HUMAN GENETICS

Genome-wide pleiotropy analysis of coronary artery disease and pneumonia identifies shared immune pathways

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Coronary artery disease (CAD) remains the leading cause of death despite scientific advances. Elucidating shared CAD/pneumonia pathways may reveal novel insights regarding CAD pathways. We performed genome-wide pleiotropy analyses of CAD and pneumonia, examined the causal effects of the expression of genes near independently replicated SNPs and interacting genes with CAD and pneumonia, and tested interactions between disruptive coding mutations of each pleiotropic gene and smoking status on CAD and pneumonia risks. Identified pleiotropic SNPs were annotated to *ADAMTS7* and *IL6R*. Increased *ADAMTS7* expression across tissues consistently showed decreased risk for CAD and increased risk for pneumonia; increased *IL6R* expression showed increased risk for CAD and decreased risk for pneumonia. We similarly observed opposing CAD/pneumonia effects for *NLRP3*. Reduced *ADAMTS7* expression conferred a reduced CAD risk without increased pneumonia risk only among never-smokers. Genetic immune-inflammatory axes of CAD linked to respiratory infections implicate *ADAMTS7* and *IL6R*, and related genes.

INTRODUCTION

Despite continued advances, coronary artery disease (CAD) remains the leading cause of mortality and disability-adjusted life-years (DALYs) worldwide (*1*). Acute respiratory infections such as pneumonia, from influenza, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and other pathogens, are common among individuals with chronic CAD (*2*, *3*) and can precipitate CAD events or exacerbate CAD symptoms (*4*), and influenza vaccination reduces CAD risk (*5*–*7*). These observations implicate the operation of immune-related CAD pathways. Elucidating shared pathways may reveal novel insights toward addressing the sizable persistent CAD risk in the population.

Prior human genetic studies identified interleukin 6 receptor (IL-6R) as a putative causal factor for CAD (*8*, *9*), bolstered by the CANTOS (Canakinumab Anti-Inflammatory Thrombosis Outcomes Study) trial showing that inhibition of Interleukin-1β (IL-1β), a cytokine immediately upstream of IL-6, reduces CAD risk (*10*). However, key questions persist: Since IL-1β inhibition was associated with increased infection risk, does this extend to other targets in the IL-1β signaling pathway? Are there other inflammatory pathways implicating CAD and pneumonia? Can environmental factors influence the CAD and pneumonia risk associated with these pathways?

Here, we leveraged the pleiotropy between CAD and pneumonia to dissect jointly the unaddressed axis of CAD linked to pneumonia. We started with genome-wide pleiotropy analyses of CAD and pneumonia using summary statistics from CARDIoGRAMplusC4D [Coronary ARtery DIsease Genome wide Replication and Meta-analysis (CARDIoGRAM) plus The Coronary Artery Disease (C4D) Genetics] and FinnGen R4. Then, we examined the causal effects of genes near the pleiotropic loci that were independently replicated, as well as other closely interacting genes according to the STRING database of protein-protein interactions, on CAD and pneumonia through Mendelian randomization (MR). Last, we examined for interactions between those genes and smoking status on incident CAD and pneumonia risks in the UK Biobank. Our observations support genetic immune-inflammatory axes of CAD linked to respiratory infections and implicate *ADAMTS7* and *IL6R*, and related genes.

RESULTS

Our primary study population included 450,899 participants in the UK Biobank, who were mean (SD) age 56.6 (8.0) years, 53.9% female, 45.0% ever-smokers, and 83.6% European ancestry. At baseline, the prevalences of CAD, pneumonia, hypertension, hypercholesterolemia, and type 2 diabetes were 3.1, 2.1, 29.3, 15.1, and 2.5%, respectively. Over 11.1-year median follow-up, the number of incident cases of CAD, pneumonia, and type 2 diabetes was 13,374 (3.1%), 18,574 (4.2%), and 23,007 (5.2%), respectively (Table 1). The workflow for our study is depicted in fig. S1.

Genome-wide pleiotropy search

We applied the PLeiotropic Analysis under COmposite null hypothesis (PLACO) to summary statistics for CAD from CARDIoGRAMplusC4D 2015 (*11*) and for pneumonia from FinnGen v4. A total of 115 single-nucleotide polymorphisms (SNPs) with significant genetic pleiotropy between CAD and pneumonia defined as $P_{PLACO} < 5 \times 10^{-8}$ were identified. Among them, 88 also demonstrated evidence of association ($P < 0.05$) with CAD and pneumonia risk in an independent dataset, which was a meta-analysis of the UK Biobank and Mass General Brigham Biobank. The CAD and pneumonia effects of all replicated SNPs were of opposite directions. These SNPs mapped to two distinct loci, and the annotated closest genes were *ADAMTS7* and *IL6R* (Fig. 1 and table S1).

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Table 1. Characteristics of the study population in the UK Biobank (*N* = 450,899).*

Metric†	Value
Age (years)	56.6 (8.0)
Male	207,968 (46.1%)
European ancestry	376,785 (83.6%)
Ever smoked	203,026 (45.0%)
Coronary artery disease	13,797 (3.1%)
Pneumonia	9,687 (2.1%)
Hypertension	132,186 (29.3%)
Hypercholesterolemia	68,089 (15.1%)
Type 2 diabetes	11,136 (2.5%)
Events during follow-up	
Incident coronary artery disease	13,374 (3.1%)
Incident pneumonia	18,574 (4.2%)
Incident type 2 diabetes	23,007 (5.2%)

*The study population was restricted to unrelated individuals in the UK Biobank, with unrelatedness defined as less than third-degree relatedness.
†Metrics are represented as mean (SD) for continuous variables and % (*n*) for categorical variables. Clinical conditions are those occurring before enrollment unless noted as incident.

Causal relations examination

We used expression quantitative trait loci (eQTL) data from the Genotype-Tissue Expression (GTEx) v8 to perform MR to assess the tissue-specific effects of increased *ADAMTS7* and *IL6R* expression on CAD and pneumonia risk (*12*). Since both *ADAMTS7* and *IL6R* had disruptive coding variants, *ADAMTS7* p.Ser214Pro (rs3825807, allele frequency = 43.8%) and *IL6R* p.Asp358Ala (rs2228145, allele frequency = 40.1%), that can mimic functional inhibition of that gene, we additionally conducted single-instrument MR analysis with those variants. These two coding variants were also identified as pleiotropic SNPs by PLACO. On the basis of known biology, the genetic effects of tissue-specific expression of *ADAMTS7* were assessed in aorta, tibial artery, and left ventricle, and those of *IL6R* were assessed in tibial artery and whole blood. Across all those tissues, we observed that genetically increased *ADAMTS7* expression consistently correlated with significantly decreased risk for CAD and significantly increased risk for pneumonia, and genetically increased *IL6R* expression correlated with significantly increased risk for CAD and significantly decreased risk for pneumonia. Using inverse variance–weighted fixed-effects (IVW-FE) method, one SD increase in the normalized gene expression of *ADAMTS7* was genetically associated with 0.85 odds [95% confidence interval (CI): 0.83 to 0.88; $P = 9.1 \times 10^{-28}$] for CAD and 1.07 odds (95% CI: 1.03 to 1.11; $P = 0.001$) for pneumonia in tibial artery, and one SD increase in genetic *IL6R* expression was associated with 1.18 odds (95% CI: 1.13 to 1.24; $P = 1.1 \times 10^{-11}$) for CAD and 0.86 odds (95% CI: 0.80 to 0.93; $P = 0.0001$) for pneumonia in the same tissue (Fig. 2). Using single coding variants yielded consistent results with significant associations for both CAD and pneumonia with opposing effect directions [artery tibial: *ADAMTS7* rs3825807: β_{CAD} (SE_{CAD}) = −0.20 (0.02), $P_{CAD} = 2.39 \times 10^{-26}$; $\beta_{pneumonia}$ ($SE_{pneumonia}$) = 0.09 (0.03), $P_{pneumonia} = 3.89 \times 10^{-4}$; *IL6R* rs2228145: β_{CAD} (SE_{CAD}) = 0.20 (0.03), $P_{CAD} = 7.39 \times 10^{-14}$; $\beta_{pneumonia}$ ($SE_{pneumonia}$) = −0.15 (0.04), $P_{pneumonia} = 4.09 \times 10^{-4}$]. Sensitivity analyses using other MR methods, including summary data–based MR (SMR), MR-Egger, weighted median, weighted mode, and Mendelian randomization using the robust adjusted profile score (MR-RAPS), showed consistent results (fig. S2 and table S2).

Among the top 10 genes whose corresponding proteins closely interact with ADAMTS7 protein according to STRING (fig. S3A), three (*ADAMTS13*, *ADAMTSL1*, and *ADAMTSL3*) had valid eQTL gene expression for tibial artery in GTEx. None of the eQTL instruments for the three genes showed significant associations with either CAD or pneumonia (Fig. 3A). As the expression of *IL6R* is well recognized to be influenced by the concentrations of IL-1β and NLRP3, we seeded STRING with *IL6R*, *IL1B*, and *NLRP3* for interacting genes in this pathway. Combining the top 10 genes whose corresponding proteins closely interact with each of IL-6R, IL-1β, and NLRP3 proteins resulted in a total of 28 distinct genes, among which 24 had valid eQTL instruments for their expression concentrations in whole blood of data from the eQTLGen consortium, including *IL6*, *IL6ST*, *JAK1*, *JAK2*, *JAK3*, *STAT1*, *SAT3*, *STAT6*, *TYK2*, *IL1R1*, *IL1R2*, *IL1RAP*, *IL4*, *IL10*, *IL18*, *TNF*, *AIM2*, *DHX33*, *CASP1*, *CASP5*, *CARD8*, *NEK7*, *NLRC4*, and *TXNIP*. We tested *IL6R*, *IL1B*, and *NLRP3* together with the 24 genes and found that three of them had significant effects on both CAD and pneumonia: *IL6R*, *NLRP3*, and *DHX33*. Consistent with the results using tissue-specific eQTL data from GTEx, increased *IL6R* expression showed increased risk for CAD and decreased risk for pneumonia ($P_{CAD} = 3.8 \times 10^{-4}$; $P_{pneumonia} = 0.03$); the expression of *NLRP3* also demonstrated opposing directions of effects but with increased expression leading to decreased CAD risk and increased pneumonia risk ($P_{CAD} = 0.009$; $P_{pneumonia} = 0.004$); and decreased *DHX33* gene expression was associated with decreased risk for both CAD and pneumonia ($P_{CAD} = 0.009$; $P_{pneumonia} = 0.008$) (Fig. 3, B to D). Our sensitivity analysis with using only cis-eQTL data for selecting instruments or using multiple MR methods yielded consistent results (figs. S4 and S5 and table S3). When limiting to cis-eQTLs only, similar to *NLRP3*, decreased expression of the related *AIM2* inflammasome was associated with decreased CAD risk and increased pneumonia risk (fig. S4C).

Gene-environment interaction examination

We used *ADAMTS7* p.Ser214Pro and *IL6R* p.Asp358Ala as the genetic proxy for the function inhibition for *ADAMTS7* (*13*, *14*) and *IL6R* (*8*, *15*, *16*), respectively, and tested their interactions with smoking status on incident CAD and pneumonia risk. In parallel, we also examined the smoking interaction for each independent genome-wide significant eQTL as well as their weighted linear combination (i.e., eQTL score). In the UK Biobank, among participants who never smoked, the presence of *ADAMTS7* p.Ser214Pro was associated with a significantly reduced risk of incident CAD [hazard ratio (HR): 0.89, 95% CI: 0.84 to 0.93; $P = 1.1 \times 10^{-5}$] for never-smokers but not those who ever smoked (HR: 0.96; 95% CI: 0.92 to 1.01; $P = 0.14$), revealing a statistical interaction between smoking status and *ADAMTS7* p.Ser214Pro ($P_{interaction} = 0.01$). In contrast, the presence of *ADAMTS7* p.Ser214Pro was associated with a significantly increased risk of pneumonia only among those who ever smoked (HR: 1.08, 95% CI: 1.03 to 1.12; $P = 4.4 \times 10^{-4}$) but not those who never smoked (HR: 0.96, 95% CI: 0.92 to 1.01; $P = 0.15$; $P_{interaction} = 2.8 \times 10^{-4}$) (Table 2). We did not observe statistically significant interactions between *IL6R* p.Asp358Ala and smoking

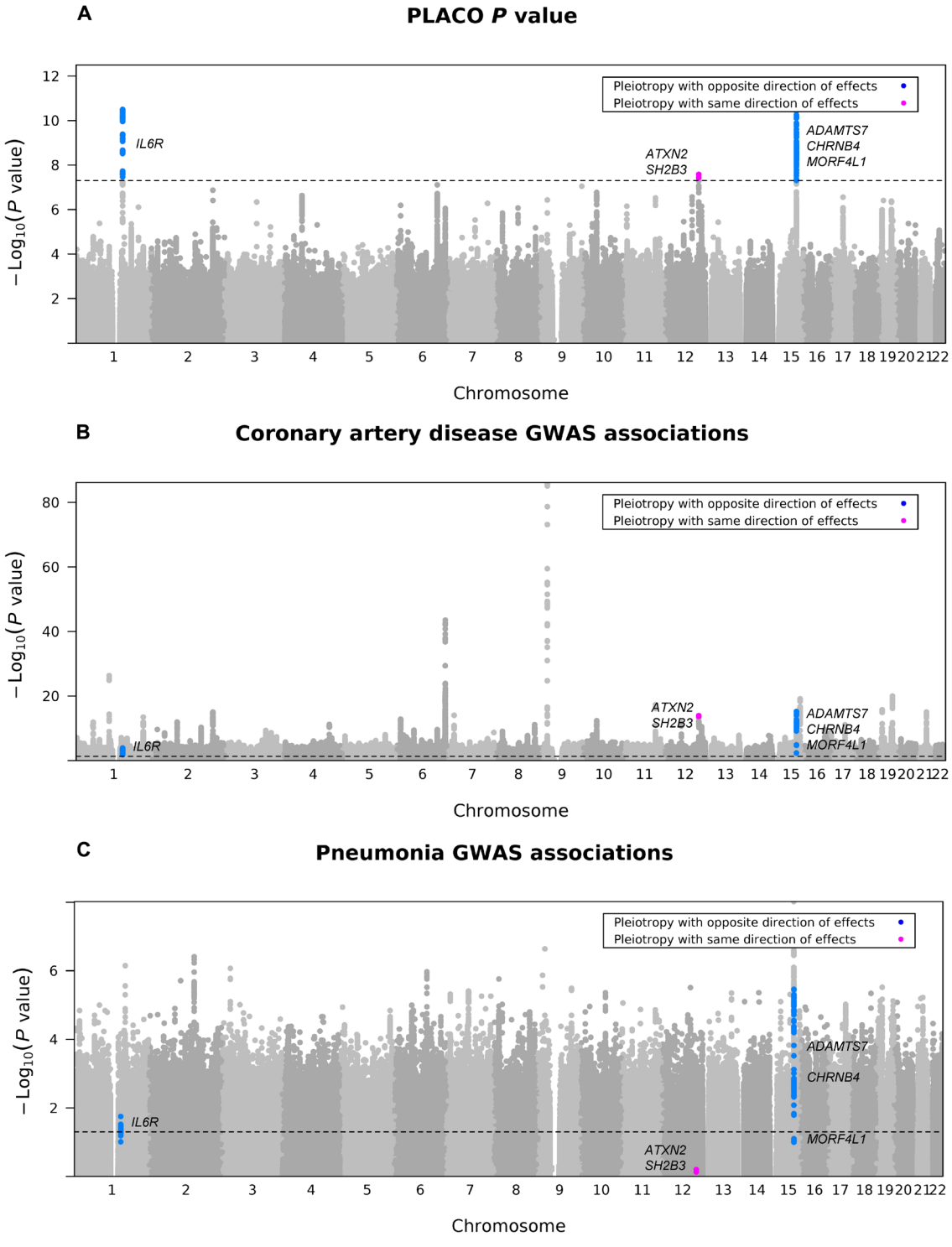

Fig. 1. Manhattan plots for genome-wide analyses of genetic pleiotropy between coronary artery disease (CAD) and pneumonia. Genetic pleiotropy is defined as PLACO *P* values below genome-wide significance (5.0×10^{-8}) with input GWAS of CAD from CARDIoGRAMplusC4D and that of pneumonia from FinnGen. GWAS results of CAD and pneumonia are from meta-analysis of UK Biobank and Mass General Brigham Biobank. A total of 115 SNPs with statistically significant evidence of genetic pleiotropy between CAD and pneumonia are highlighted: 113 SNPs with opposite direction of effects on CAD and pneumonia (nearest genes: *IL6R*, *CHRNB4*, *ADAMTS7*, and *MORF4L1*) are highlighted in blue; 2 SNPs with same direction of effects (nearest genes: *SH2B3* and *ATXN2*) are highlighted in purple. The black horizontal dashed line in (**A**) corresponds to genome-wide significance (5.0×10^{-8}) and that in (**B**) and (**C**) corresponds to nominal significance (0.05).

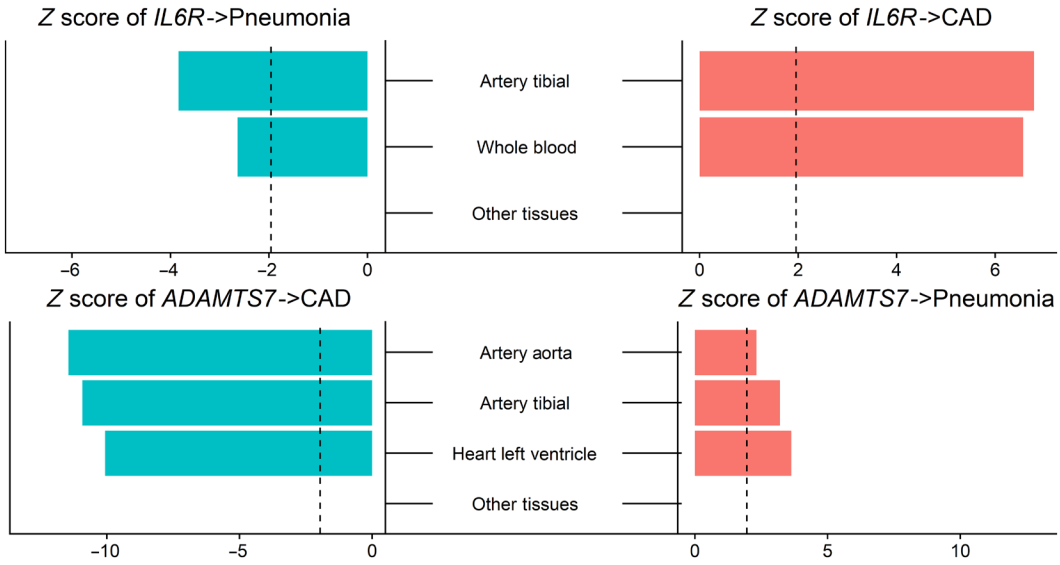

Fig. 2. Tissue-specific causal effects of the expression of *ADAMTS7* and *IL6R* gene on CAD and pneumonia. Mendelian randomization with inverse variance–weighted methods was used for this analysis. eQTL data were from GTEx v8. Relevant tissues included whole blood, spleen, small intestine terminal ileum, lung, liver, heart left ventricle, heart atrial appendage, artery tibial, artery coronary, artery aorta, adrenal gland, adipose visceral omentum, and adipose subcutaneous. Red bars indicate positive causal relations. Green bars indicate negative causal relations. The methods use was Black dashed lines indicate *Z* scores of 1.96, corresponding to $P = 0.05$.

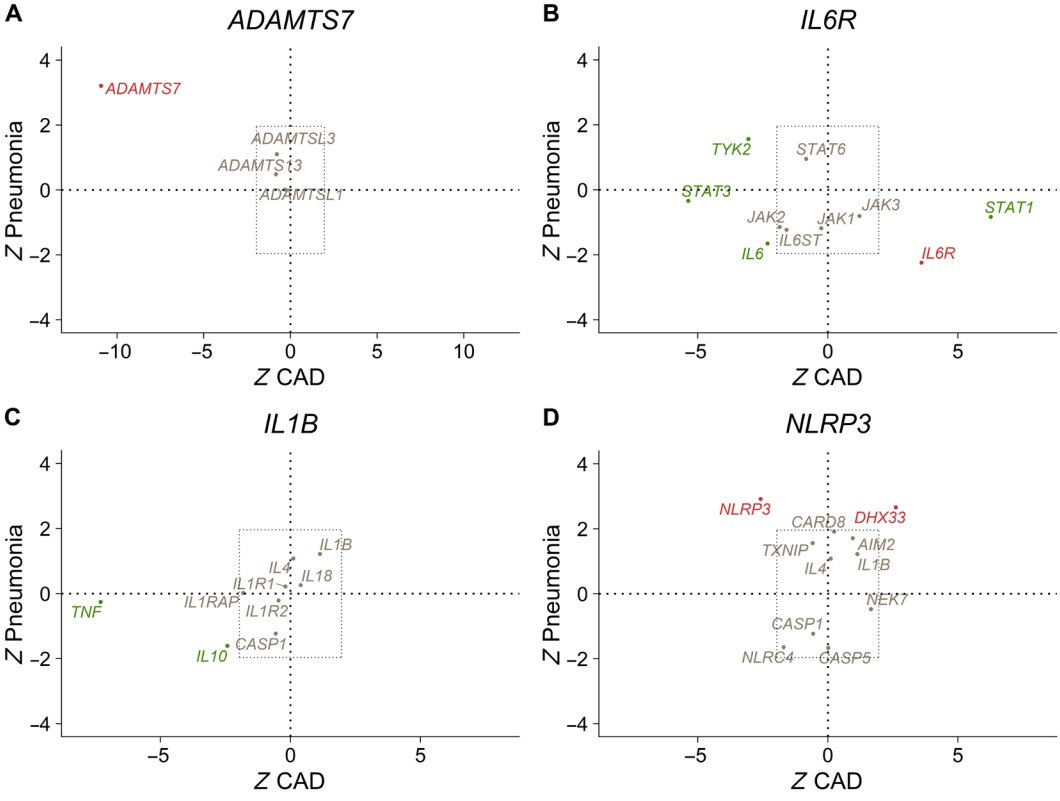

Fig. 3. Causal effects of the expression of selected inflammatory genes on CAD and pneumonia. eQTL data derived from tibial artery tissue for *ADAMTS7*-related genes were from GTEx v8. eQTL data derived from whole blood for *IL6R*-, *IL1B*-, and *NLRP3*-related genes were from the eQTLGen consortium. Mendelian randomization with inverse variance–weighted methods was used for this analysis. Red dots indicate significant causal relations with both CAD and pneumonia. Green dots indicate significant causal relations with either CAD or pneumonia. Gray dots indicate significant causal relations with neither CAD nor pneumonia. Black dashed lines indicate *Z* scores of 1.96, corresponding to $P = 0.05$.

Table 2. CAD and pneumonia event incidence stratified by smoking status and genetically determined *ADAMTS7* level.

	Coronary artery disease*,†					Pneumonia*,‡				
	At risk	Incident events	*P* value	Hazard ratio	*P* for interaction	At risk	Incident events	*P* value	Hazard ratio	*P* for interaction
Nonsmoker	77,938	2,023	Ref	1.00	0.01	78,090	2,392	Ref	1.00	2.8×10^{-4}
Nonsmoker, *ADAMTS7* p.Ser214Pro	165,159	3,875	1.1×10^{-5}	0.89		165,137	4,899	0.15	0.96	
Ever smoked	60,835	2,377	Ref	1.00		62,282	3,358	Ref	1.00	
Ever smoked, *ADAMTS7* p.Ser214Pro	133,082	5,099	0.14	0.96		135,615	7,925	4.4×10^{-4}	1.08	

*Model adjusted for age, age^2, sex, race, first 10 principal components of ancestry, diagnosis of type 2 diabetes mellitus, and genotyping array. †Study population included 437,014 unrelated individuals without prevalent CAD in the UK Biobank with unrelatedness defined as less than third-degree relatedness. CAD was defined as self-reported, hospitalization with, or death due to myocardial infarction, or hospitalization with OPCS4 (Office of Population Censuses and Surveys) codes for coronary artery bypass grafting (K40, K41, and K45) or coronary angioplasty with or without stenting (K49, K50.2, and K75). ‡Study population included 441,124 unrelated individuals without prevalent pneumonia in the UK Biobank with unrelatedness defined as less than third-degree relatedness. Pneumonia was defined as self-reported, hospitalization with, or death due to pneumonia.

status or between eQTLs for *IL6R* and smoking status on either CAD or pneumonia. However, the eQTL score for *ADAMTS7* yielded nominal interaction with smoking status on pneumonia on the same direction as *ADAMTS7* p.Ser214Pro ($P_{interaction} = 0.01$), but not on CAD.

DISCUSSION

Using a genome-wide pleiotropy scan, we demonstrated a genetic immune-inflammatory axis of CAD linked to pneumonia implicating *ADAMTS7* and *IL6R*, and related genes. For both genes as well as *NLRP3*, genetic analyses were consistent with opposing causal effects on CAD and pneumonia. We also found significant interactions between the expression of *ADAMTS7* and smoking status on incident CAD as well as pneumonia risk, indicating a cardioprotective effect without heighted pneumonia risk among nonsmokers. Our study provides a framework leveraging genetic pleiotropy to yield new biological and therapeutic insights.

Our approach uses a hypothesis-driven approach to examine immunity and CAD through concomitant analysis of pneumonia, a common comorbid infectious disease. Observational epidemiology and translational research efforts have led to notable progress in improving the understanding of the pathophysiology underlying CAD during the past decades (*17*, *18*). However, despite effective treatment for traditional risk factors such as lipids and hypertension, CAD remains the leading causes of mortality and DALYs among population above age 50 (*1*). Recent pandemics of influenza, coronavirus disease 2019 (COVID-19), and other respiratory infections brought to the forefront their complex interplay with atherosclerosis, highlighting the potential separate risk of immune inflammation on CAD (*2*, *3*). Probing the genetic correlation between CAD and pneumonia revealed the involvement of the immune-inflammatory genes *ADAMTS7* and *IL6R*.

Our results may have important implications for the prevention of CAD. First, smoking status may provide important information toward precision medicine immunomodulatory approaches for CAD. *ADAMTS7* belongs to the ADAMTS family of secreted metalloproteinases characterized with at least one thrombospondin type I repeat domains (*19*, *20*). Genome-wide association studies (GWASs) previously revealed and independently replicated associations between multiple genetic variants at the *ADAMTS7* locus and susceptibility to CAD (*21*–*23*), among which rs3825807 represents an A to G coding SNP, resulting in replacement of Ser^{214} by Pro, thus affecting protein function (*23*). *ADAMTS7* has also been validated as the causal gene by both in vitro and in vivo experiments (*24*, *25*). ADAMTS7 concentrations in human atherosclerotic plaque link to histological characteristics of plaque instability (*26*). *ADAMTS7* has opposing effects between its gene expression and gene inactivation for loss-of-function variants. *ADAMTS7* loss of function consistently shows protective effects for atherosclerosis in animal models, and the *ADAMTS7* coding variant, rs3825807, G allele (Pro^{214}) has been associated with decreased atherosclerotic activity in multiple human studies. As a contrast, the G allele was associated with increased expression levels across all tissues in which rs3825807 is a significant eQTL in GTEx (*13*, *14*, *22*, *24*, *27*–*30*). Our study demonstrated that *ADAMTS7* participates in CAD and pneumonia but in opposing directions. Consistent with our findings, it has been reported that mice deficient for *ADAMTS7* have an impaired adaptive immune response to influenza viral infections, resulting in overall higher viral loads compared to littermate controls (*31*). However, we note that in the cellular context, silencing *ADAMTS7* in the human A549 lung epithelial cell line was shown to decrease influenza virus replication (*32*). Moreover, from our analysis we independently observed that *ADAMTS7* p.Ser214Pro confers CAD protection in never-smokers but not in those who ever smoked (33). Conversely, we also found that *ADAMTS7* p.Ser214Pro significantly increased risk of pneumonia only among ever-smokers but not among never-smokers. These findings indicate that therapeutic targeting of ADAMTS7 may be most effective in never-smokers, i.e., greater decrease in CAD risk without increased pneumonia risk.

Second, our approach aims to genetically prioritize therapeutic targets for CAD in the NLRP3/IL-1β/IL-6 pathway. Previously, the common *IL6R* p.Asp358Ala was shown to be associated with reduced cardiovascular disease risk (*8*, *16*). CANTOS showed that, compared to placebo, patients with CAD and elevated high-sensitivity C-reactive protein concentrations had reduced cardiovascular disease risk with canakinumab, a monoclonal antibody targeting IL-1β

(*10*). Furthermore, the therapeutic effect was closely tied to the extent of IL-6 concentration reduction (*34*). Consistent with our human genetic observations, canakinumab versus placebo yielded a higher incidence of fatal infection in CANTOS (*10*). Now, there are multiple inhibitors of IL-6 and NLRP3 that are in clinical development (*35*, *36*). We now provide human genetic validation for NLRP3 inhibition and CAD risk. However, our analyses indicate the possibility of increased infection risk as observed in CANTOS. While our germline genetic analyses model organism-wide perturbations, pharmacologic specificity may overcome these anticipated on-target adverse effects. In secondary analyses of interacting proteins, we observed that decreased *DHX33* gene expression was associated with decreased risk for both CAD and pneumonia. Therefore, alternate related targets may more optimally modulate immunity for both CAD and infectious disease.

The current study is strengthened by our robust design for genome-wide pleiotropy scan and causal relationship examinations: (i) In addition to having statistically significant evidence on pleiotropy, defined as $P_{PLACO} < 5 \times 10^{-8}$, only SNPs whose associations with CAD and pneumonia replicated in independent cohorts were carried forward for further steps; (ii) leveraging eQTL data from both GTEx and eQTLGen, our causal inference results of *IL6R* and *ADAMTS7* on CAD and pneumonia are consistent across tissues and data resources; and (iii) sensitivity analysis with applying multiple MR methods on both cis- and trans-, and cis-only eQTL data also demonstrates the robustness of our findings. Our study also has limitations. (i) Because of the unavailability of valid instruments for measurement of *ADAMTS7* expression in whole blood, the causal inferences for *ADAMTS7* and its interacting genes were conducted using eQTL data of tibial artery from GTEx, which has smaller sample size and only cis-eQTL data versus the *IL6R*-related analyses that used data from the eQTLGen consortium. (ii) Our gene-smoking interaction exploration dichotomized smoking status to ever-smoker and never-smoker without examining for the potential dose response of smoking on disease risk due to the large number of missingness of corresponding variables in the UK Biobank. Heterogeneity among ever-smokers may exist. (iii) While our human genetic study provides strong causal inference, perturbation in controlled model systems and prospective human randomized controlled trials are necessary to definitively establish causality, and perturbational experiments in controlled model systems are needed for understanding the underlying mechanisms. (iv) As the study population consisted of mostly participants with European ancestry, similar studies are necessary in non-European populations to assess generalizability.

In conclusion, leveraging novel statistical methods, eQTL data from multiple tissues and resources, together with large-scale population cohort, we demonstrated that genetic immune-inflammatory axes of CAD linked to respiratory infections implicate *ADAMTS7* and *IL6R*, and related genes.

MATERIALS AND METHODS

Study population

The UK Biobank is a prospective cohort consisting of approximately 500,000 adult participants recruited between 2006 and 2010 from 22 assessment centers across the United Kingdom (*37*). Our analysis included 450,899 unrelated individuals in the UK Biobank. Samples were excluded for the following reasons: genotypic sex did not match reported sex, kinship was not inferred, putative sex chromosome aneuploidy, consent withdrawn, or excessive heterozygosity or missingness, based on centralized sample quality control performed by UK Biobank. Excluded related individuals were defined as one individual in each pair within the third degree of relatedness determined based on kinship coefficients centrally calculated by UK Biobank (*37*). Outcomes of this analysis were incident CAD and pneumonia: CAD was defined as self-reported, hospitalization with, or death due to myocardial infarction, or hospitalization with OPCS4 (Office of Population Censuses and Surveys) codes for coronary artery bypass grafting (K40, K41, and K45) or coronary angioplasty with or without stenting (K49, K50.2, and K75). Pneumonia was defined as self-reported, hospitalization with, or death due to pneumonia. Prevalent cases were removed when analyzing the corresponding incident outcomes.

Mass General Brigham Biobank is an ongoing hospital-based cohort study of patients across the Mass General Brigham (formerly Partners HealthCare) health system. It is enriched with longitudinal electronic medical records (EMR) data, genomic data, and electronic health and lifestyle survey data (*38*). The present secondary analyses were approved by the Massachusetts General Hospital Institutional Review Board.

Genome-wide pleiotropy search

We applied PLACO to conduct a genome-wide search for SNPs influencing risks of both CAD and pneumonia. Briefly, PLACO is a novel statistical method for identifying pleiotropic loci between two traits by testing the composite null hypothesis that a locus is associated with zero or one of the traits. It only needs summary statistics as input, and the test statistic is formed as the product of the Z statistics of the SNP in each of the two studies that assumed to follow a mixture distribution (*39*). Input genome-wide summary statistics for CAD were from CARDIoGRAMplusC4D 2015 (*11*), and those for pneumonia were from FinnGen R4 (https://www.finngen.fi/en). CARDIoGRAMplusC4D 2015 is a meta-analysis of GWASs including 60,801 CAD case and 123,504 control participants with mainly European, South Asian, and East Asian ancestries (*11*). The FinnGen Study is a Finnish, nationwide GWAS meta-analysis that linked with EMR data from national health registries. In R4, there were 20,389 pneumonia cases defined as phenotype ICD10-J10 pneumonia and 156,510 controls. There were no overlap of study populations underlying the CAD and pneumonia GWAS. We removed SNPs with $Z^2 > 80$ as extremely large significance may disproportionately influence the analysis (*39*, *40*). For pleiotropic SNPs with statistically significant evidence of genome-wide pleiotropy, defined as $P_{PLACO} < 5 \times 10^{-8}$, we independently assessed for nominal association with both CAD and pneumonia in a meta-analysis of UK Biobank (*41*) and Mass General Brigham Biobank. We clumped variants in ±500-kb radius and linkage disequilibrium (LD) threshold of $r^2 > 0.2$ into a single genetic locus using FUMA (SNP2GENE function, v1.3.6a). The gene annotations for all loci are based on proximity to the most significant/lead SNPs as mapped by FUMA (*42*).

Genetic relations examination

We evaluated the genetic relations of tissue-specific expression of genes annotated to the pleiotropic SNPs on CAD and pneumonia using MR toward causal inference. In addition, based on existing literature, we identified common disruptive coding variants of each pleiotropic gene as genetic proxies for putative inhibition of each gene and conducted single-instrument MR analyses. eQTL data of

13 tissues relevant to CAD and pneumonia, i.e., whole blood, spleen, small intestine terminal ileum, lung, liver, heart left ventricle, heart atrial appendage, artery tibial, artery coronary, artery aorta, adrenal gland, adipose visceral omentum, and adipose subcutaneous, were obtained from the GTEx project (v8; https://gtexportal.org/home/). These analyses were limited to cis-eQTL, which were defined as variants within 1 Mb of the transcription start site of each gene, given data availability (*12*). Summary statistics of CAD were from meta-analysis of CARDIoGRAMplusC4D and UK Biobank (*43*), and those of pneumonia were from meta-analysis of FinnGen R4 and UK Biobank (*41*).

We extended the causal relation evaluations for both identified pleiotropic genes to their interacting genes identified through STRING, a protein-protein interaction database (v11; https://string-db.org/), using same MR approaches. For index pleiotropic gene(s) that is expressed in whole blood, we used eQTL data derived from whole blood in >31,000 individuals from the eQTLGen consortium (http://www.eqtlgen.org) for evaluating their and their interacting genes' causal effects on CAD and pneumonia. As the eQTLGen consortium provided summary statistics of both cis- and trans-eQTL results, we included both cis- and trans-eQTL for primary analysis to maximize power and because recent studies showed that only a modest fraction of trait-heritability can be explained by cis-mediated bulk gene expressions (*44*). We also conducted sensitivity analysis using cis-eQTL results only to address potential pleiotropy. As the eQTLGen consortium only included eQTL data derived from whole blood, for other index pleiotropic gene(s) and their interacting genes not highly expressed in whole blood, we used eQTL data of tibial artery, due to similarity to coronary artery, from the GTEx project. As the GTEx project only included cis-eQTL data, we used cis-eQTLs for primary analysis.

For both sets of causal relation analyses, we selected instruments from each dataset using independent ($r^2 < 0.05$) SNPs that met genome-wide significance ($P < 5 \times 10^{-8}$). For datasets that did not have valid instruments, the corresponding analyses were not conducted. We applied two-sample MR to estimate the causal relationship between eQTLs and cardiovascular disease and pneumonia using the MR-Base R package (version 0.5.5) (*45*). For genes that were instrumented with a single SNP, Wald ratio MR method was used; for those with more than one valid instrument, we conducted MR analyses using IVW-FE as the primary method (*46*), as well as the SMR method that is less prone to false-positive findings, and other alternative MR methods (i.e., MR-Egger, weighted median, weighted mode, or MR-RAPS) that may be more powerful under various model assumptions for sensitivity analyses (*47*–*51*). As the use of SMR requires eQTL data in BESD format and provided GTEx v7 eQTL data in that format, we used GTEx v7 eQTL data when using SMR. A reference panel of European individuals from the phase 3 1000 Genomes project was used to compute LD estimation for all analyses (*52*).

Gene-environment interaction examination in human

With coding variants used in single-instrument MR analysis, we performed a prospective, time-to-event analysis for the incident CAD and pneumonia outcomes in the UK Biobank stratified by the genotype statuses of each instrument. This smoking interaction testing was also conducted for single independent genome-wide significant eQTLs and composite eQTL scores. Cox proportional hazard models were adjusted for age, age^2, sex, race, first 10 genetic principal components (PCs), diagnosis of type 2 diabetes mellitus, and genotyping array. To test for proportional hazards assumption for the genetic instruments, we examined whether their corresponding scaled Schoenfeld residuals were independent of follow-up time and found no statistically significant evidence suggesting violation of the assumption. Race was determined by self-reported ancestry and followed by outlier detection based on genetic PCs centrally calculated by UK Biobank. Since smoking represents a key shared risk factor for both CAD and pneumonia, we evaluated the interaction between smoking status and each instrument on the primary outcomes. Analyses used R version 3.6.2 software (The R Foundation), two-tailed P values, as well as statistical significance level of $P < 0.05$ except for the identification of genome-wide signals, which was $P < 5 \times 10^{-8}$.

SUPPLEMENTARY MATERIALS

Supplementary material for this article is available at https://science.org/doi/10.1126/sciadv.abl4602

View/request a protocol for this paper from *Bio-protocol*.

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Acknowledgments
Funding: H.K.F. was funded by NIH grant DP5 OD024582 and by Eric and Wendy Schmidt. P.L. receives funding support from the National Heart, Lung, and Blood Institute (1R01HL134892), the American Heart Association (18CSA34080399), the RRM Charitable Fund, and the Simard Fund. P.N. is supported by grants from the National Heart, Lung, and Blood Institute (R01HL142711, R01HL148050, R01HL151283, R01HL148565, R01HL135242, and R01HL151152), Fondation Leducq (TNE-18CVD04), and Massachusetts General Hospital (Paul and Phyllis Fireman Endowed Chair in Vascular Medicine). **Author contributions:** Conceptualization: Z.Y., H.K.F., and P.N. Methodology: Z.Y., H.K.F., and P.N. Investigation: Z.Y. and P.N. Visualization: Z.Y. Supervision: P.N. Writing—original draft: Z.Y. Writing—review and editing: Z.Y., S.M.Z., S.H., R.B., B.T.M., P.L., H.K.F., and P.N. **Competing interests:** P.L. is an unpaid consultant to, or involved in clinical trials for, Amgen, AstraZeneca, Baim Institute, Beren Therapeutics, Esperion Therapeutics, Genentech, Kancera, Kowa Pharmaceuticals, Medimmune, Merck, Norvo Nordisk, Novartis, Pfizer, and Sanofi-Regeneron. P.L. is a member of scientific advisory board for Amgen, Caristo, Cartesian, Corvidia Therapeutics, CSL Behring, DalCor Pharmaceuticals, Dewpoint, Kowa Pharmaceuticals, Olatec Therapeutics, Medimmune, Novartis, PlaqueTec, and XBiotech Inc. P.L.'s laboratory has received research funding in the past 2 years from Novartis. P.L. is on the board of directors of XBiotech and has a financial interest in XBiotech, a company developing therapeutic human antibodies. P.L. is listed as an inventor on patent application no. 20200239564, "Use of canakinumab" (filed on 24 August 2018, published on 30 July 2020). P.L.'s interests were reviewed and are managed by Brigham and Women's Hospital and Partners HealthCare in accordance with their conflict-of-interest policies. P.N. reports investigator-initiated grants from Amgen, Apple, Boston Scientific, and AstraZeneca; personal fees from Apple, Blackstone Life Sciences, Foresite Labs, Genentech, and Novartis; and spousal employment at Vertex, all unrelated to the present work. The other authors declare no competing interests. **Data and materials availability:** All the summary-level data used are available for download at the public repositories. UK Biobank individual-level data are available for request by application (www.ukbiobank.ac.uk). Mass General Brigham Biobank individual-level data are available from https://personalizedmedicine.partners.org/Biobank/Default.aspx but need to be used under Institutional Review Board approval. All data needed to evaluate the conclusions in the paper are present in the paper and/or the Supplementary Materials.

Submitted 15 July 2021
Accepted 9 March 2022
Published 22 April 2022
10.1126/sciadv.abl4602