SUPPLEMENTAL MATERIAL

Methods Supplement

UK Biobank

The UK Biobank (UKBB) cohort consists of 502,620 participants, recruited between 2006 and 2010 from across the United Kingdom, and is described elsewhere in detail[33]. Participants were assessed at baseline using questionnaires that included components for ascertaining medical conditions, lifestyle, and demographic information. Additional interviews were conducted by trained medical staff to assess medical history, health status and medication intake. We used available self-reported doctor-diagnosed medical conditions and ICD10 codes derived from the UKBB hospital episode inpatient data set (retrieved 03/21/2019) to define medical conditions of interest. Participants were genotyped on two closely related genotyping arrays: UK BiLEVE: N = 49,939, and UK Biobank Axiom: 438,343. In total, 488,282 participants were genotyped. All genotypes were then imputed using reference sequence data as previously described[41]. The National Health Service National Research Ethics Service (ref. 11/NW/0382) gave approval for the UK Biobank study, with each participant providing written informed consent.

OSA status assessment

We defined cases and controls as follows: Cases of OSA must have had self-reported snoring AND at least one of the following sleep apnea diagnoses:

1) an ICD10 code G47.3 for sleep apnea (N = 6643)

OR

2) a self-report of doctor diagnosed sleep apnea documented during an interview with a trained medical professional (UKBB field 20002, coding 1123: sleep apnoea) (N = 1757).

Controls were non-cases. Individuals who could not be confidently defined as either cases or controls were excluded. To reduce the possibility of including cases of central sleep apnea ascertained using sleep apnea diagnostic codes, we required snoring (a cardinal symptom of OSA), documented by self-report in the UKBB sleep questions interview. Among participants without OSA we excluded those who self-reported both snoring and daytime sleepiness, two common symptoms of OSA. A total of 471,877 participants (4,974 OSA cases) with complete covariate data were available after making these exclusions.

Note that ICD9 records were not analyzed as A) ICD9 codes come from a unique subset of 20k Scottish participants with available hospital inpatient episodes from 1980 to 1996, whereas the ICD10 data was collected almost exclusively after 1996 B) the fact that these ICD9s contain no instances of sleep apnea codes 327.23 or 327.2, nor any sleep codes in the 327 range.

CAD status assessment

Coronary artery disease (CAD) cases were assessed based on a composite definition, including UKBB participants with self-reported heart attack/myocardial infarction, phecode 411.2 or UKBB algorithmic ascertainment for myocardial infarction, including self-report, hospital admission, or death certificate.

Covariate Assessment

Diagnostic information for medical conditions were obtained from the UKBB data sets for self-reported doctor-diagnosed non-cancer illness and hospital episode inpatient diagnostic codes. ICD10 codes were collapsed to medically interpretable groupings using the phecode system[42], using Phecode Map version 1.2 for WHO ICD10's. Hypertension, type 1 (T1D) and type 2 diabetes (T2D), COPD, asthma, and pulmonary fibrosis were ascertained as composite

phenotypes, as described in Supplemental Table I. Additional covariates were self-reported race, genotype platform (BiLEVE vs Axiom) and UK Biobank-provided genetic PCs.

Statistical Analysis

Analysis Steps: We studied the interaction of OSA case status with pathway-specific risk for CAD in several steps. 1) We attempted to annotate each marker identified by Khera *et al* to one or more associated genes (Figure 1). SNV markers that were not annotated were discarded, resulting in a QC-filtered, gene-annotated, genome-wide set of markers. 2) We selected pathways of interest and defined pathway-based SNV-sets implied by the SNV-gene and gene-pathway assignments. 3) We computed pathways-specific genetic risk scores (PS-PRS), as a sum of allele counts weighted by per-allele effect size and direction across the pathway SNV-set. 4) We tested the associations of PS-PRS and OSA status, and their GxE interaction, on the composite CAD outcome, in a logistic generalized additive model, controlling for the mutual interaction of age and BMI by sex (via tensor-product splines) as well as smoking and its interaction with sex[43], self-reported white race, the first 5 genetic PCs, genotype platform (BiLEVE), asthma and chronic obstructive pulmonary disease (COPD). (As two of the most common pulmonary diseases, COPD and asthma were controlled for as both are associated with both OSA and CAD, and can potentially affect gas exchange and exacerbate hypoxia.)

GAM models: The GAM setting was motivated by the need to adjust for two interacting continuous confounders, age and BMI, while conditioning on sex, due to the well-accepted role for age and BMI in OSA and in CAD, and sex-differences in BMI, CAD and OSA. GAMs, as implemented in the *R* package *mgcv*, were set to default options, allowing data-driven allocation degrees of freedom to spline terms[44]. Standard logistic regression models are unable to account for these continuous interactions without making restrictive assumptions on the parametric form

of these continuous interactions. By contrast the GxE interaction terms of interest were specified within the parametric portion of the model, so that standard test procedures, interval estimation, and interpretation all proceed as in the analogous generalized linear model.

Primary and secondary analyses: The ten pathways of interest described were allocated Type-1 error in the primary analysis, with Bonferroni-corrected significance level of 5E-3. In a secondary analysis, to further explore whether module and gene-level PRS showed consistent associations with CAD, as well as to suggestively localize effects estimated in the primary analysis, we looked at pathway sub-modules and individual genes. For each core-gene module we modeled GxE interaction for the gene-specific risk scores (GSRS) of the constituent genes, and for each KEGG pathway, we modeled sub-module PS-PGRSs and GSRSs and reported those with both nominally significant risk-amplifying main effects and nominally significant GxE interactions. We tested the 30 pathway sub-modules and the 268 individual genes nested within the KEGG pathways of interest, using the Bonferroni significance level adjusted for the respectively higher multiple testing burdens incurred by each of these alternative approaches to GxE interaction. This secondary analysis was performed to serve as a comparator to our primary pathway-level analysis, by examining gene-level GS-PRS and module-level PS-PRS associations with CAD, reporting any significant interaction effects at the more stringent significance levels, as well as to suggestively localize independent signals contributing to significant interaction results in the primary analysis.

Sensitivity analyses: We further performed the following sensitivity analyses: including comorbidity covariates potentially mediating the OSA-CAD relationship (hypertension, Type 1 and Type 2 diabetes, along with their sex-interactions[43], and pulmonary fibrosis); excluding

individuals with heart failure or stroke; sex-stratified analysis; and an analysis limited to self-reported white Europeans (the predominant ancestry in the CAD GWAS).

PS-PRS associations with C reactive protein: We additionally performed an association analysis between each PS-PRS in the primary analysis and the CAD biomarker log-transformed C reactive protein (CRP), in all available UKBB subjects (N = 459,290). This analysis was performed using linear regression and adjusted for the interaction of BMI by sex, and separately age by sex, along with the remaining covariates used in the primary analysis.

Polygenic Risk Score Construction

We based our analysis of genetic CAD risk on a published PRS described by Khera *et al*[34], with single nucleotide variant (SNV) effects estimated for each of 6,630,150 SNVs, using the linkage disequilibrium (LD) aware PRS algorithm LDPred[35] and summary statistics from the CARDIoGRAMplusC4D Consortium CAD GWAS of 60,801 cases and 123,504 controls of mainly European ancestry[36].

Pathway specific polygenic risk scores (PS-PRSs) were calculated for each individual as the effect-weighted sum of the count of risk alleles at each locus across all pathway SNVs:

$$PS-PRS_k = \sum_{i:a_i \in pathway\ k} w_i a_i$$

where w_i is the LD-adjusted additive genetic effect and a_i is the count (or imputed dosage) of the risk alleles at locus i of pathway k. PS-PRSs for select biological pathways were derived based on subsets of SNVs assigned to various pathways. Pathways are defined as sets of genes (see Supplemental Table II), and SNVs are assigned to genes via annotations derived from external functional genomics reference data sets, including state-of-the-art transcriptomics technologies (such as cap analysis of gene expression (CAGE), promoter-capture HiC (PC-HiC),

and tissue-specific expression quantitative trait (eQTL) analysis) capable of characterizing the regulatory region, in addition to genomic position (see below). We also calculated gene-specific risk scores, GSRS_j, i.e. PS-PRSs for a single gene, where the above sum is taken over loci $i: a_i \in gene\ j$ for a single gene of interest.

We tested the associations of PS-PRS and OSA status, and their GxE interaction, on the composite CAD outcome, in a logistic generalized additive model, controlling for the mutual interaction of age and BMI by sex (via tensor-product thin plate cubic penalty regression splines) as well as smoking and its interaction with sex[43], self-reported white race, the first 5 genetic PCs, genotype platform (BiLEVE), asthma and chronic obstructive pulmonary disease (COPD). (As two of the most common pulmonary diseases, COPD and asthma were controlled for as both are associated with both OSA and CAD, and can potentially affect gas exchange and exacerbate hypoxia.)

***Selecting genomic variants and annotating genes*:** We obtained 6.6 million common SNVs (minor allele frequency > 0.01) available in UK Biobank imputed data which passed quality control filters in a prior GWAS and subsequent PRS analysis of CAD conducted by Khera et al. These SNVs were then given genetic annotations using a sequential multi-stage methodology as described below in the text and shown in Figure 1.

Concretely, we annotated SNVs in sequential rounds, prioritizing annotations with high specificity. SNVs assigned in prior rounds were set aside and were not annotated with less-specific data (Figure 1). We ordered the annotation resources as follows: GenCode v34 exons[45], cap analysis of gene expression in FANTOM5[46], Promoter-Capture HiC experiments involving white blood cells as described Javierre *et al*[47], GTEx v7 statistically significant eQTLs[48] derived from artery (aorta, coronary and tibial), heart (atrial appendage and left ventricle) and whole

blood tissues, GeneHancer v4.4[49] predicted gene annotations passing minimum enhancer score threshold of 0.3 and minimum gene score threshold of 4.0, and finally GenCode protein-coding regions (including all loci from 20kbp upstream of transcription start site to 10kbp downstream of transcription stop site), and noncoding transcript sequence regions. Within a single data set a SNV may be assigned to multiple genes, in which case both annotations are accepted. Gene-annotated CAD PRS data will be available for download from **Open Science Framework (https://osf.io/)**.

Calculating genetic risk scores: After defining pathways and associated SNVs, we calculated a PS-PRS for each participant using a SNV-set representing each of the pathways of interest. For each PS-PRS, we took the subset of SNVs annotated to genes in that pathway and calculated a PS-PRS using the corresponding genetic effects from the Khera et al PRS. We standardized polygenic risk scores including individual PS-PRSs to mean zero and variance one in the total UKBB study population. To facilitate our secondary analysis, we additionally calculated GSRS for each gene in the HIF-1, VEGF, NFκB, and TNF KEGG pathways.

Defining pathways of interest: Based on our *a priori* hypotheses on the role hypoxemia plays in CAD, inducing angiogenesis and inflammation, we selected four pathways from the literature, for which the nominal genes, namely *HIF1A*, *VEGFA*, *NFKB1/NFKB2* and *TNF*, have been shown to be differentially expressed in OSA[25-32]. For each, we created gene-pathways using two approaches. First, we selected the core-gene pathways, defined as the nominal gene(s) and their receptors (for HIF1, core genes selected were: *HIF1A* and *ARNT*, for VEGF: *VEGFA*, *FLT*, and *KDR*, for NFκB: *NFKBIA*, *NFKB1*, *RELA*, *NFKB2*, *RELB*, and for TNF: *TNF*, *TNFRSF1A*, and *TNFRSF1B*). Second, we selected more comprehensive gene pathways based the Kyoto Encyclopedia of Genes and Genomes (KEGG) database: HIF-1 signaling (KEGG pathway code:

hsa04066), VEGF signaling (hsa04370), NFκB signaling (hsa04064), and TNF signaling (hsa04668). We also included, as comparators, the full PRS on 6.6M SNVs, as well as a curated CAD/OSA pathway consisting of 225 genes involved in both OSA and CAD based on literature review. Because KEGG pathway boundaries are somewhat arbitrary and include varying levels of completeness in upstream and downstream gene modules, we also organized each KEGG pathway into sub-modules. For example, the KEGG VEGF pathway was organized into several partially overlapping downstream submodules according to the KEGG pathway diagram, including: endothelial proliferation (15 genes), endothelial migration (9 genes) and endothelial survival (12 genes). For complete pathway and module definitions see Supplemental Table II.

Modeling and testing associations: For each PRS we created a single CAD outcome model and tested: A) the association of the PS-PRS with CAD, and B) the interaction of the PS-PRS with OSA status, controlling for demographics and comorbidities. We modeled the binary CAD outcome via generalized additive models (GAM) with logistic link, controlling for the covariates discussed above[43].

Statistical significance was assessed at level $\alpha = 0.05$. For our primary analysis testing interaction of PS-PRS and OSA status, we adopted the Bonferroni-adjusted significance threshold $\alpha = 0.005$ on ten interaction tests. In secondary analysis of GSRS, we only report those genes that had risk-amplifying genetic main effects on CAD (in OSA controls) and passed an $\alpha = 0.05$ genetic main effect significance threshold.

Software: Statistical calculations were conducted using *R* version 3.5.2, and code used to perform these analyses will be posted to a publicly accessible repository (https://github.com/MatthewOGoodman/UKB_PS-PRSxOSA_GxE_study_of_CAD). The functional genetic reference data sets are publicly available in the following web repositories:

- KEGG: https://www.kegg.jp
- ENSEMBL: https://www.ensembl.org
- GenCode v34: https://www.gencodegenes.org/human/release_34.html
- FANTOM5: https://fantom.gsc.riken.jp/5/
- Promoter-Capture HiC, Javierre et al: https://osf.io/u8tzp/
- GTEx v7: https://gtexportal.org/home/datasets#datasetDiv6
- GeneHancer v4.4: https://www.genecards.org/Guide/GeneCard#enhancers

R v3.5.2 software packages used to manipulate functional genetic data and annotate genes include *tidyverse* v1.2.1 and *bioconductor* v3.8. A guide to use of these packages and data repositories, with example scripts for annotation of SNV's to genes can be found at https://f1000research.com/articles/7-121#[50]. The *R* package *mgcv* v1.8-27 was used to fit the GAM models[44].

Results Supplement

Clinical characteristics:

As expected, OSA cases tended to have a higher prevalence of several CAD risk factors and comorbidities. Individuals classified with OSA were predominantly male, had a higher mean BMI, and included more ever-smokers. Pulmonary diseases, including COPD and asthma also tended to have a higher prevalence among OSA cases (Table 1). There was a higher percentage of OSA cases genotyped on the BiLEVE platform, as opposed to the UKBB Axiom platform, consistent with the fact that the BiLEVE pilot study was enriched for pulmonary disease.

Discussion Supplement

Primary and secondary results:

The KEGG VEGF risk-inverting GxE effects appear to be largely driven by the VEGF endothelial migration submodule. However, there appear to be two additional congruent independent signals contributing the overall KEGG VEGF pathway effect: the VEGF core-genes risk-inverting effects, and a separate independent signal distributed among the VEGF endothelial permeability, endothelial survival and PI3K/AKT submodules, which are correlated to one another due to shared genes. This suggests the utility of pathway level analyses in circumstances where consistent effects are combined across many statistically independent genes or loci, which do not reach significance thresholds on their own, but contribute signal to detection of GxE at the pathway level.

Note that the KEGG HIF-1 pathway contains sub-modules with contrasting GxE effects including the KEGG HIF1 angiogenesis (risk-inverting) and the HIF1 core-genes (risk-amplifying) modules. As observed in Supplementary Figure S3, the risk scores for these gene modules are both positively correlated with the KEGG HIF1 PS-PRS as a whole, being component terms in the sum. This observation suggests that the KEGG HIF1 signaling pathway may contain opposing signals which together attenuate overall HIF1 pathway effect modification. This situation illustrates the limitations of targeting large heterogeneous pathways in studying GxE effect modification and underscores the utility of also examining pathways limited to genes or sub-modules that better ensure specificity. Nonetheless, since pathway boundaries can be vague and subjective, further research is needed to investigate data-driven methods for aggregating co-regulated genes to modules and pathways that may respond similarly to stimuli such as IH.

A natural question is whether the strong biological relationships among the chosen pathways challenge our interpretation. Clearly the selected pathways implicated in both IH and CAD are co-regulated: notably VEGF is explicitly regulated by HIF1, but cross-talk and co-regulation among all four pathways including NFκB and TNF likely exists, and gene expression levels may be correlated as a result. Nevertheless, our analysis does not directly analyze gene expression but rather genetic variation and its perturbation of this signaling network due to risk alleles specific to each pathway that are largely statistically independent across pathways. Note that as pathways largely come from disjoint regions of the genome and, due to genetic recombination, allele counts from distal variants with low LD (e.g. in separate non-adjacent genes) will be nearly uncorrelated statistically. Hence the low observed correlation between participants' genetic risk scores in the majority of pathway pairs is expected due to statistical independence of the non-overlapping variants, and conversely, observed correlations are driven by the PS-PRS components attributable to the shared genes.

Strengths and limitations:

The number of ascertained OSA cases is low compared to expected population prevalence estimates, however it comports with expectation of prevalence of clinical diagnosis. Nonetheless, we expect our ascertainment of OSA to be specific (likely identifying more severe and hypoxic individuals) if not sensitive, and we took additional steps to reduce misclassification of cases and controls using cardinal symptoms of OSA. Also, the use of a binary classification for OSA also did not allow us to characterize OSA according to severity of hypoxemia or sleep fragmentation, which precluded our ability to test dose-response associations or associations with specific OSA stressors.

Additionally, previously studied sex differences indicate that cardiovascular risk may operate differently in women in general and in women with OSA in particular (Won et al., 2020). We included interaction terms for relevant covariates to attempt to account for these differences in background CVD risk. Due to low numbers of joint CAD and OSA cases in women (N=71) power for sex-stratified analysis in women was low and our results are likely driven by the men in our sample. Nevertheless, the VEGF KEGG pathway interaction was qualitatively similar and nominally significant in women. The limitations of the sample studied here and the differential manifestations of OSA in women warrant further research to identify GxE interaction effects specific to females with OSA. For example, women with OSA tend to have shorter events, more hypopnea and less apnea, as well as lower arousal threshold than men. Additionally, post-menopausal adiposity changes may lead to OSA in women, meaning that average age of OSA onset may be later, and consequently the period of chronic exposure to OSA-induced intermittent hypoxia may be shorter on average for a given age group in women.

Summary:

Prior work has investigated phenotypic factors, biomarkers, and genetic variation to understand better and dissect the heterogenous effects of OSA on CAD, including multiple variables, such as age, gender and comorbid diagnoses that may moderate associations of OSA and CVD, as well as blood-based biomarkers of CVD[16,17]. Nonetheless, prior research using genetic variation to explore the divergent individual responses to hypoxic conditions has been limited, despite suggestions advocating this approach to risk stratification of patients with OSA[19]. Our use of PS-PRS, applied to core gene modules and pathways, provides a novel means for interrogating pathway-level effect-measure modification in large-scale data to uncover biological heterogeneity.

The existence of large-scale genetic data such as the UK Biobank opens up new avenues in understanding genotype-phenotype relationships in the context of different environments, host factors and comorbid diseases. Genome-wide data on genetic risk variants and novel genomic risk scores enabled by new LD-aware PRS algorithms such as LDPred present opportunities to develop robust pathway-level characterization of genetic risk. Building on these novel PS-PRSs we deploy an interaction analysis that allows us to probe relationships between OSA, CAD genetics and CAD outcomes that localize to particular molecular pathways. In turn we can gain a deeper understanding of genetic disease architecture, including modification of pre-existing genetic risk by exposures such as OSA.

Supplemental Tables

Supplemental Table I: Phenotype definitions and data sources

Phenotype	UKBB field: Code	Description
CAD:	UKBB 20002: 1075	Self-reported heart attack / MI
	UKBB 41202, 41204 derived phecode: 411.2	Myocardial infarction
	UKBB 42001	Myocardial infarction: algorithmically-defined
Sleep Apnea:	UKBB 41202, 41204 ICD10: G47.3	
	UKBB 20002: 1123	sleep apnoea: self-report of doctor diagnosed sleep apnea documented during an interview with a trained medical professional
Inclusion/Exclusion:		
Snoring	UKBB 1210	Self-reported snoring
Daytime sleepiness	UKBB 1220	Self-reported daytime sleepiness
Covariates:		
Sex	UKBB 22001	Genetic sex
BMI	UKBB 21001	Body Mass Index
Age	UKBB 21022	Age at recruitment
Smoking status	UKBB 1239	Current Tobacco Smoking
	UKBB 1249	Past Tobacco Smoking
	UKBB 20002: 1112	COPD: self-report

COPD (chronic obstructive pulmonary disease)	UKBB 41202, 41204 derived phecodes: 496, 496.1, 496.2, or 496.21	Chronic airway obstruction, Emphysema, Chronic bronchitis, Obstructive chronic bronchitis, Bronchiectasis
Asthma	UKBB 20002: 1111	Asthma
	UKBB 41202, 41204 derived phecodes: 495, 495.1, 495.11, or 495.2	Asthma, chronic obstructive asthma, asthma with exacerbation, chronic obstructive asthma with exacerbation
UKBB BiLEVE genotype platform	UKBB 22000	Binary covariate: whether the participant was genotyped on the pilot study BiLEVE genotype platform, or the UKBB Axiom platform.
Potentially Mediating Covariates:		
Hypertension	UKBB 20002: 1065 Derived phecode: 401	Hypertension
Likely Type 1 Diabetes	Algorithm of Eastwood et al.	Type 1 Diabetes
Likely Type 2 Diabetes	Algorithm of Eastwood et al.	Type 2 Diabetes
Pulmonary fibrosis	UKBB 20002: 1121	Pulmonary fibrosis
	UKBB 41202, 41204 derived phecodes: 502, 504, or 504.1	Postinflammatory pulmonary fibrosis, Other alveolar and parietoalveolar pneumonopathy, Idiopathic fibrosing alveolitis

Daytime sleepiness was recoded as “present” (moderate or severe) or “absent” (none or mild). Smoking status was recoded as “never smoked,” “past smoker,” “current smoker (occasionally),”and “current smoker (most days).” Diagnostic information for medical diagnoses was obtained from the following UKBB data fields: Non-cancer illness, self-reported (20002),

Hospital Episode Inpatient data: Diagnoses - main ICD10 (41202), Diagnoses - secondary ICD10 (41204), ICD10 codes were collapsed to medically interpretable groupings using the phecode system using Phecode Map version 1.2 for the World Health Organization ICD10 codings.

Supplemental Table II: Pathway and module definitions

Pathway Gene Membership

a. KEGG signaling pathways

i. HIF1 https://www.genome.jp/kegg-bin/show_pathway?hsa04066

ii. VEGF https://www.genome.jp/kegg-bin/show_pathway?hsa04370

iii. TNF https://www.genome.jp/kegg-bin/show_pathway?hsa04668

iv. NFκB https://www.genome.jp/kegg-bin/show_pathway?hsa04064

b. Core Gene modules:

i. HIF1 pathway core-gene module: *HIF1A, ARNT*

ii. VEGF pathway core-gene module: *VEGFA, FLT, KDR*

iii. TNF pathway core-gene module: *TNF, TNFRSF1A, TNFRSF1B*

iv. NFκB pathway core-gene module: *NFKBIA, NFKB1, RELA, NFKB2, RELB*

c. Curated OSA/CAD pathway:

(225 genes related to OSA and CAD, selected by literature review):

ACE, ACP1, ACP2, ACP5, AGT, AGTR1, AKT1, AKT1S1, AKT2, AKT3, ALOX12, ALOX12B, ALOX15, ALOX15B, ALOX5, APOE, ARG1, ARG2, ATF1, ATF2, ATF3, ATF4, ATF5, ATF6, ATF6B, ATF7, BCS1L, CALM1, CAT, CAV1, CDH5, CUL3, CXCL8, CXCR2, CYC1, DEPTOR, ENPP1, ENPP3, EPO, FGA, FGB, FGG, FLAD1, FOS, FOSB, FOXO1, GCH1, GCLC, GCLM, GLRX, GPX1, GPX3, GPX4, GSR, GSS, GSTA1, GSTA2, GSTA3, GSTA4, GSTA5, GSTK1, GSTM1, GSTM2, GSTM3, GSTM4, GSTM5, GSTO1, GSTO2, GSTP1, GSTT2, GSTZ1, HES1, HES5, HEY1,

HEY2, HIF1A, HMOX1, HSP90AA1, HSP90AB1, ICAM1, IL1B, IL1R1, IL1RN, IL6, IL6R, IL6ST, ITGA1, ITGA10, ITGA11, ITGA2, ITGA2B, ITGA3, ITGA4, ITGA5, ITGA6, ITGA7, ITGA8, ITGA9, ITGAD, ITGAE, ITGAL, ITGAM, ITGAV, ITGAX, ITGB1, ITGB2, ITGB3, ITGB4, ITGB5, ITGB6, ITGB7, ITGB8, JUN, JUNB, JUND, KDR, KEAP1, LYRM7, MAFF, MAFG, MAFK, MAPK1, MAPK10, MAPK11, MAPK12, MAPK13, MAPK14, MAPK15, MAPK3, MAPK4, MAPK6, MAPK7, MAPK8, MAPK9, MAPKAP1, MEF2A, MEF2C, MEF2D, MGST1, MGST3, MLST8, MPO, MTOR, NDUFA1, NDUFA10, NDUFA11, NDUFA12, NDUFA2, NDUFS1, NDUFS2, NDUFS3, NDUFS4, NDUFS6, NDUFS7, NDUFV1, NDUFV2, NFE2L2, NFKB1, NFKB2, NKRF, NOS2, NOS3, NOX1, NOX3, NOX4, NOX5, NQO1, PIK3C2B, PIK3C2G, PIK3CA, PIK3CB, PIK3CD, PIK3CG, PIK3R2, PIK3R3, PIK3R4, PIK3R5, PIK3R6, PRKAA1, PRKAA2, PRKAB1, PRKAB2, PRKAG1, PRKAG2, PRKAG3, PRKCA, PRKCB, PRR5, PTS, RFK, RHOA, RICTOR, ROCK1, ROCK2, RPTOR, SELE, SELL, SELP, SELPLG, SOD1, SOD2, SOD3, SPR, SREBF1, SREBF2, TELO2, TNF, TTC19, TTI1, TXN, TXN2, TXNRD1, TXNRD2, TXNRD3, UQCC2, UQCC3, UQCRB, UQCRC2, UQCRQ, VCAM1, VEGFA, XDH

d. Submodules

1. KEGG HIF1 GF RTK HIF1a translation: *EGF, EGFR, ERBB2, IGF1, IGF1R, INS, INSR.*
2. KEGG HIF1 MTOR HIF1a translation: *EIF4E, EIF4E1B, EIF4E2, EIF4EBP1, MTOR, RPS6, RPS6KB1, RPS6KB2.*

3. KEGG HIF1 IH HIF1a degradation: *CYBB, EGLN1, EGLN2, EGLN3, PLCG1, PLCG2, PRKCA.*
4. KEGG HIF1 HIF1a degradation ubiquitin: *CUL2, ELOB, ELOC, RBX1, VHL.*
5. KEGG HIF1 IH HIF1b activation: *ARNT, CAMK2A, CAMK2B, CAMK2D, CAMK2G, CREBBP, CYBB, EP300, PLCG1, PLCG2.*
6. KEGG HIF1 RBC: *EPO, TF, TFRC.*
7. KEGG HIF1 angiogenesis: *ANGPT1, ANGPT2, ANGPT4, EGF, FLT1, SERPINE1, TEK, TIMP1, VEGFA.*
8. KEGG HIF1 vascular tone: *EDN1, HMOX1, NOS2, NOS3, NPPA.*
9. KEGG HIF1 glucose inhibit citrate: *PDHA1, PDHA2, PDHB, PDK1, SLC2A1.*
10. KEGG HIF1 glucose promote anaerobic metabolism: *ALDOA, ENO1, ENO2, ENO3, ENO4, GAPDH, HK2, HK3, HKDC1, LDHA, PFKFB3, PFKL, PGK1.*
11. KEGG HIF1 glucose regulate proliferation: *BCL2, CDKN1A, CDKN1B.*
12. KEGG VEGF proliferation: *HRAS, KRAS, MAP2K1, MAP2K2, MAPK1, MAPK3, NRAS, PLCG1, PLCG2, PRKCA, PRKCB, PRKCG, RAF1, SPHK1, SPHK2.*
13. KEGG VEGF PGI2 production: *NFATC2, PPP3CA, PPP3CB, PPP3CC, PPP3R1, PPP3R2, PTGS2.*
14. KEGG VEGF migration: *CDC42, MAPK11, MAPK12, MAPK13, MAPK14, MAPKAPK2, MAPKAPK3, PTK2, PXN.*
15. KEGG VEGF endothelial permeability: *AKT1, AKT2, AKT3, NOS3, PIK3CA, PIK3CB, PIK3CD, PIK3R1, PIK3R2, PIK3R3, RAC1, RAC2, RAC3, SRC.*

16. KEGG VEGF endothelial survival: *AKT1, AKT2, AKT3, BAD, CASP9, PIK3CA, PIK3CB, PIK3CD, PIK3R1, PIK3R2, PIK3R3, SRC.*

17. KEGG HIF1 VEGF shared MAPK genes: *MAP2K1, MAP2K2, MAPK1, MAPK3, MKNK1, MKNK2.*

18. KEGG HIF1&VEGF shared PI3K.AKT genes: AKT1, *AKT2, AKT3, PIK3CA, PIK3CB, PIK3CD, PIK3R1, PIK3R2, PIK3R3.*

19. KEGG HIF1 NFkB-related genes: *IFNG, IFNGR1, IFNGR2, IL6, IL6R, STAT3, TLR4.*

20. KEGG NFkB atypical pathway: *BCL2A1, BCL2L1, CSNK2A1, CSNK2A2, CSNK2A3, CSNK2B, EGF, EGFR, ERBB2, NFKB1, NFKBIA, PLAU, RELA.*

21. KEGG NFkB atypical upstream*: BAG4, IL1B, IL1R1, IRAK1, IRAK4, MYD88, RIPK1, TNF, TNFRSF11A, TNFRSF1A, TNFSF11, TRADD, TRAF2, TRAF5, TRAF6.*

22. KEGG TNF pathway JNK: *FOS, JUN, MAP2K4, MAP2K7, MAP3K7, MAPK10, MAPK8, MAPK9, TAB1, TAB2.*

23. KEGG TNF pathway p38: *ATF2, ATF4, ATF6B, CREB1, CREB3, CREB3L1, CREB3L2, CREB3L3, CREB3L4, CREB5, MAP2K3, MAP2K6, MAP3K7, MAPK14, RPS6KA4, RPS6KA5, TAB1, TAB2.*

24. KEGG NFKB TNF pathway: *BIRC2, BIRC3, CHUK, IKBKB, IKBKG, MAP3K14, MAP3K7, NFKB1, NFKBIA, RELA, RIPK1, TAB1, TAB2, TAB3, TNF, TNFRSF1A, TRADD, TRAF2, TRAF5.*

25. KEGG NFKB pathway survival: *BCL2, BCL2A1, BCL2L1, CFLAR, GADD45B, TRAF1, XIAP.*

26. KEGG NFKB pathway inflammation: *CCL4, CCL4L1, CCL4L2, CXCL1, CXCL2, CXCL3, CXCL8, PTGS2, TNFAIP3, VCAM1.*

27. KEGG TNF pathway apoptosis: *CASP10, CASP3, CASP7, CASP8, CFLAR, FADD, ITCH.*

28. KEGG TNF pathway necroptosis: *DNM1L, MLKL, PGAM5, RIPK1, RIPK3.*

29. KEGG TNF immune signaling: *BCL3, CCL2, CCL20, CCL5, CSF1, CSF2, CX3CL1, CXCL1, CXCL10, CXCL2, CXCL3, CXCL5, FAS, IL15, IL18R1, IL1B, IL6, JAG1, LIF, LTA, RAF1, SOCS3, TNFAIP3.*

30. KEGG TNF intracellular signaling: *EDN1, FOS, ICAM1, JUN, JUNB, MMP14, MMP3, MMP9, NOD2, PTGS2, SELE, VCAM1, VEGFC.*

Supplemental Table III: Supplementary analysis. OSA and PS-PRS (main) effects from models with no GxE interaction terms, but with same covariates as the primary analysis

PS-PRS	OSA effect		PS-PRS effect in combined sample (OSA cases and OSA controls)		
	OR	CI	OR	CI	p-value
OSA effect in a model with without PS-PRS or GxE					
N/A	1.51	(1.38, 1.64)	N/A	N/A	N/A
A) Selected pathways: core-gene modules					
HIF1 core genes	1.51	(1.38, 1.64)	1.024	(1.011, 1.037)	2.96E-04
VEGF core genes	1.51	(1.38, 1.64)	1.030	(1.017, 1.043)	4.95E-06
NFκB core genes	1.51	(1.38, 1.64)	1.030	(1.017, 1.044)	8.00E-06
TNF core genes	1.51	(1.38, 1.64)	1.019	(1.006, 1.032)	4.26E-03
B) Selected pathways: KEGG signaling pathways					
HIF1 KEGG	1.51	(1.38, 1.65)	1.063	(1.049, 1.076)	1.13E-20
VEGF KEGG	1.51	(1.38, 1.64)	1.037	(1.023, 1.050)	5.65E-08
NFκB KEGG	1.51	(1.38, 1.64)	1.057	(1.043, 1.070)	8.24E-17
TNF KEGG	1.51	(1.38, 1.64)	1.050	(1.037, 1.064)	4.03E-14
C) Selected aggregated pathway comparators					
CAD PRS	1.51	(1.39, 1.65)	1.695	(1.672, 1.718)	<1.0E-99
OSA genes	1.51	(1.38, 1.65)	1.104	(1.090, 1.119)	6.21E-50

In Supplemental Table III, each row in A), B), and C) depicts a separate PS-PRS model showing the OSA and PS-PRS main effects in a model of the form logit(CAD) = OSA + PS-PRS + covariates, whereas the first row is a model of the form logit(CAD) = OSA + covariates. Three groupings representing different types of pathways are included: A) core-gene modules B) KEGG-defined signaling pathways, and C) aggregate pathways. These ten pathways are allocated Type-1 error in the primary analysis. Nominally significant (*) GxE results do not pass Bonferroni-corrected significance (†) level 5E-3. Covariates adjusted in a logistic generalized additive model: mutual interaction of age and BMI by sex (via tensor-product thin plate cubic

penalty regression splines) as well as smoking and its interaction with sex, self-reported white race, the first 5 genetic PCs, genotype platform (BiLEVE), asthma and chronic obstructive pulmonary disease. OR: odds ratio; CI: confidence interval; OSA: Obstructive sleep apnea, CAD: coronary artery disease, KEGG: Kyoto encyclopedia of genes and genomes, HIF1: hypoxia inducible factor 1, VEGF: vascular endothelial growth factor, NFκB: nuclear factor kappa- beta, TNF: tumor necrosis factor, PRS: polygenic risk score, PS-PRS: pathway-specific polygenic risk score.

Supplemental Table IV: Secondary Analysis: Genes and Submodules of selected CAD pathways: Covariate-adjusted odds of CAD per s.d. of standardized PS-PRSs, with effect modification by OSA status

A) Core-gene modules with all constituent genes										
	OSA		PS-PRS in OSA Controls			PS-PRS in OSA Cases			OSA x PS-PRS Interaction	
	OR	CI	OR	CI	p-value	OR	CI	p-value	OR	p-value
HIF1 core genes	***1.50***	***(1.38, 1.64)***	***1.022***	***(1.009, 1.035)***	***1.06E-03***	***1.114***	***(1.025, 1.212)***	***1.10E-02***	***1.090***	***4.46E-02****
HIF1A	1.51	(1.38, 1.64)	1.005	(0.992, 1.018)	4.59E-01	0.978	(0.899, 1.063)	5.95E-01	0.973	5.21E-01
ARNT	1.50	(1.38, 1.64)	1.022	(1.009, 1.035)	1.10E-03	1.115	(1.025, 1.212)	1.08E-02	1.091	4.36E-02*
VEGF core genes	***1.51***	***(1.38, 1.64)***	***1.032***	***(1.019, 1.045)***	***1.66E-06***	***0.952***	***(0.874, 1.037)***	***2.58E-01***	***0.922***	***6.70E-02***
VEGFA	1.51	(1.38, 1.64)	1.018	(1.005, 1.031)	7.36E-03	0.941	(0.866, 1.022)	1.50E-01	0.924	6.52E-02
FLT1	1.51	(1.38, 1.64)	1.030	(1.017, 1.043)	7.73E-06	0.961	(0.882, 1.046)	3.56E-01	0.933	1.14E-01
KDR	1.51	(1.38, 1.64)	1.002	(0.989, 1.015)	7.56E-01	0.972	(0.894, 1.057)	5.09E-01	0.970	4.83E-01
NFκB core genes	***1.51***	***(1.38, 1.64)***	***1.031***	***(1.018, 1.045)***	***4.45E-06***	***0.981***	***(0.903, 1.066)***	***6.54E-01***	***0.952***	***2.45E-01***
NFKBIA	1.51	(1.38, 1.64)	1.005	(0.992, 1.018)	4.69E-01	1.010	(0.927, 1.100)	8.28E-01	1.005	9.16E-01
NFKB1	1.51	(1.38, 1.64)	1.006	(0.993, 1.019)	4.05E-01	0.938	(0.862, 1.019)	1.30E-01	0.932	1.05E-01
RELA	1.51	(1.38, 1.64)	1.025	(1.012, 1.039)	2.20E-04	1.003	(0.923, 1.089)	9.51E-01	0.978	6.04E-01
NFKB2	1.51	(1.38, 1.64)	1.018	(1.004, 1.031)	9.02E-03	1.076	(0.990, 1.170)	8.51E-02	1.058	1.95E-01
RELB	1.50	(1.38, 1.64)	1.015	(1.001, 1.028)	2.89E-02	0.914	(0.842, 0.992)	3.16E-02	0.901	1.37E-02*
TNF core genes	***1.51***	***(1.38, 1.64)***	***1.019***	***(1.006, 1.033)***	***4.44E-03***	***1.013***	***(0.931, 1.102)***	***7.59E-01***	***0.994***	***8.94E-01***
TNF	1.51	(1.38, 1.64)	1.013	(1.000, 1.027)	4.59E-02	1.022	(0.941, 1.110)	6.07E-01	1.009	8.43E-01
TNFRSF1A	1.51	(1.38, 1.64)	1.014	(1.000, 1.027)	4.32E-02	1.008	(0.927, 1.097)	8.46E-01	0.995	9.05E-01
TNFRSF1B	1.51	(1.38, 1.64)	1.014	(1.001, 1.027)	3.53E-02	1.010	(0.928, 1.098)	8.24E-01	0.996	9.18E-01

B) KEGG pathway sub-modules with suggestive GxE										
	OSA		PS-PRS in OSA Controls			PS-PRS in OSA Cases			OSA x PS-PRS Interaction	
	OR	CI	OR	CI	p-value	OR	CI	p-value	OR	p-value
HIF1 module: IH-induced HIF1-α degradation	1.51	(1.38, 1.64)	1.032	(1.019, 1.045)	1.82E-06	0.928	(0.853, 1.009)	8.05E-02	0.899	1.42E-02*
HIF1 module: angiogenesis	1.51	(1.38, 1.64)	1.032	(1.019, 1.046)	1.21E-06	0.947	(0.869, 1.032)	2.18E-01	0.918	5.25E-02
VEGF module: endothelial migration	1.51	(1.39, 1.65)	1.014	(1.001, 1.027)	3.66E-02	0.881	(0.810, 0.958)	3.05E-03	0.869	1.16E-03†
VEGF module: endothelial permeability	1.51	(1.38, 1.64)	1.020	(1.007, 1.034)	3.20E-03	0.913	(0.838, 0.994)	3.63E-02	0.895	1.17E-02*
VEGF module: endothelial survival	1.51	(1.38, 1.64)	1.013	(1.000, 1.027)	4.47E-02	0.911	(0.837, 0.990)	2.88E-02	0.899	1.35E-02*
HIF1&VEGF: shared PI3K/AKT module	1.51	(1.38, 1.64)	1.019	(1.006, 1.033)	4.79E-03	0.912	(0.837, 0.992)	3.23E-02	0.894	1.08E-02*

C) Top five genes from KEGG HIF1, VEGF, NFκB or TNF pathways suggestive of risk-inverting GxE										
	OSA		PS-PRS in OSA Controls			PS-PRS in OSA Cases			OSA x PS-PRS Interaction	
	OR	CI	OR	CI	p-value	OR	CI	p-value	OR	p-value
RELB	1.50	(1.38, 1.64)	1.015	(1.001, 1.028)	2.89E-02	0.914	(0.842, 0.992)	3.16E-02	0.901	1.37E-02*
PIK3R3	1.50	(1.38, 1.64)	1.02	(1.007, 1.033)	2.51E-03	0.928	(0.843, 1.021)	1.27E-01	0.910	5.63E-02
IRF1	1.51	(1.38, 1.64)	1.026	(1.013, 1.040)	9.50E-05	0.944	(0.869, 1.025)	1.71E-01	0.919	4.99E-02
VEGFA	1.51	(1.38, 1.64)	1.018	(1.005, 1.031)	7.36E-03	0.941	(0.866, 1.022)	1.50E-01	0.924	6.52E-02
PLCG1	1.51	(1.38, 1.64)	1.023	(1.010, 1.037)	4.25E-04	0.954	(0.877, 1.038)	2.71E-01	0.932	1.06E-01
D) Top five genes from KEGG HIF1, VEGF, NFκB or TNF pathways suggestive of risk-amplifying GxE										
	OSA		PS-PRS in OSA Controls			PS-PRS in OSA Cases			OSA x PS-PRS Interaction	
	OR	CI	OR	CI	p-value	OR	CI	p-value	OR	p-value
ARNT	1.50	(1.38, 1.64)	1.022	(1.009, 1.035)	1.10E-03	1.115	(1.025, 1.212)	1.08E-02	1.091	4.36E-02*
MAPK1	1.50	(1.38, 1.64)	1.015	(1.002, 1.028)	2.70E-02	1.095	(1.007, 1.191)	3.44E-02	1.079	7.92E-02
PDHB	1.50	(1.38, 1.64)	1.015	(1.002, 1.028)	2.69E-02	1.088	(1.000, 1.183)	5.05E-02	1.072	1.11E-01
NFKB2	1.51	(1.38, 1.64)	1.018	(1.004, 1.031)	9.02E-03	1.076	(0.990, 1.170)	8.51E-02	1.058	1.95E-01
IL6R	1.51	(1.38, 1.64)	1.033	(1.020, 1.046)	9.71E-07	1.091	(1.002, 1.187)	4.45E-02	1.056	2.13E-01

Supplemental Table IV. Analysis of module and gene-level estimates of genetic effects in OSA cases and controls, presented as a secondary post-hoc analysis suggestively localizing primary analysis results. In section A, each core-gene module, defined as the nominal gene and its receptors, is accompanied by each of its constituent genes; in section B, each KEGG pathway is accompanied with those submodules that showed nominally significant main and interaction effects; in section C, genes with the largest risk-inverting and risk-amplifying estimated interaction effects, having nominally significant main effects, are presented. Core-gene modules and KEGG pathways were allocated type I error in the primary analysis. Secondary analysis is underpowered to comprehensively identify driver genes and modules. Nominally significant

GxE results (*) do not pass Bonferroni (†) thresholds for multiple testing for 30 pathway modules (1.67E-3), and 268 genes (1.87E-4) with membership in the KEGG HIF1, VEGF, NFκB or TNF pathways. Comprehensive secondary analysis gene- and module-level results for these KEGG pathways are presented in Supplemental Table III. OR: odds ratio; CI: confidence interval; OSA: Obstructive sleep apnea, CAD: coronary artery disease, KEGG: Kyoto encyclopedia of genes and genomes, HIF1: hypoxia inducible factor 1, VEGF: vascular endothelial growth factor, NFκB: nuclear factor kappa- beta, TNF: tumor necrosis factor, PRS: polygenic risk score, PS-PRS: pathway-specific polygenic risk score.

Supplemental Table V: Comprehensive secondary analysis GxE testing results for KEGG HIF1, VEGF, NFκB or TNF pathways. (See Excel File)

A) module-level GxE results

B) gene-level GxE results

Supplemental Table VI: Sensitivity Analysis results

(See Excel File)

C) Adjusting for potential mediators (hypertension, T1D, T2D and pulmonary fibrosis)

D) Males only

E) Females Only

F) White Europeans only

Supplemental Table VII: Supplemental CRP Analysis results

PS-PRS	**Estimate**	**Std. Err.**	**P-value**
A) Selected pathways: core-gene modules			
HIF1 core genes	2.74E-04	1.39E-03	8.44E-01
VEGF core genes	3.65E-03	1.38E-03	8.13E-03
NFκB core genes	2.95E-03	1.39E-03	3.36E-02
TNF core genes	-1.80E-03	1.39E-03	1.94E-01
B) Selected pathways: KEGG pathways			
HIF1 KEGG	4.44E-02	1.38E-03	1.22E-227
VEGF KEGG	-7.80E-03	1.38E-03	1.79E-08
NFκB KEGG	4.90E-03	1.39E-03	4.44E-04
TNF KEGG	2.78E-03	1.38E-03	4.35E-02
C) Selected aggregated pathways			
CAD PRS	-2.16E-03	1.44E-03	1.33E-01
OSA genes	1.12E-02	1.40E-03	1.45E-15

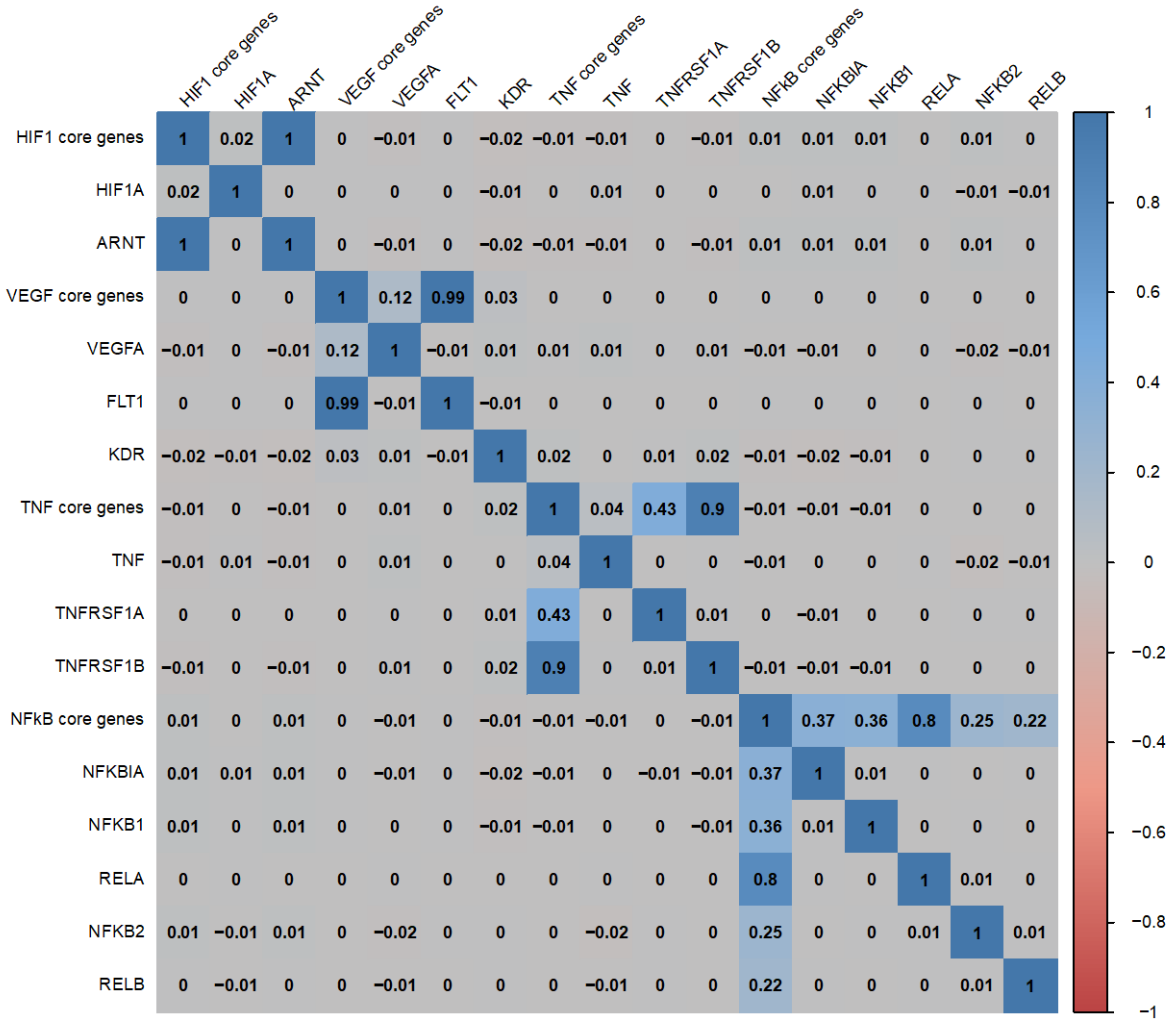
Table S8: Estimated change in log CRP per standard deviation PS-PRS. Each row depicts a separate PS-PRS model showing the PS-PRS main effects in a linear model of the form log(CAD) = OSA + PS-PRS + PS-PRSxOSA + covariates + error. Three groupings representing different types of pathways are included: A) core-gene modules B) KEGG-defined signaling pathways, and C) aggregate pathways. Covariates adjusted: interaction of age by sex and BMI by sex as well as smoking and its interaction with sex, self-reported white race, the first 5 genetic PCs, genotype platform (BiLEVE), asthma and chronic obstructive pulmonary disease. CAD: coronary artery disease, KEGG: Kyoto encyclopedia of genes and genomes, HIF1: hypoxia inducible factor 1, VEGF: vascular endothelial growth factor, NFκB: nuclear factor kappa- beta, TNF: tumor necrosis factor, PRS: polygenic risk score, PS-PRS: pathway-specific polygenic risk score.

Supplemental Table VIII: Effect estimates of covariates for model of full PRS

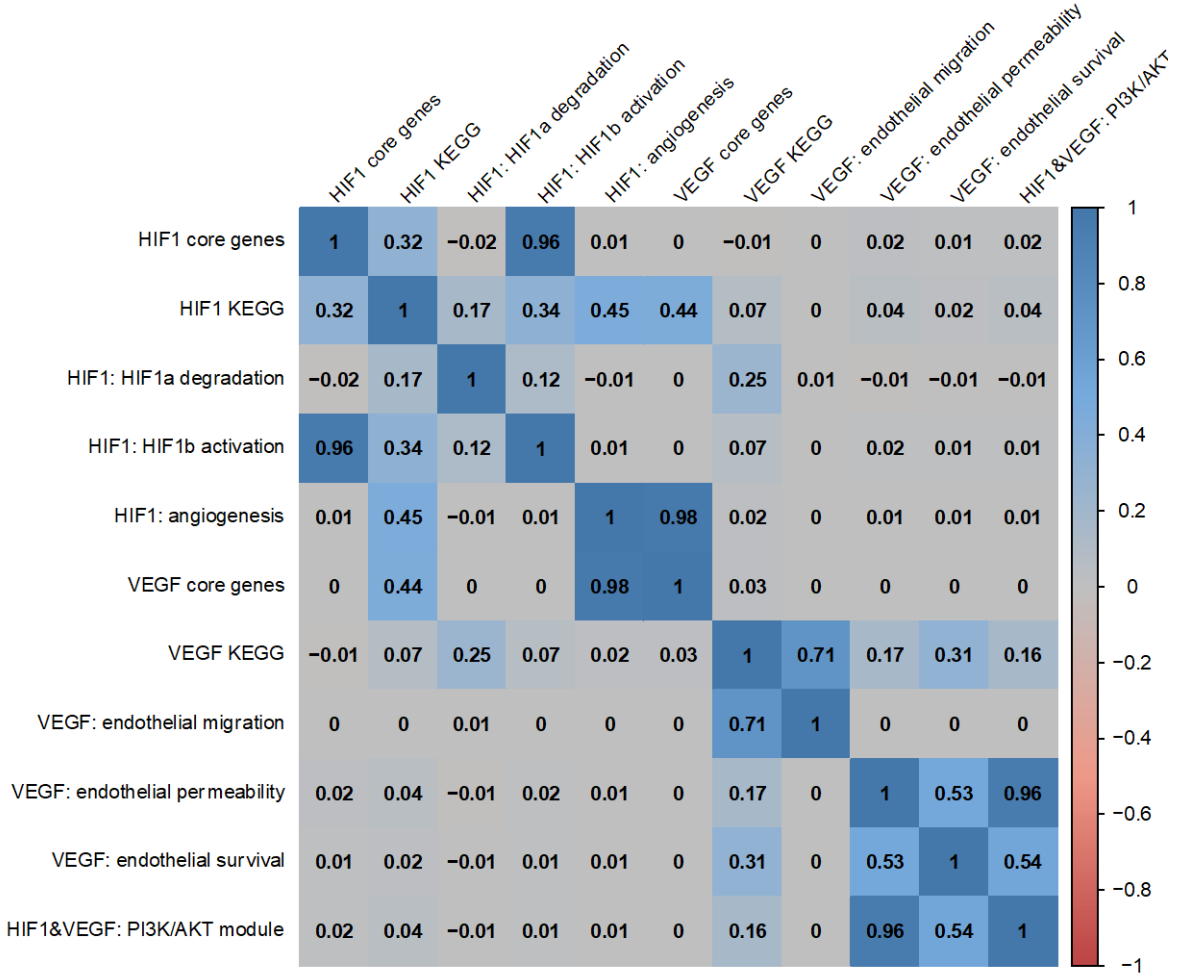
	Est.	s.e.	p-value	OR	OR CI
(Intercept)	-3.49436	0.044507	0.00E+00	0.0304	(0.028, 0.033)
sex (male)	1.04334	0.045079	1.64E-118	2.8387	(2.599, 3.101)
smoking (never)	-0.93997	0.042274	1.56E-109	0.3906	(0.360, 0.424)
smoking (occasionally)	-0.31976	0.090599	4.16E-04	0.7263	(0.608, 0.867)
smoking (previous)	-0.63896	0.043239	2.05E-49	0.5278	(0.485, 0.575)
White European identity	0.06102	0.025926	1.86E-02	1.0629	(1.010, 1.118)
Genetic PC1 (mean (SD))	0.00242	0.000192	2.71E-36	1.0024	(1.002, 1.003)
Genetic PC2 (mean (SD))	-0.00078	0.000318	1.41E-02	0.9992	(0.999, 1.000)
Genetic PC3 (mean (SD))	0.0072	0.000527	1.29E-42	1.0072	(1.006, 1.008)
Genetic PC4 (mean (SD))	0.00173	0.000691	1.23E-02	1.0017	(1.000, 1.003)
Genetic PC5 (mean (SD))	0.00857	0.000916	8.61E-21	1.0086	(1.007, 1.010)
BiLEVE	0.12948	0.01998	9.13E-11	1.1382	(1.095, 1.184)
COPD	0.79107	0.023188	4.38E-255	2.2058	(2.108, 2.308)
asthma	0.08522	0.019372	1.09E-05	1.089	(1.048, 1.131)
OSA	0.41954	0.046994	4.36E-19	1.5213	(1.387, 1.668)
CAD PRS	0.52797	0.00711	0.00E+00	1.6955	(1.672, 1.719)
sex by smoking (never)	0.34135	0.049628	6.06E-12	1.4069	(1.276, 1.551)
sex by smoking (occasionally)	-0.0056	0.102995	9.57E-01	0.9944	(0.813, 1.217)
sex by smoking (previous)	0.38252	0.050397	3.20E-14	1.4660	(1.328, 1.618)
OSA by CAD PRS	-0.01857	0.045087	6.80E-01	0.9816	(0.899, 1.072)

Supplemental Figures

Supplemental Figure I: Correlations between pathways, modules, and genes



Supplemental Figure I a) Pearson correlations between core-gene PS-PRSs and their constituent gene-specific risk scores (GSRS). Component genes are listed below each core-genes pathway.



Supplemental Figure I b) Pearson correlations between selected HIF1 and VEGF sub-module, KEGG and core-genes PS-PRSs in the secondary analysis. Pathway definitions are shown in Supplemental Table II.