Genetic determinants of cardiometabolic and pulmonary phenotypes and obstructive sleep apnoea in HCHS/SOL

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Summary

Background Obstructive Sleep Apnoea (OSA) often co-occurs with cardiometabolic and pulmonary diseases. This study is to apply genetic analysis methods to explain the associations between OSA and related phenotypes.

Methods In the Hispanic Community Healthy Study/Study of Latinos, we estimated genetic correlations ρ_g between the respiratory event index (REI) and 54 anthropometric, glycemic, cardiometabolic, and pulmonary phenotypes. We used summary statistics from published genome-wide association studies to construct Polygenic Risk Scores (PRSs) representing the genetic basis of each correlated phenotype ($\rho_g > 0.2$ and p-value < 0.05), and of OSA. We studied the association of the PRSs of the correlated phenotypes with both REI and OSA (REI ≥ 5), and the association of OSA PRS with the correlated phenotypes. Causal relationships were tested using Mendelian Randomization (MR) analysis.

Findings The dataset included 11,155 participants, 31.03% with OSA. 22 phenotypes were genetically correlated with REI. 10 PRSs covering obesity and fat distribution (BMI, WHR, WHRadjBMI), blood pressure (DBP, PP, MAP), glycaemic control (fasting insulin, HbA1c, HOMA-B) and insomnia were associated with REI and/or OSA. OSA PRS was associated with BMI, WHR, DBP and glycaemic traits (fasting insulin, HbA1c, HOMA-B and HOMA-IR). MR analysis identified robust causal effects of BMI and WHR on OSA, and probable causal effects of DBP, PP, and HbA1c on OSA/REI.

Interpretation There are shared genetic underpinnings of anthropometric, blood pressure, and glycaemic phenotypes with OSA, with evidence for causal relationships between some phenotypes.

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Keywords: Obstructive sleep apnoea; Cardiometabolic and pulmonary phenotypes; Genetic correlation; Polygenic risk score; Mendelian randomization

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Introduction

Obstructive sleep apnoea (OSA) is a common chronic condition, with estimated prevalence of ~9% to 38% in the overall population as estimated from a world-wide meta-analysis.[1] OSA is characterized by repeated collapse of the upper airway during sleep. Typical clinical features include excessive daytime sleepiness, snoring,

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Research in context

Evidence before this study

The authors reviewed the literature using traditional sources. Previous studies used traditional epidemiologic methods to show that obstructive Sleep Apnoea (OSA) often co-occurs with cardiometabolic and pulmonary diseases. A handful of studies applied genetic analysis methods to study the relationships between OSA and related phenotypes. Publications are appropriately cited.

Added value of this study

We applied sequential genetic methods of genetic correlation, Polygenic Risk Scores (PRS) and Mendelian Randomization (MR) analyses to study whether the relationship of sleep apnoea with multiple health phenotypes reflect shared environmental exposures, common genetic factors, causal or reverse causal associations. Of the studied phenotypes, 22 covering anthropometric, cardiometabolic, lung function, and insomnia phenotypes were genetically correlated with sleep apnoea trait measured by respiratory event index (REI). Among PRSs representing the genetic basis of each correlated phenotype, PRSs of BMI, WHR, diastolic blood pressure, pulse pressure, mean arterial pressure, glycated hemoglobin, fasting insulin, HOMA-B cell function, and insomnia were associated with REI and/or OSA. OSA PRS was similarly associated with a few anthropometric, blood pressure, and glycaemic traits. We identified causal associations of BMI, WHR, blood pressure and glycaemic phenotype on OSA or REI.

Implications of all the available evidence

Understanding the role of OSA within the larger context of other cardiometabolic and pulmonary phenotypes can aid in the development and prioritization of targeted interventions to address OSA and related health measures.

and arousals during sleep.[2] Several health phenotypes have been consistently reported to be related to OSA, including obesity, hypertension, diabetes, cognitive impairment, and other sleep disorders like insomnia.[3–8] However, the mechanisms underlying these associations and potential causal pathways are not clear: OSA may be either a cause or a consequence of these phenotypes, or the association could reflect shared causes of OSA and these other health conditions. Understanding the role of OSA within the larger context of other cardiometabolic and pulmonary phenotypes can aid in the development and prioritization of targeted interventions to address OSA and related health measures.

Genetic association analyses have been used to study relationships among phenotypes. Genetic correlation between a pair of phenotypes measures the degree of similarity in their genetic determinants.[9] Polygenic Risk Scores (PRS), by aggregating a set of variants associated with a phenotype into a single score, have been used to study how "genetically determined" parts of a phenotype may predict another phenotype.[10] Mendelian Randomization (MR) analysis, by using genetic variants as instrumental variables (IV), can test and estimate causal associations between phenotype pairs.[11] OSA is heritable, with heritability estimates of OSA and OSA-related phenotypes ranging from 0.06 to 0.17 in population-based studies,[12,13] and 0.33-0.37 in family-based studies.[3] Thus, we now have the opportunity to systematically employ the above analytic tools - genetic correlation, PRS, and MR analyses - to elucidate the relationship between OSA and associated phenotypes.

Figure 1 and Table 1 provide an overview of the genetic analyses performed and their characteristics. We used individual-level data from the HCHS/SOL to estimate genetic correlations between the respiratory event index (REI) and 54 cardiometabolic and pulmonary phenotypes. We then used summary statistics from GWAS independent of HCHS/SOL to construct PRSs for OSA and the identified correlated phenotypes, and studied the associations between the PRS for OSA and correlated phenotypes, and between PRSs for correlated phenotypes and sleep apnoea phenotypes. Finally, we used summary statistics from GWAS of the correlated phenotypes, and of OSA and REI, to study the causal relationship between OSA and the correlated phenotypes.

Methods

Study population

The Hispanic Community Health Study/Study of Latino (HCHS/SOL) is a Hispanic/Latino, multi-site, community-based cohort assembled to understand risk/protective factors for a wide range of health outcomes.[14,15] Participants were selected using a multi-stage probability sampling design and a total of 16,415 individuals aged 18-74 years participated in a baseline visit (2008-2011). Data, including demographics, lifestyle and socioeconomic questionnaires, laboratory tests, and home sleep apnoea testing (ARES Unicorder 5.2, (B-Alert, Carlsbad, CA)), were collected. REI was defined as the average number of apnoea and hypopnea events (≥10 seconds duration and ≥ 3% desaturation) per hour of estimated sleep, as described.[4] OSA was defined as a REI≥5. Genotyping was performed for 12,803 individuals who consented to genetic data sharing.[16] Analytic subsample consisted of individuals who maintained consent for genetic studies through their most recent informed consent form and had a sleep apnoea test.

Ethics statement

The HCHS/SOL was approved by the institutional review boards (IRBs) at each field center, where all

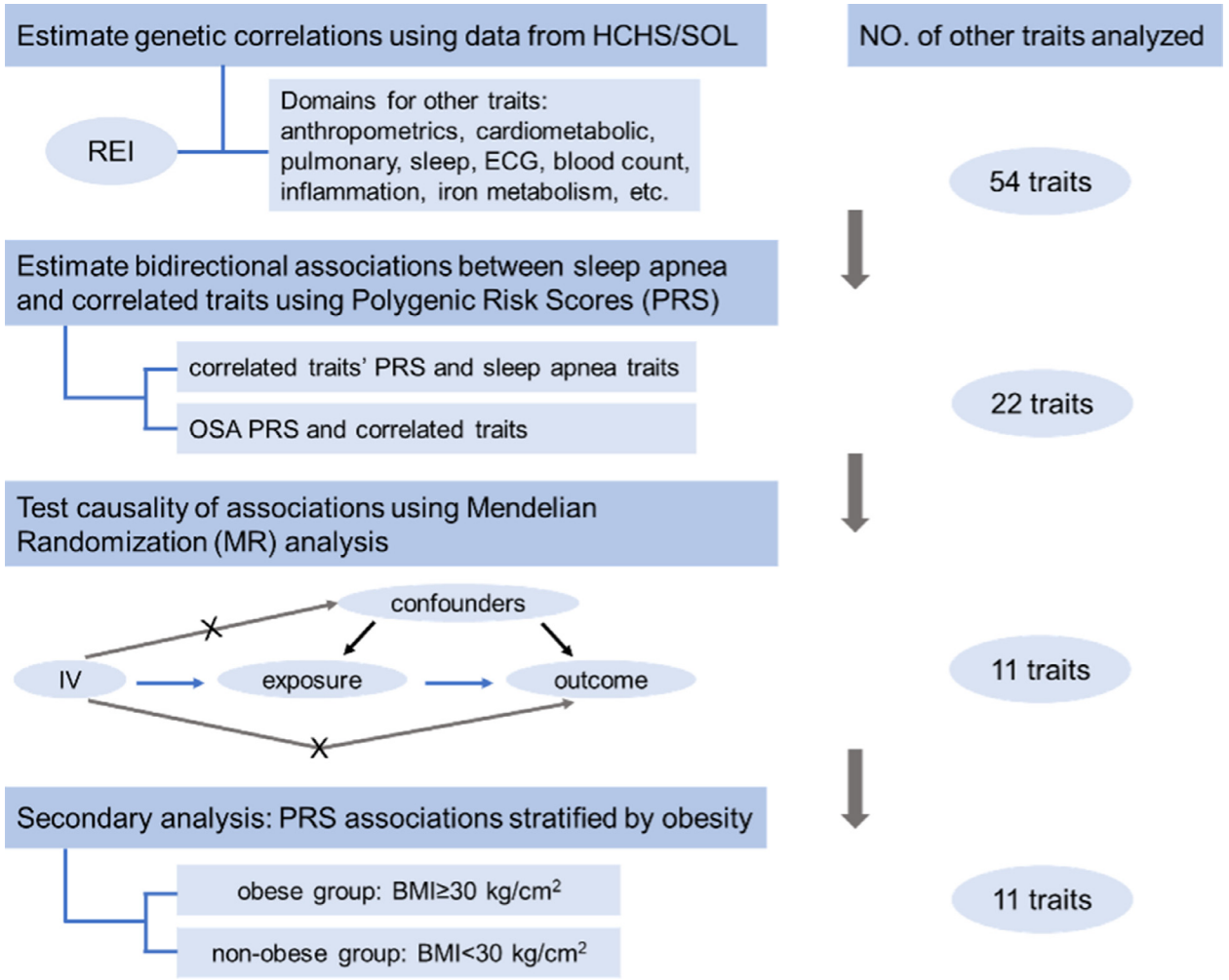

Figure 1. Overview of the study design and set of analyses performed.

Data used	Application	Findings
Genetic correlation		
Individual data from HCHS/SOL study sample	To estimate the degree of shared genetic background between phenotypes	22 traits genetically correlated with REI: BMI, WHR, DBP, MAP, PP, Fasting Insulin, HbA1c, HOMA-B, HOMA-IR, TC, TG, LDL, HR, FEV/FVC, Insomnia, Sleep duration, HCT, HGB, RBC, LYM, WBC, EOS
Polygenetic risk score (PRS)		
Summary statistics from published GWAS and individual data from HCHS/SOL study sample	PRS represent the "genetically determined" parts of a phenotype. Here they were used to study the association between genetically determined phenotypes and REI/OSA, and the other way around	10 genetically determined traits associated with REI and/or OSA: BMI, WHR, WHRadjBMI, Insomnia, DBP, PP, MAP, Fasting Insulin, HbA1c, HOMA-B; OSA PRS associated with other 7 phenotypes: BMI, WHR, DBP, Fasting Insulin, HbA1c, HOMA-B, HOMA-IR;
Mendelian Randomization (MR)		
Summary statistics from published GWAS	To estimate and test the causal direction and effect size between phenotype pairs	Robust causality on OSA: BMI, WHR Robust causality on REI: WHRadjBMI Probable causality on OSA: DBP Probable causality on REI: PP, HbA1c

***Table 1*: Summary of genetic analysis methods and findings.**
Definition of abbreviations refer to Figure 2. "Robust causality" refers to causal association supported by all MR sensitivity analysis. "Probable causality" refers to causal association supported by at least two sensitivity analyses.

participants gave written informed consent, and by the Non-Biomedical IRB at the University of North Carolina at Chapel Hill, to the HCHS/SOL Data Coordinating Center. All IRBs approving the study are: Non-Biomedical IRB at the University of North Carolina at Chapel Hill. Chapel Hill, NC; Einstein IRB at the Albert Einstein College of Medicine of Yeshiva University. Bronx, NY; IRB at Office for the Protection of Research Subjects (OPRS), University of Illinois at Chicago. Chicago, IL; Human Subject Research Office, University of Miami. Miami, FL; Institutional Review Board of San Diego State University, San Diego, CA.

Genotyping and imputation

Genotyping was performed using an Illumina custom array, SOL HCHS Custom 15041502 B3, as described by Conomos et al.,[17] which further describes genetic ancestry inference and the construction of principal components (PCs) of genetic data, kinship matrix, and "genetic analysis groups", representing groups of participants who self-identify with specific Hispanic/Latino background with some modification to increase the genetic similarity within the groups. In this work we used the genetic analysis groups as an adjusting covariate in PRS association analyses, but refer to them as Hispanic/Latino background, for ease of communication in the main manuscript. For PRS construction, we further used imputed genetic data based on TOPMed freeze 5b reference panel.[18]

Estimation of genetic correlation between the REI and other phenotypes

We first used the GCTA software[19] and estimated heritability and variance explained by household environment for all phenotypes. Two considered phenotypes were excluded due to low estimated heritability (<1%).

We then estimated the genetic correlations between REI and each of the 54 cardiometabolic and pulmonary phenotypes using individual-level data and a method of moment estimator reported in Elgart et al.[20] Mimicking the fully adjusted two-stage procedure for genetic association tests,[21] all traits were first regressed on covariates, residuals were obtained, rank-normalized, and then used as the phenotypes in the estimation of genetic correlation, further adjusting for the same covariates again. Because REI is highly skewed, prior to analysis we added 0.5 to all zero values, then applied log transformation. We used a body mass index (BMI) unadjusted model (BMI_unadj), adjusted for age, sex, log of sampling weights (adjusting for sampling design), centre, and first 5 genetic PCs, and a BMI adjusted model (BMI_adj), further adjusted for BMI. Phenotypes genetically correlated to REI were defined as estimated genetic correlation $\hat{\rho}_g > 0.2$ with p-value<0.05. We also estimated the correlation between phenotypes due to household sharing, an environmentally induced correlation.

Summary statistics from GWAS of OSA-related traits and correlated traits

We identified summary statistics from GWAS for each of the phenotypes that was correlated to REI

(Supplementary Table 2).[22–33] We also identified summary statistics from a multi-ethnic GWAS of BMI-adjusted REI (or Apnoea Hypopnea Index, AHI),[34] and from GWAS of clinically identified OSA using ICD-codes, unadjusted for BMI[12] (Supplementary Table 3). REI GWAS had a relatively small sample size (~20,000 individuals), but the phenotype is well measured, because all studies that participated in the meta-analysis GWAS measured REI in all consenting individuals from their parent cohorts, without indication for OSA. In contrast, the OSA GWAS has larger sample size (217,955 individuals and ~16,761 OSA patients), but potentially suffers from under-diagnosis of OSA as it performed in a biobank-based analysis. Notably, the REI GWAS was a meta-analysis that included the HCHS/SOL. Therefore, we could not use the REI summary statistics in analyses using individual-level HCHS/SOL due to overfitting, and only used it for MR analysis.

Summary statistics for the OSA GWAS were provided in hg38, while all other summary statistics were in hg19. Because our genetic data files were in hg38, we lifted over summary statistics to hg38 when constructing PRS and to hg19 when performing MR (PRS construction and MR analyses are described below). To lift over genomic coordinates, we used chain files downloaded from the UCSC genome browser[35] and the GenomicRanges R package.[36]

PRS construction

We constructed PRS using summary statistics referenced in Supplementary Table 2-3. PRS were constructed in the HCHS/SOL using LDPred2[37] implemented in the bigsnpr R package.[38] Because the package can handle up to about 1.2M SNPs, we filtered to the HapMap SNP,[39] in addition to imputation quality filter requiring imputation INFO score>0.8, MAF $\geq$ 0.01, and missing genotype rate $\leq$ 0.01 in HCHS/SOL. We computed LD reference panel based on the HCHS/SOL dataset. We implemented LDPred2 with the "auto" option. The specific command used for LDPred2 PRS construction is provided in Supplementary Note 2.

Associations between genetically correlated-trait PRS and OSA and vice versa

We first validated the association of the various PRS with their intended traits, and next tested the association of the PRSs of the genetically correlated traits with REI and OSA, and of OSA PRS with the genetically correlated traits (Figure 1). Association analyses were done using mixed models implemented in the GENESIS R/Bioconductor package[40] to account for genetic relatedness and structural correlation between individuals. Thus, we used random effects corresponding to a dense kinship matrix, and matrices modelling household and block unit sharing among individuals. The BMI unadjusted model was adjusted for age, sex, study centre, 5 PCs and genetic analysis group. The BMI adjusted model was additionally adjusted for BMI. Because REI is highly skewed, we log-transformed it prior to analysis. For some individuals having REI values of zero, we added 0.5 before to their REI before log transformation. We concluded that the genetically determined trait was predictive of REI (or OSA) if the association p-value between its PRS and REI (or OSA) was < 0.05. Additionally, we computed False Discovery Rate (FDR) adjusted p-values for each group. Similarly, we studied the associations of genetically determined OSA with genetically correlated-traits.

PRS associations between genetically-correlated traits and OSA stratified by obesity

We estimated PRS associations between genetically-correlated traits and REI and OSA in strata defined by obesity. Obesity was defined as BMI$\geq$30kg/m^2, while no obesity was defined as BMI<30kg/m^2. As before, we performed both BMI_unadj and BMI_adj analysis and highlight associations with p-value <0.05, and computed FDR-adjusted p-values as well. Because the obesity and no obesity strata have some correlated individuals (individuals living in the same household, and/or genetically related), to test for differences between the associations estimated in the two strata we performed another analysis including the pooled cohort and further adjusted for the interaction between the PRS and obesity status, and to main effect of obesity. We used the interaction term as the test statistic.

Mendelian randomization (MR) analysis to study causal association with correlated traits

To estimate the causal relationship between genetically correlated traits to OSA whose PRS predicted REI/OSA, or where OSA PRS predicted them, we performed bidirectional two sample MR analysis using the TwoSampleMR R package.[41] To study the causal effect of the OSA-correlated traits on OSA and REI, we selected genome-wide significant variants ($p<5\times10^{-8}$) from the relevant correlated-trait GWAS (Supplementary Table 2), and to study the causal effect of OSA phenotypes on the correlated traits, we used REI (SNPs with p-value$<5\times10^{-6}$), and OSA (SNPs with p-value$<5\times10^{-8}$) GWAS (Supplementary Table 3). We used more liberal threshold for REI because the REI GWAS used smaller sample size, and none of the SNPs reached genome-wide significance with p-value$<5\times10^{-8}$.

We used similar methodology for each MR analysis. First, we clumped the SNPs from the exposure phenotypes based on European population in the 1000 genomes reference panel. One exception was for mean arterial pressure (MAP): its GWAS was based on Japanese

populations,[26] so we used the East Asian 1000 genomes reference panel. We used clumping parameters such that SNPs in a window of distance 1,000Kb of each index SNP and LD with R^2>0. 1 were removed. In secondary analysis we used more stringent clumping conditions, with distance of 10,000Kbp and R^2 threshold of 0.001. Next, we matched and harmonized summary statistics from the outcome phenotype to those from the exposure phenotype. Then, we applied a few MR methods.

The primary method was inverse variance weighted method (IVW), which require the instrumental variable (IV) to fulfil 3 assumptions: (1) the IV should be associated with exposure; (2) the IV should not be associated with confounders of exposure and outcome association; (3) the effect of the IV on outcome is exclusively through the exposure. When its assumptions are valid, IVW is the most powerful method for MR. However, MR analysis may give false results (indicate causal association even if it is null) if the IV assumptions are violated for some of the instruments. We performed several sensitivity analyses. First, potential violation of assumptions may be detected by heterogeneity of the associations across the individual IVs using the Q-test by IVW and MR-Egger. Second, we applied MR-Egger to estimate horizontal pleiotropy, by which genetic variants are independently associated with the exposure and the outcome, based on the MR-Egger intercept. These are addressed by additional analyses using MR methods that have different modelling assumptions and strengths.[42] Third, we used the Radial MR package[43] to detect and remove outliers. Then, we applied the IVW again, and added MR-Egger, weighted median (robust to outliers), and the MR-RAPS (robust to outliers by downweighing them, more powerful when the instruments are weak) MR methods. Fourth, we applied the Mendelian Randomization Pleiotropy RESidual Sum and Outlier (MR-PRESSO) to correct for horizontal pleiotropy. Fifth, we used single SNP analysis and leave-one-out analysis to assess the possibility that a single SNP drives the observed associations. Finally, we applied multivariable MR (MVMR) to account for potential confounding across multiple potentially causally-associated traits by testing them jointly.

Role of the funding source

The funder did not have any role in the design and execution of the analysis in this manuscript, data interpretation, manuscript writing, and nor in the decision to submit the paper for publication.

Results

Sample characteristics and genetic correlations

The sample included 11,155 HCHS/SOL participants (mean age 46.2; 41.1% men); sample characteristics and phenotype distributions are shown in Table 2 and Supplementary Table 1. Individuals with and without OSA differed in their age, sex, and obesity distribution: individuals with OSA tended to be older (mean age 53.0 versus 43.1), more male (51.9% versus 36.2%) and with higher obesity levels (60.8% versus 33.6%). Supplementary Figure 1 visualizes the patterns of genetic ancestry represented by HCHS/SOL individuals, including the varying proportions of European, African, and

Traits, unit	Overall	OSA, obesity	OSA, no obesity	no OSA, obesity	no OSA, no obesity
Participants, N	11155	2101	1353	2581	5090
Age, years	46.18 (13.80)	51.91 (10.86)	54.82 (10.46)	43.34 (13.31)	42.96 (14.18)
Sex, Male (%)	4581 (41.1)	979 (46.6)	815 (60.2)	722 (28.0)	2050 (40.3)
Obesity (%)	4682 (42.1)	2101 (100.0)	0 (0.0)	2581 (100.0)	0 (0.0)
REI, event/h	6.43 (12.25)	20.41 (19.65)	13.78 (10.98)	1.64 (1.44)	1.16 (1.31)
BMI, kg/m^2	29.79 (6.00)	35.89 (5.38)	26.96 (2.21)	34.57 (4.54)	25.60 (2.88)
WHR	0.92 (0.07)	0.96 (0.07)	0.94 (0.06)	0.93 (0.07)	0.90 (0.07)
WHIIRS	7.06 (5.40)	7.32 (5.42)	6.89 (5.39)	7.28 (5.51)	6.89 (5.34)
MAP, mmHg	89.45 (12.34)	94.92 (12.64)	92.11 (12.19)	89.73 (11.68)	86.32 (11.60)
DBP, mmHg	73.14 (10.99)	78.38 (11.31)	74.15 (10.88)	74.29 (10.25)	70.11 (10.24)
PP, mmHg	48.93 (12.77)	49.61 (13.35)	53.88 (14.14)	46.33 (12.65)	48.66 (11.76)
FastInsl, mU/L	13.34 (12.75)	19.16 (13.53)	11.52 (21.44)	17.08 (12.20)	9.47 (6.56)
HbA1c, %	5.90 (1.28)	6.32 (1.41)	6.09 (1.41)	5.91 (1.23)	5.67 (1.14)
HOMA_B	140.79 (174.77)	171.65 (117.79)	113.72 (166.54)	186.67 (291.38)	111.52 (89.22)
HOMA_IR	3.60 (4.34)	5.54 (5.82)	3.19 (6.28)	4.57 (4.14)	2.39 (2.11)

***Table 2*: Characteristics of traits correlated with REI and OSA in HCHS/SOL study sample, stratified by obesity and OSA status.**
OSA is defined as REI ≥ 5 events/hour. Obesity is defined as BMI ≥ 30kg/m^2.
Values expressed as n and percentage (%) or mean and SD.
Definition of abbreviations: REI= Respiratory Event Index; BMI= Body Mass Index; WHR=Waste Hip Ratio; WHIIRS =Women's Health Initiative Insomnia Rating Scale; MAP=Mean Arterial Pressure; DBP=Diastolic Blood Pressure; PP=Pulse Pressure; FastInsl=Fasting Insulin; HbA1c= Glycosylated Hemoglobin; HOMA_B=homeostasis model assessment of beta-cell function; HOMA_IR=homeostasis model assessment of insulin resistance.
Table 12.

Amerindian genetic ancestries across HCHS/SOL individuals, and genetic PC coordinates of the participants. These figures highlight the six major Hispanic/Latino background groups (Mexican, Cuban, etc.) represented in the dataset, demonstrating shared patterns between individuals with the same background. Importantly, one can see that Hispanic/Latino individuals have substantial proportions of European ancestries, supporting the expectation (confirmed by multiple studies in HCHS/SOL) that many genetic associations discovered in populations of primarily European ancestries generalize to Hispanics/Latinos.[44–46]

Two considered phenotypes were excluded due to low estimated heritability (<1%) (Supplementary Figure 2). Genetic and household correlation estimates are shown in Figure 2. Their p-values were computed based on the Fisher's transformation followed by a normal approximation, i.e. assuming that the genetic and household correlation estimates were normally distributed after Fisher's transformation. Eighteen phenotypes were significantly genetically correlated with REI in the BMI-unadjusted model, with estimated ρ_g ranging from 0.23 to 0.56 in absolute value. After BMI adjustment, eight from the above eighteen traits were still significant. Another four phenotypes were observed as genetically correlated with REI ($\hat{\rho_g} > 0.2$ and p-value<0.05) only in the BMI-adjusted model.

Figure 2 also visualizes how the estimates of genetic and household correlations from the BMI adjusted and unadjusted models cluster across phenotypes. For some phenotypes, the directions of the genetic and household contributions to the correlation between REI and other phenotypes are similar, e.g., BMI, waist hip ratio (WHR), diastolic blood pressure (DBP), glycosylated hemoglobin (HbA1c) and homeostasis model assessment of insulin resistance (HOMA-IR). There are also phenotypes in which the genetic and household contributions to the correlations are of opposite directions, among which only one passed the significance threshold in both genetic and household correlation analyses: sleep duration. Specifically, in BMI adjusted analysis, the household correlation between REI and sleep duration was negative (higher REI tracked with shorter sleep duration), while the genetic correlation was positive (higher REI tracked with longer sleep duration).

PRS association with their intended phenotypes

We constructed PRS using summary statistics from GWAS referenced in Supplementary Table 2-3. All PRSs of correlated traits were associated with their corresponding phenotypes (Supplementary Figure 3). Figure 3 demonstrates that the OSA PRS was associated with elevated REI as well as with increased OSA risk in both BMI_unadj and BMI_adj models.

The association of genetically determined phenotypes with measured REI and OSA

Figure 4 visualizes the associations of the PRSs of the correlated phenotypes with REI and OSA, provided by PRS effect estimates (after exponentiating, to provide estimates in the original phenotype scale), without and with BMI adjustment. Supplementary Tables 4-5 provide association effect size estimates per 1 SD increase in the PRS value. In the BMI-unadjusted model, PRSs of seven phenotypes were associated (p-value<0.05) with multiplicated change in REI. P-values were computed by the GENESIS R package based on a mixed model results. Four associations passed FDR multiple testing correction: BMI (effect size: 1.14 [1.11, 1.16]; FDR p-value<0.001), WHR (effect size:1.07 [1.05, 1.10]; FDR p-value<0.001), insomnia (effect size: 1.04 [1.01, 1.06]; FDR p-value=0.01), pulse pressure (PP) (effect size: 0.97 [0.95, 0.99]; FDR p-value=0.01). Additional associations were observed at the p-value<0.05 level but did not pass FDR adjustment: mean arterial pressure (MAP) (effect size: 1.02 [1.00, 1.04]), fast insulin (FastInsl) (effect size: 0.98 [0.95, 1.00]) and HbA1c (effect size: 1.02 [1.00, 1.05]). In BMI-adjusted analysis, the PRSs for insomnia, PP, HbA1c and another PRS for WHRadjBMI trait (PRS created based on a GWAS of WHR adjusted for BMI) were associated with REI (p<0.05), but did not pass multiple testing correction. The associations with the dichotomous OSA were similar, with a subset of these associations also passing FDR multiple-testing adjustment, including PRSs for BMI (OR: 1.21 [1.16, 1.27]), WHR (OR: 1.09 [1.04, 1.14]) and insomnia (OR: 1.07 [1.02, 1.11]). Additionally, the PRSs for DBP and homeostasis model assessment of beta-cell function (HOMA-B) were associated with OSA risk with p-value <0.05 in BMI adjusted and BMI unadjusted models individually, but did not pass FDR correction.

The association of genetically determined OSA with correlated phenotypes

In a BMI unadjusted analysis (Supplementary Figure 4, Supplementary Table 6), the OSA PRS was associated with anthropometric and glycaemic traits and the FDR p-value<0.05 level (BMI, WHR, FastInsl, HbA1c, HOMA_B, HOMA_IR) and with DBP at the p-value<0.05 level. However, once adjusting for BMI, the OSA PRS was only associated with increased WHR and HbA1c with p<0.05. P-values were computed by the GENESIS R package based on a mixed model results.

Obesity-stratified PRS analysis

In the Supplementary Information we provided results from secondary analysis stratified by obesity (Supplementary Figure 5-6, Supplementary Table 7-9). P-values were computed by the GENESIS R package based on a mixed model results. At the FDR<0.05 level, OSA PRS

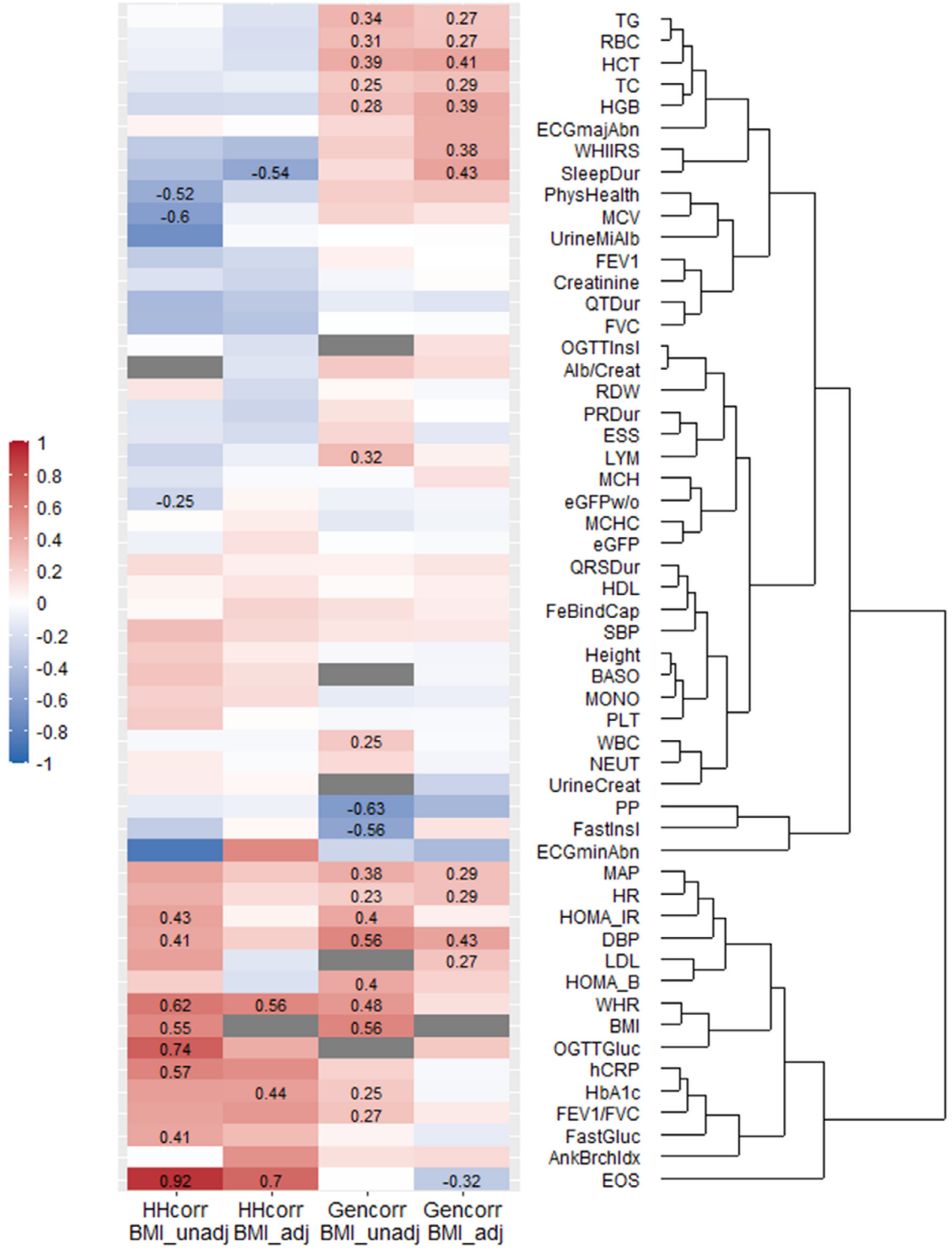

Figure 2. Estimated genetic and household correlations and cluster analysis between REI and other traits based on HCHS/SOL study sample. Dendogram was constructed based on the computed estimates of genetic and household correlations between REI and other traits. BMI unadjusted model (BMI_unadj) was adjusted for age, sex, HCHS/SOL sampling weights, centre and PCs, BMI adjusted model (BMI_adj) was additionally adjusted for BMI. Significant correlation estimates (p-value<0.05) were labelled with the values. P-values were computed based on the Fisher's transformation to the estimated correlation coefficient and the effective sample size, and assuming normal approximation to the distribution after transformation. A few parameters were not estimated due to model none-convergence and are coloured in gray. GenCorp=genetic correlation; HHcorr=household correlation.

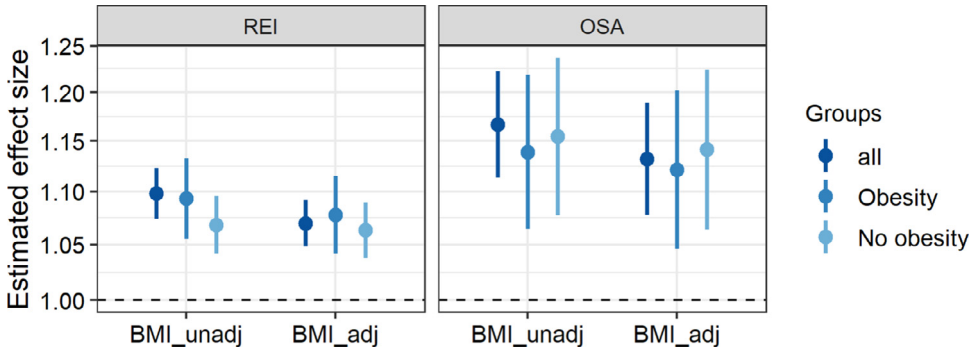

Figure 3. OSA PRS association with measured REI and OSA in HCHS/SOL study sample. BMI unadjusted model (BMI_unadj) was adjusted for age, sex, centre, PCs and Hispanic/Latino background, and BMI adjusted model (BMI_adj) was additionally adjusted for BMI. REI was log-transformed in association analysis, and the estimates were back-transformed to show the association. Estimates are per 1 SD increase of OSA PRS, and for REI they represent multiplicative increase in events per hour, while for OSA risk they represent odds ratios (OR). All associations were significant with p-value<0.05 and also passed FDR-test. P-values were computed in association analyses via mixed models implemented in the GENESIS R package. Obesity is defined as BMI≥30kg/m^2.

was associated with BMI and WHR in both strata while with glycaemic traits only in the no obesity stratum. Insomnia PRS was associated with REI and OSA in the no obesity stratum with FDR p-values <0.05. Other correlated traits PRSs, especially BMI and DBP PRSs (which had FDR p-values <0.05), tended to have strong associations with REI and OSA in the obesity stratum. However, none of the interaction tests between PRS and obesity on REI or OSA were statistically significant after correcting for multiple testing (Supplementary Table 10-11).

Mendelian randomization: causal associations between PRS-associated pairs

In causality analysis by two-sample MR, we estimated causal effects (p-value<0.05 based on the primary IVW with multiplicative random effects model) of HbA1c (effect size: 0.18 [0.04, 0.33]; FDR p-value=0.06), PP (effect size: -0.005 [-0.01, -0.0003]; FDR p-value=0.13) and WHRadjBMI (effect size: 0.08 [0.03, 0.13]; FDR p-value=0.01) on BMI-adjusted REI, and of BMI (OR: 2.04 [1.92, 2.16]; FDR p-value<0.001), DBP (OR: 1.007 [1.000, 1.013]; FDR p-value=0.13) and WHR (OR: 1.56 [1.43, 1.70]; FDR p-value<0.001) on OSA risk by the primary method of IVW (Figure 5A). Estimated effect size, 95% CIs, p-values and FDR p-values are provided in Supplementary Table 12, however we note that for REI effect size estimates are not interpretable because REI/AHI GWAS rank-normalized the outcomes. Still, the direction of estimated causal association is correct. Although no obvious pleiotropy was detected by the MR-Egger intercept for these associations, high heterogeneity was detected for several associations (Supplementary Table 13). Extensive sensitivity analysis provided generally consistent associations after accounting for heterogeneity and horizontal pleiotropy by removing outliers or in MR-PRESSO method (Figure 5B and Supplementary Figure 7, Supplementary Table 14-15), and results were consistent in single SNP analysis and in leave-one-out analysis.

When using REI or OSA as exposures, there were no estimated causal associations with analysed correlated traits in IVW MR (Supplementary Figure 8, Supplementary Table 16-18).

We also tested the causality of above associated anthropometric traits (BMI, WHR and WHRadjBMI)

Definition of trait abbreviations (ordered alphabetically): AnkBrchIdx=overall ankle brachial index; Alb/Creat=albumin/creatinine ratio; BMI= body mass index; BASO=basophils count; DBP=diastolic blood pressure; ESS= Epworth sleepiness scale; ECGAbn_min=-minor ECG abnormalities; ECGAbn_maj=major ECG abnormalities; EOS=eosiniphils count; eGFPw/o=eGRP based on serum cystatin C w/o demographics; eGFP=eGRP based on serum cystatin C, serum creatinine, gender, age and race; FEV1= Forced Expiratory Volume in 1 s; FVC = Forced Vital Capacity; FEV1/FVC= FEV1 to FVC ratio; FastGluc=fasting glucose; FastInsl=fasting insulin; FeBindCap=-total iron binding capacity; HbA1c= glycosylated hemoglobin; HOMA_B=homeostasis model assessment of beta-cell function; HOMA_IR=homeostasis model assessment of insulin resistance; HDL=high-density lipoprotein cholesterol; HR=heat rate; HGB=hemoglobin; HCT=hematocrit; hCRP=high sensitivity C-reactive protein; LDL=low-density lipoprotein cholesterol; LYM=lymphocyte count; MAP=mean arterial pressure; MONO=monocyte count; MCV=mean corpuscular volume; MCH=mean corpuscular hemoglobin; MCHC=mean corpuscular hemoglobin concentration; NEUT=neutrophils count; OGTTGluc=post OGTT glucose; OGTTInsl=post OGTT insulin; PP=pulse pressure; PRDur=PR duration; PLT=platelet count; PhysHealth=aggregate physical health scale; QRSDur=QRS duration; QTDur=QT duration; REI= respiratory event index; RBC=red blood count; RDW=RBC cell distribution width; SleepDur=average sleep duration; SBP=systolic blood pressure; TG=triglycerides; TC=Total cholesterol; UrineCreat=Urine Creatinine; UrineMiAlb=Urine microalbumin; WHR=waste hip ratio; WHIIRS =Women's Health Initiative Insomnia Rating Scale; WBC=white blood count.

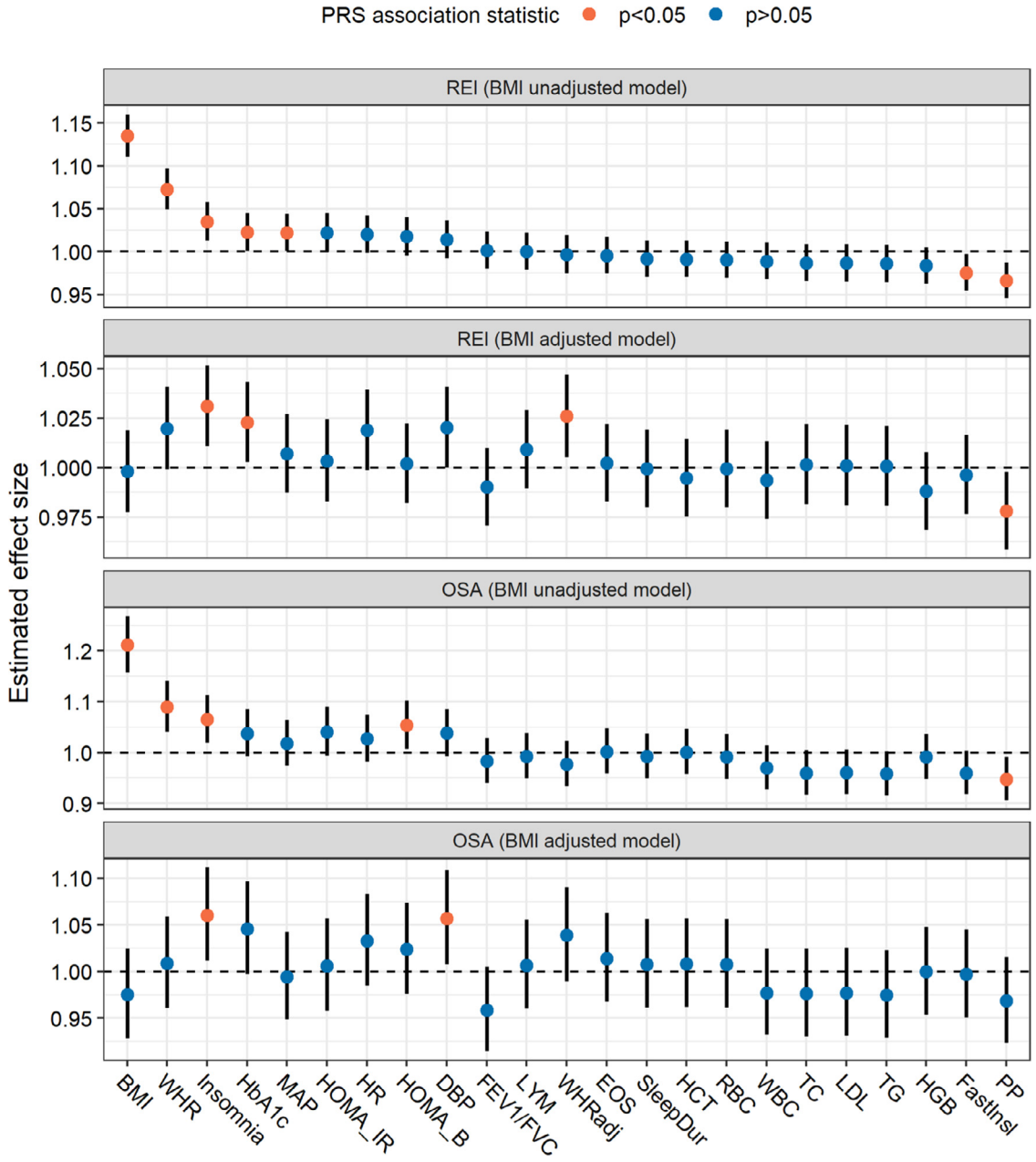

Figure 4. The association between PRS for genetically-determined traits with measured sleep apnoea traits in HCHS/SOL study sample. Effect sizes are per 1 SD increase in PRS for each genetically-determined trait, and represent multiplicative increase in REI (events per hour), or odds ratio (OR) for OSA risk. The traits were ordered by the decreasing effect estimate in association with REI from BMI unadjusted models. The BMI-unadjusted model (BMI_unadj) was adjusted for age, sex, centre, PCs and Hispanic/Latino background. The BMI adjusted model (BMI_adj) was additionally adjusted for BMI. The threshold for statistical significance was set at $p<0.05$. *P*-values were computed in association analyses via mixed models implemented in the GENESIS R package. For definitions of abbreviations please refer to Figure 2, WHRadj=WHRadjBMI, a GWAS of WHR adjusted for BMI.

and obesity-related cardiometabolic traits (DBP, PP and HbA1c) together on sleep apnoea traits in a multivariable MR. The results suggest that the causal effects for WHRadjBMI (effect size: 0.09 [0.04, 0.14]) and PP (effect size: -0.007 [-0.013, -0.002]) on REI, and BMI (OR: 1.94 [1.79, 2.11]), WHR (OR: 1.15 [1.04, 1.29]) and DBP (OR: 1.014 [1.005, 1.024]) on OSA risk were still significant (Supplementary Table 19).

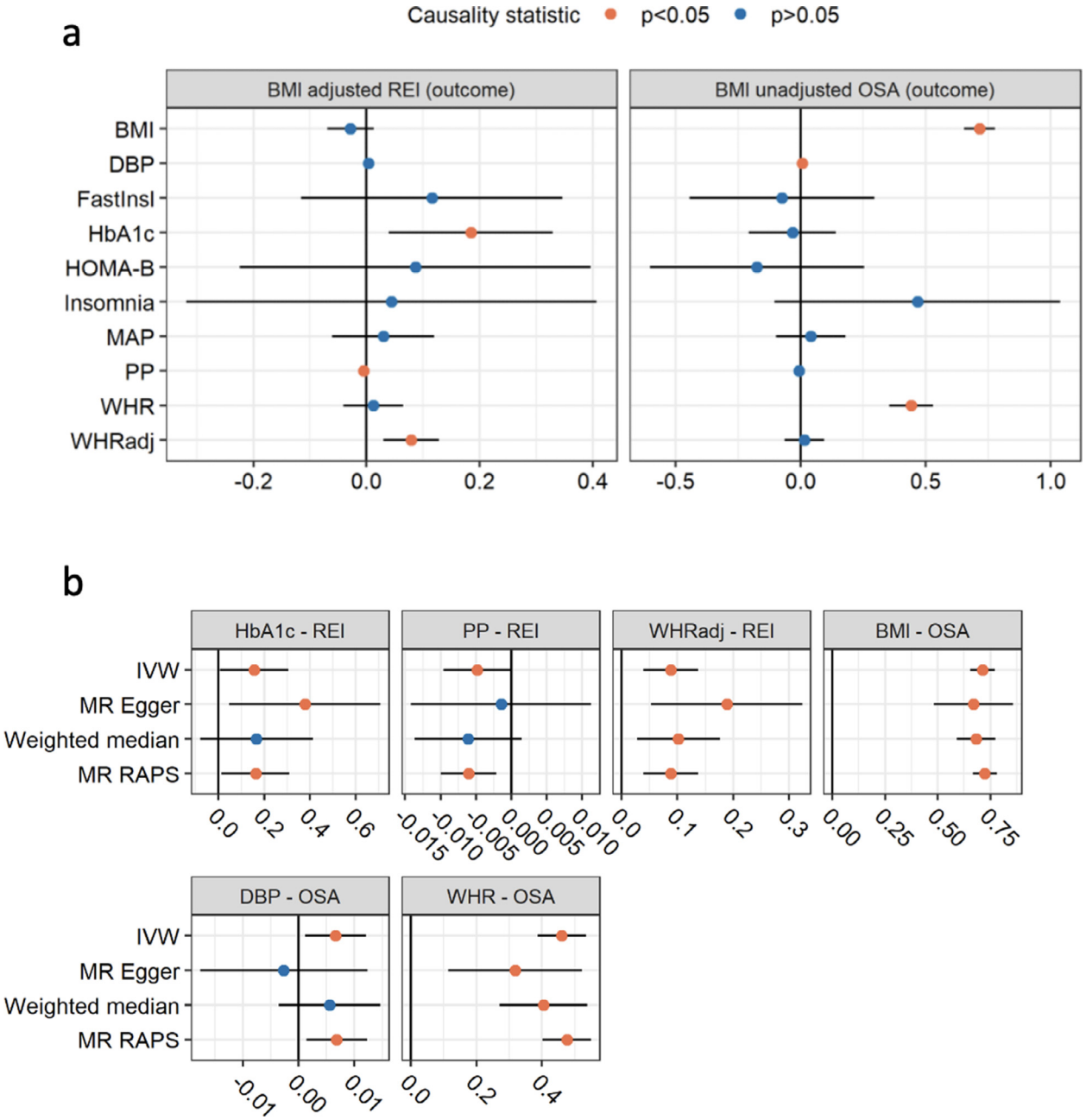

Figure 5. Estimated causal relationships between correlated traits as exposures and sleep apnoea traits as outcomes. MR analysis uses a two-sample approach with summary statistics from published GWAS. REI GWAS was adjusted for BMI, therefore causal effects are interpreted as independent of BMI. OSA GWAS was not adjusted for BMI, so estimated causal effect may be mediated by BMI. **a)**: MR analysis by inverse variance weighted (IVW) method for correlated traits as exposures and SDB traits of REI **(left)** or OSA (**right**) as outcomes. The clumping criteria for instrumental variant (IV) were as follows: distance=1000kb, r^2=0.1. **b):** sensitivity analysis for IVW significant pairs (p-value<0.05, where p-values were computed based on the IVW MR method with random effects), after outliers were identified using the RadialMR package and removed. For definitions of abbreviations refer to Figure 2, WHRadj=WHRadjBMI, a GWAS of WHR adjusted for BMI. Exact values are provided in supplementary table 12.

Files providing information on instrumental variables (SNPs) used in primary and secondary MR analyses are provided as Supplementary eTables 1-9. For SNPs used as instrumental variables for REI analyses as an exposure, we report approximate F-statistics[47] because they had p-values$>5\times10^{-8}$ in their GWAS. The F-statistics for each SNP and the mean F-statistics for used SNPs were all >10, indicating that it is appropriate to use these SNPs as instrumental variables of REI.

Discussion

While OSA co-occurs with multiple other conditions, it is unclear whether associations reflect shared environmental exposures, common genetic factors, causal or reverse causal associations. In this study, we applied a comprehensive set of genetic analyses to study the relationship of sleep apnoea with multiple health phenotypes in a large sample of Hispanic/Latino adults (Table 1). Of the studied phenotypes, 22 covering anthropometric, cardiometabolic, lung function, and insomnia phenotypes were genetically correlated with sleep apnoea. Among these, PRSs for anthropometric, blood pressure, glycaemic control, and insomnia phenotypes were associated with REI and/or OSA risk. A PRS for OSA was associated with anthropometric, blood pressure and glycaemic control traits. Finally, we detected a causal association of BMI, WHR, blood pressure and glycaemic phenotypes on OSA or REI.

Fat accumulation and obesity are among the strongest risk factors for OSA,[48] and our results support common genetic risk factors for these traits as well as a causal relationship between obesity (both BMI and WHR) and OSA. Moreover, the PRS of WHRadjBMI, constructed based on BMI-adjusted GWAS of WHR was associated with OSA even after adjusting for BMI. These results suggest that body fat distribution, independent of weight and height, is an important predictor, and a cause, of OSA. In addition to BMI and WHR, we identified 12 other phenotypes that were genetically correlated with REI in BMI-adjusted analyses, suggesting that OSA often shares genetic mechanisms apart from BMI with multiple other phenotypes. These traits contained lipids, blood pressure, heart rate, sleep duration, insomnia, and blood cell counts.

We also observed household correlations between OSA and several phenotypes, including anthropometric, glycaemic phenotypes, blood pressure, and sleep duration, suggesting influences of shared household exposures (e.g., environment, health behaviours) on the aggregation of OSA with other health conditions. For example, weight-loss dietary/lifestyle interventions (e.g., a Mediterranean diet or a Mediterranean lifestyle, low-energy diets) can benefit weight, glycaemic and blood pressure control, and OSA severity.[49–51] Other relevant exposures could relate to socioeconomic status, ambient environment of noise pollution, passive smoking, and urban physical features like walkability and population density.[52–55]

Observational studies have shown that OSA is associated with an increased incidence of hypertension and diabetes mellitus,[56] which may be attributed to OSA induced intermittent hypoxia, sleep fragmentation, and sympathetic nervous system activation.[57,58] Our analysis provides evidence for both shared genetic risk factors and causal associations for cardiometabolic phenotypes and sleep apnoea, where, in addition to anthropometric traits, other cardiometabolic traits appeared to be causal risk factors for OSA. The complex shared and causal associations may help partially explain the inconsistent evidence of treatment benefit for several cardiometabolic phenotypes with OSA treatment.[59–63] Our findings of a causal effect of diabetes (particularly HbA1c) on OSA is consistent with recent reports from longitudinal cohort studies,[64] and may reflect the effects of glucose dysregulation on upper airway function or body fat distribution. There are some experimental evidences from studies in rats, supporting the suggestive causal association of BP on OSA: one study reported a reduction in apnoea events followed by induction of hypotension.[65] Another study reported sleep disordered breathing in rats who were genetically predisposed for hypertension, despite being normotensive.[66] The finding of a stronger genetic association between glycaemic traits and sleep apnoea in non-obese individuals and between DBP and sleep apnoea in obese individuals suggests heterogeneity in the underlying mechanisms for sleep apnoea and cardiovascular disease among obese and non-obese individuals with sleep apnoea.

Snoring is a cardinal symptom of OSA. Genetic correlation analysis of snoring conducted by Campos et al. showed that sleep apnoea had the highest genetic correlation with snoring among analysed traits, and that snoring PRS was associated with probable sleep apnoea.[67] Campos et al. further reported genetic correlation between snoring and, similar to our results, BMI, lung function and cardiometabolic traits.[67] In MR analysis, Campos et al. reported a bidirectional causal association between snoring and BMI and heart attack, and identified snoring as a cause of increased blood pressure.[67] As snoring is a symptom, rather than an underlying condition, these results are hypothesized to be attributed to sleep apnoea. However, we did not identify a causal association of OSA on blood pressure.

Another interesting finding was that insomnia PRS was associated with REI and OSA, with findings driven by the non-obese stratum (though test for interaction was not significant). Mounting evidence has shown that sleep apnoea and insomnia often co-exist, an entity termed Comorbid Insomnia and Sleep Apnoea (COMISA).[68] We observed both genetic and household correlations between insomnia and REI. In the PRS association, genetically determined insomnia was associated with increased REI and OSA, rather than the

reverse direction. This could be due to limitations in GWAS of OSA (OSA cases misclassified as controls in the GWAS), limiting the data used for analysis. On the other hand, it is possible that individuals reporting insomnia in the original insomnia GWAS have insomnia due to their undiagnosed OSA, leading to the observed insomnia PRS association with OSA. Alternatively, an increased frequency of arousal from sleep due to insomnia may cause an elevated AHI, as the airway is most susceptible to collapse at the wake-sleep transition. Finally, we did not detect a robust causal relationship from either direction between OSA and insomnia. More research is needed to study the underlying mechanisms for the association between OSA and insomnia.

We applied several methods that rely on genetics to study relationships among phenotypes (Table 1). Our first approach was genetic correlation analysis. The strength of genetic correlation analysis in our setting is that essentially all HCHS/SOL individuals participated in both the genetics and the sleep study (individuals with genetic measures were a random subset of the HCHS/SOL cohort), and therefore the REI and OSA measures are unbiased by selection of individual with more severe disease, as is the case in studies based on sleep clinic or electronic health records.[12,69] Further, our genetic correlation estimates are robust to population structure, while population structure limits other analyses: for example, existing OSA GWAS was performed in population of Finnish Europeans,[12] potentially limiting the accuracy of its finding in another population, such as Hispanics/Latinos in the U.S. Therefore, genetic correlation using GWAS summary statistics would not accurately reflect Hispanics/Latinos.

The second genetic analysis approach was PRS analysis. PRSs are useful for genetic phenotype prediction on new individuals. PRS analysis alone does not measure causal association. For example, if OSA is highly affected by BMI, while OSA does not affect BMI, it is possible that a PRS of OSA may still predict BMI because the GWAS of OSA reflects some BMI associations. Interestingly, we found that a PRS of insomnia was associated with REI and OSA (in BMI unadjusted and adjusted models), while MR analysis suggests that insomnia is not causally associated with REI and OSA, demonstrating the potential difference in results between PRS and MR analyses.

Lastly, MR analysis specifically estimates causal relationship between phenotypes. It uses less SNPs compared to PRS, because its goal is to use SNPs as instrumental variables (IVs), that causally affect the exposure while not being associated with the outcome, and do not confound the exposure-outcome association. Several sensitivity analyses are used in MR analysis to address potential departures from the assumptions on the IVs.

Our study has a few limitations. First, our PRSs were not optimized specifically to Hispanics/Latinos due to limited available data, potentially attenuating the strength of associations using these PRSs. While we did have access to a multi-ethnic AHI GWAS, many of its participants were from HCHS/SOL, so we could not perform PRS association due to overfitting effect. Hispanics/Latinos are admixed with predominantly three continental genetic ancestries: European, African, and Amerindian. Studying the effect of varying LDs and differences in allele frequencies between GWAS and evaluation population on PRS, and potential differences in effect sizes by ancestry (due to gene-gene interactions, for example), also potentially leading to differences in PRS performance, is an active area of research. Still, we found in our recent work using summary statistics from large GWAS (hundreds of thousands of individuals) that PRS constructed based on GWAS in a population of a predominately European ancestry tend to generalize to Hispanics/Latinos, often with similar or only slightly attenuated performance.[70,71] If PRS have attenuated performance, we expect that estimated effect sizes will be biased towards the null compared to the effect sizes of optimal PRSs, rather than lead to false detections of associations. Second, the OSA GWAS that we used was based on ICD codes from a health care system, and is likely limited by under diagnosis of OSA. Therefore, the variants identified in this GWAS may be biased towards by diagnosis (e.g., preferential recognition of OSA in patients with obesity and co-morbidities). Our MR analysis was limited by the availability of GWAS. For example, while we were able to stratify PRS association analyses by obesity, we were not able to perform MR analysis within these strata. Third, GWAS summary statistics used were based on European, Asian, or multi-ethnic populations, and never the same population as the Finnish and multi-ethnic populations used in the OSA and REI GWAS, respectively. This may reduce the power of MR analysis as proxy SNPs to the causal ones may have different LD patterns with the causal SNPs in different population, so that estimated proxy SNP effect sizes should be a bit different across populations. We note that while this reduces power, it should not increase the chances of false associations. In particular, rigorous analysis with multiple secondary and sensitivity MR analysis supports our main findings. Fourth, while OSA is highly affected by BMI, the OSA GWAS in our study was based on a BMI unadjusted analysis. We also used an AHI GWAS, which was adjusted for BMI. However, the AHI GWAS was limited by small sample size, so that MR analysis with AHI as exposure has low statistical power. Finally, individuals with OSA are different than individuals without OSA on average (different age, sex, and BMI distributions). We do not expect that this affected the (age-adjusted) estimated genetic correlations, nor the association between PRS and OSA status, as the PRS does not depend on age. Still, there

could be complex relationships between the traits and the genetic associations used for PRS construction, so we cannot rule out that systematic differences in characteristics of individuals with and without OSA led to some biases in association estimates.

In conclusion, we found that REI is genetically correlated with multiple phenotypes, including phenotypes measuring adiposity, blood pressure, lipid levels, glycaemic control, lung function, and insomnia. Several "genetically determined" cardiometabolic and obesity phenotypes, defined according to their PRSs, are associated with REI and OSA and OSA PRS is also associated with glycaemic and adiposity traits, perhaps reflecting diagnosis bias where individuals with obesity and diabetes are more likely to be evaluated for OSA, potentially biasing the published OSA GWAS that was used for PRS construction. BMI and WHR presented robust causal effect on OSA. Blood pressure phenotypes PP and DBP, and the glycaemic trait HbA1c showed suggestive causal association with OSA or REI. The PRS relationships sometimes differed across individuals with and without obesity. Future research is needed to further resolve these complex associations and further clarify the genetic basis of OSA that is distinct from that of adiposity and obesity.

Contributors

Study concept and design: Y. Zhang and T. Sofer. Acquisition of data: M. Daviglus, P.C. Zee, J. Cai, and S. Redline. Analysis of data: Y. Zhang, M. Elgart, N. Kurniansyah, B.W. Spitzer, and T. Sofer. Interpretation of data: Y. Zhang, M. Elgart, N. Kurniansyah, B.W. Spitzer, H. Wang, N. Shah, M. Daviglus, P.C. Zee, J. Cai, D. J. Gottlieb, B.E. Cade, S. Redline, and T. Sofer. Drafting the manuscript: Y. Zhang and T. Sofer. Critical revision of the manuscript for important intellectual content: M. Elgart, N. Kurniansyah, B.W. Spitzer, H. Wang, D. Kim, N. Shah, M. Daviglus, P.C. Zee, J. Cai, D.J. Gottlieb, B.E. Cade, and S. Redline. T. Sofer and N. Kurniansyah had full access to all the data in the study and take responsibility for the accuracy and integrity of the work. T. Sofer and Y. Zhang were responsible for the decision to submit the manuscript. All authors read and approved the final version of the manuscript.

Data sharing statement

Summary statistics from MVP lipid GWAS are available from dbGaP by application to study accession phs001672. HCHS/SOL data are available via controlled-access application to dbGaP (study accession phs000810) or via approved data use agreement with the Data Coordinating Centre of the HCHS/SOL and the University of North Carolina. For more details see https://sites.cscc.unc.edu/hchs.

Declaration of interests

Dr. Gottlieb reports receiving fees for clinical consulting from Advance Medical and Teladoc, and membership on the Scientific Advisory Boards of Signifier Medical Technologies and Wesper, Inc. Dr. Redline reports consulting fees from Eli Lilly Inc, Jazz Pharma, and Apnimed Inc, serving as an unpaid board member in the Alliance for Sleep Apnoea Partners, and receipt of loaned oxygen concentrators from Philips Respironics and loaned polysomnography equipment from Nox Medical to a multi-site study. Dr. Zee reports consulting fees from Jazz Pharma, on the topic of treatment of excessive sleepiness in OSA; payment for a CME lecture from WEBMD/Medscape; unpaid membership in the advocacy committee of the Sleep Research Society, serving as an unpaid president of the World Sleep Society, and spousal ownership of stock or stock options of Teva. Dr. Shah reports receiving a grant from NHLBI R01HL143221, and a grant from the AASM Foundation 250-SR-21.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.ebiom.2022.104288.

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