs to better understand genetic influence on complex traits that may otherwise be obscured when assessing only main effects. Incorporating multiple risk factor PRSs and their interactions may capture the genetic etiology of AD more fully and help explain variability in the relationship between genetic risk for AD and clinical outcomes. When examining only main effects in the current study, it would appear that genetic risk for CAD would not appear to increase the risk of MCI. Yet the significant interactions illustrate how additional genetic factors may exert their influence by moderating the relationship between primary AD risk genes and disease outcomes.

The incident and prevalent CAD-PRSs both included genes relating to transporter activity, vascular morphogenesis, and regulation of response to stimulus. The prevalent CAD-PRS additionally included genes associated with nucleic acid binding and extracellular structure organization (see Supplemental Methods, Supplemental Figure S1, **and** Supplemental Table S5 for more details on genes and gene sets that overlap or were unique to each PRS). Genetic loci identified in GWAS of both incident and prevalent cases of CAD should be associated with poor cardiovascular health. Potential mechanisms for this added risk are that vascular factors such as hypertension can weaken the blood brain barrier, exposing the brain to harmful systemic elements (Skoog, 2000); vascular risk factors may contribute to formation or disrupt clearance of amyloid (Gottesman et al., 2017; Ramanathan et al., 2015); and vascular risk factors may potentiate the toxic effects of amyloid on brain tissue (Villeneuve et al., 2014). Individuals with a high incident CAD-PRS may therefore have cardiovascular systems more vulnerable to AD-related pathological processes.

The seemingly protective interaction effect between the prevalence-based CAD-PRS and the AD-PRS, as well as the higher rate of ischemic heart disease among cognitively normal participants compared to those with MCI may seem counterintuitive. However, a potential explanation for this is the incidence-prevalence (or Neyman) bias (Dehghan et al., 2016; Hill et al., 2003). When including prevalent cases in a case-control design of a disease with relatively high case-fatality rates, the sample will be inherently biased toward individuals with longer survival times. Likewise, individuals with ischemic heart disease in the VETSA sample (and higher incident CAD-PRS) were the subset of cases that not only survived a cardiac event, but were healthy enough to travel and participate in the study. Thus, the apparent protective main effect of the incident CAD-PRS may in fact be another example of the incidence-prevalence bias. It would be the genetic influences that confer resilience in the face of cardiovascular events—not genetic influences on cardiovascular disease itself—that have some protective effects. Conversely, it suggests that in the absence of other risk factors, AD risk alleles alone would play a greater role in risk for developing MCI or AD.

The primary focus of the present study was not to dissociate effects of *APOE* from other AD risk loci, but there were nevertheless some interesting findings. The interaction effects of

both incident and prevalent CAD-PRSs with genetic risk for AD appeared to be weakened when the *APOE* genotype was included separately. When separated out, the interactions with the AD-PRS (excluding the *APOE* region) were no longer significant. However, the interaction effects remained in the opposite directions. This suggests that the interaction effect is at least partially driven by the *APOE*-ε4 allele. It is perhaps not surprising that there would be some links between a CAD-PRS and *APOE* given that the *APOE*-ε4 allele is itself a risk factor for CAD, and that vascular risk factors are more strongly related to cognitive decline among *APOE*-ε4 carriers (Eichner et al., 2002; Helzner et al., 2009; Hofman et al., 1997; Song et al., 2004). Interestingly, death from CAD appears to be heritable (Marenberg et al., 1994) and *APOE*-ε4 further increases mortality in cases of CAD (Rosvall et al., 2009; Stengard et al., 1998). The incidence-prevalence bias may therefore be exacerbated in individuals at genetic risk for both AD and CAD. However, the interactions between the CAD-PRSs and *APOE* genotype were not significant. Thus, the synergistic effect of genetic risk for CAD and AD on aMCI status appears to be polygenic in nature.

There are a few limitations to this study. The first is that the VETSA is an all-male sample, and therefore these particular results may not generalize to women. However, there is no reason to believe that the potential for interactions of genetic risk occur in men but not women. Second, we do not know the biomarker status of our MCI cases. However, the Jak-Bondi approach has been well-validated and performs favorably compared to other MCI classification schemes with regards to biomarker positivity, clinical progression, and reduced rates of reversion to cognitively normal. Moreover, we previously showed that these individuals diagnosed as MCI with this approach have higher genetic risk for AD (also indicated by the significant main of the AD-PRS in the current analysis) based on an AD-PRS that has been validated in autopsy-confirmed AD (Escott-Price et al., 2017a). It is also important to note that the presence or absence of biomarker confirmation does not alter the interpretation of the key finding here that genetic risk for one disease may modify the impact of genetic risk for another. The genetic influence on mortality from CAD is strongest during middle age, the age at which VETSA participants were assessed in this study, and weakens at older ages (Ewbank, 2002). Additional factors beyond age that may differ across studies are whether vascular burden is an exclusion criterion, whether the sample is community or clinic-based, and whether non-amnestic MCI participants are included. Therefore, further research is needed to directly compare studies with different design and sample characteristics to clarify the impact incidence-prevalence bias has on putative risk indices of disease. Furthermore, a comprehensive comparison of the genetic pathways enriched in prevalent versus incident CAD may further clarify which genes are associated with disease onset or resilience.

The current study raises three important points. The first is that PRSs can be valuable measures for better understanding genetic influences on Alzheimer's disease. Here, the interaction effects of interest were only apparent when using a more comprehensive measure of polygenic risk rather than the *APOE*-ε4 allele alone. Second, examining interactions between multiple sources of risk is an important approach to better clarify genetic influences on complex disease. The extent of this influence may be obscured if only main effects are examined. More fully describing factors that contribute to variability will aid in identifying individuals most at risk and help predict the likelihood and/or rate of disease progression.

Third, ascertainment methods of GWAS used to calculate PRSs must be considered to appropriately interpret what traits the effect alleles actually represent, particularly when there is a high case-fatality rate. As shown here, this can even result in the reversal of expected effects, with susceptibility loci demonstrating a protective moderating effect on genetic risk for a given disease. This is a crucial design element for any study to consider when interpreting or using data generated by genetic association studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Mild cognitive impairment may have a heterogeneous genetic etiology
- Tested interaction of Alzheimer's and coronary artery disease polygenic risk scores
- Incidence and prevalence-based coronary artery disease scores had opposite effects
- Genetic risk for one condition may modify impact of genetic risk for another

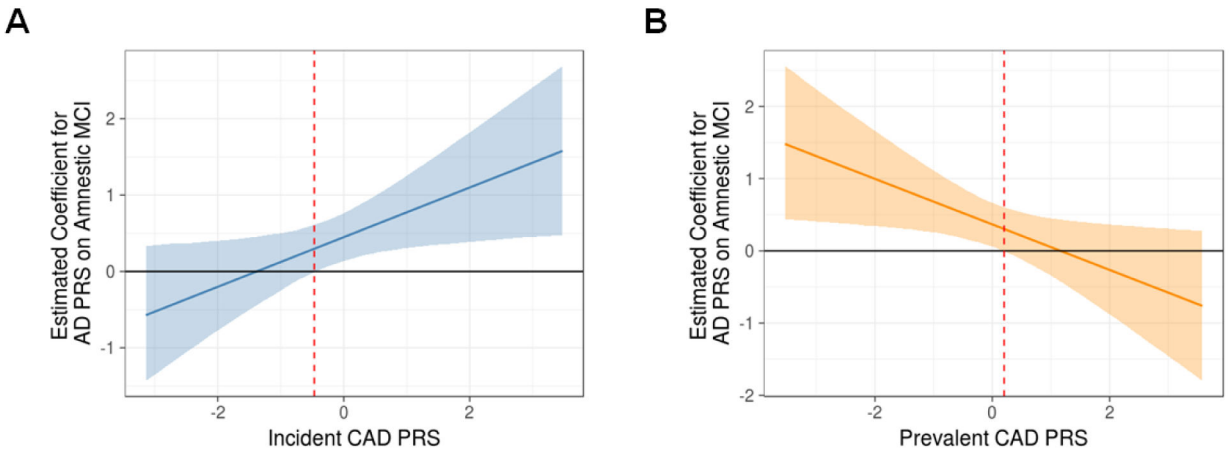

Figure 1. Interaction effects of polygenic risk scores for Alzheimer's disease and coronary artery disease.

Plots of the interaction of an Alzheimer's disease polygenic risk score with A) a prevalent coronary artery disease polygenic risk score (CAD-PRS) and B) an incident CAD-PRS on amnestic mild cognitive impairment (MCI) status. The regression coefficient of the AD-PRS on amnestic MCI status is on the y-axis and is plotted across varying levels of CAD-PRSs on the x-axis. The dashed red line indicates the threshold of statistical significance for the AD-PRS as a predictor of aMCI status (i.e., where the 95% confidence intervals do not include 0). In 1A the AD-PRS is more predictive of risk for aMCI to the right of the dashed line (i.e., people with higher AD-PRSs are more likely to have aMCI if they also have *higher incident* CAD-PRSs). In 1B the AD-PRS is a significant predictor of increased risk for aMCI to the left of the dashed line but is not significant to the right of the dashed line (i.e., people with higher AD-PRSs are only are higher risk for aMCI if they also have *lower prevalent* CAD-PRSs).

Table 1.

Sample characteristics.

Group	Cognitively Normal	Amnestic MCI	Test statistic	P-value
N	1119	89		
Age	56.7 (3.3)	57.2 (3.5)	t = 1.19	0.237
APOE-ε4+	29.4%	26.2%	$\chi^2 = 0.247$	0.006
Ischemic Heart Disease *	13.3%	3.5%	$\chi^2 = 5.990$	0.014
Depression	7.8 (7.6)	9.0 (8.4)	t = 1.29	0.199
Diabetes	10.7%	11.5%	$\chi^2 = 0.001$	0.857

* Ischemic heart disease variable is a summary measure that includes history of myocardial infarction, cardiac procedure or angina.