

Overall Obesity Not Abdominal Obesity Has a Causal Relationship with Obstructive Sleep Apnea in Individual Level Data

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Objective: Both obstructive sleep apnea (OSA) and obesity are highly prevalent worldwide, and are intrinsically linked. Previous studies showed that obesity is one of the major risk factors for OSA, but the causality of the relationship is still unclear. The study was to investigate the causal relationships of overall obesity and abdominal obesity with OSA and its quantitative traits.

Methods: In this case-control study, a total of 7134 participants, including 4335 moderate-to-severe OSA diagnosed by standard polysomnography and 2799 community-based controls were enrolled. Anthropometric and biochemical data were collected. Mendelian randomization (MR) analyses were performed using the genetic risk score, based on 29 body mass index (BMI)- and 11 waist-hip-ratio (WHR)-associated single nucleotide polymorphisms as instrumental variables. The causal associations of these genetic scores with OSA and its quantitative phenotypes were analyzed.

Results: Obesity was strongly correlated with OSA in observational analysis ($\beta = 0.055$, $P = 3.7 \times 10^{-5}$). In MR analysis, each increase by one standard deviation in BMI was associated with increased OSA risk [odds ratio (OR): 2.21, 95% confidence interval (CI): 1.62–3.02, $P = 5.57 \times 10^{-7}$] and with 2.72-, 4.68-, and 3.25-fold increases in AHI, ODI, and MAI, respectively (all $P < 0.05$) in men. However, no causal associations were found between WHR and OSA risk or OSA quantitative traits in men and women.

Conclusion: Compared to abdominal obesity, overall obesity showed a causal relationship with OSA and its quantitative traits, especially in men.

Keywords: body mass index, Mendelian randomization, obesity, obstructive sleep apnea, waist-hip ratio

Backgrounds

Obstructive sleep apnea (OSA) is a common sleep disorder characterized by recurrent episodes of partial or complete upper airway obstruction that result in intermittent hypoxemia during sleep and sleep disruption.^{1,2} Individuals with OSA are at increased risk of cardiovascular diseases, diabetes, and other diseases with significant morbidity, underscoring the need to better understand the etiology of OSA.³

OSA involves complex interactions between genetic and environmental factors.⁴ A recent large-scale genome-wide association study (GWAS) of OSA based on the FinnGen Study dataset identified five genome-wide loci associated with OSA, most of which were correlated with obesity.⁵ Numerous studies showed that obesity is the strongest risk factor for

the development of OSA, and the incidence of obesity is relatively high among OSA patients.^{6,7} Obesity has been hypothesized to alter breathing during sleep via multiple mechanisms, including alteration of upper airway structure and function, and disturbance of the balance between respiratory drive and load compensation.^{8,9} OSA may predispose individuals to sleep deprivation, daytime somnolence, and poor sleep; it also increases sympathetic activation and insulin resistance, thereby potentially exacerbating obesity.^{7,10} Furthermore, OSA may be associated with changes in leptin, ghrelin, and orexin levels, as well as increased appetite and caloric intake, which also exacerbate obesity.^{9,11} Obesity and OSA appear to form a vicious circle and show a bidirectional relationship. However, most studies have used an observational design and could not demonstrate causal relationships due to confounding factors, reverse causation, or selection bias.

The gold standard for causal inference is the randomized controlled trial (RCT). However, RCTs are costly and take a great deal of time, and so can be impractical. An alternative approach to allow causal inference is Mendelian randomization (MR), which analyzes genetic variants that are randomly assorted during meiosis and unassociated with confounders to allow causality to be inferred for a given outcome.^{12,13} Genetic variants that promote increased weight would have several advantages over traditional measures of obesity, ie, they would not be related to potential confounding factors or affected by reverse causation, and may act as a lifelong markers of increased body weight.^{14,15} MR studies about sleep reported to date have concentrated on the relationships of insomnia, sleep disturbance, and sleep duration with stroke,¹⁶ cardiovascular disease,¹⁷ cancer,¹⁸ etc. With regard to sleep apnea, it was reported that OSA was a causal factor in breast cancer in women,¹⁹ cardiometabolic disease,⁵ and atrial fibrillation.²⁰ However, no MR studies on OSA and obesity have been reported to date. Therefore, the causal relationship between obesity and OSA is still unclear.

In the present case-control study, we performed MR analyses of individual-level data to explore the potential causal relationship between obesity and OSA diagnosed based on standard polysomnography (PSG). We identified 29 body mass index (BMI)-associated single nucleotide polymorphisms (SNPs) and 11 waist-hip-ratio (WHR)-associated SNPs, and constructed genetic risk scores (GRSs) for use as instrumental variables to examine whether general obesity and abdominal obesity contribute differentially to OSA.

Methods

Study Participants and Design

All OSA patients were recruited from the ongoing Shanghai Sleep Health Study (SSHS), performed in the sleep center of Shanghai Jiao Tong University Affiliated Sixth People's Hospital.²¹ Patients with suspected OSA referred to the SSHS were continuously enrolled, and anthropometric, genomic, and standard PSG data were collected from 2007 to 2018. Control subjects were enrolled from a community-based Han Chinese population. The inclusion criteria of controls were as follows: 1) without self-reported snoring problems; 2) without systemic diseases, cardiovascular disease; 3) without cancer, psychiatric diseases, and pregnancy. A total of 5438 patients with OSA confirmed by standard PSG, and 2989 community-based control subjects, were initially enrolled in this study. Subjects with missing data for > 15% of the SNPs, OSA quantitative traits, BMI, or WHR, and those with low genotyping call rates (< 95%), were excluded. Finally, 4335 patients with moderate-to-severe OSA and 2891 control participants were included in the analyses. Each participant provided written informed consent in accordance with the guidelines of the Ethics Committee of China. This study was performed in accordance with the Declaration of Helsinki and was approved by the Institutional Ethics Committee of Shanghai Jiao Tong University Affiliated Sixth People's Hospital.

Polysomnography and Definition of Sleep Events

Respiratory events were scored using a laboratory-based overnight PSG device (Alice 4 or 5; Respironics, Pittsburgh, PA, USA) according to the American Academy of Sleep Medicine (AASM) 2012 criteria;²² PSG recorded before 2012 were re-analyzed according to the same criteria. Apnea was defined as complete cessation of airflow lasting ≥ 10 s, and hypopnea as either a $\geq 50\%$ reduction in airflow for ≥ 10 s or a $< 50\%$ reduction accompanied by either a $\geq 4\%$ decrease in oxyhemoglobin saturation or arousal. The apnea-hypopnea index (AHI) was determined based on the number of apnea

and hypopnea events per hour during sleep. The total oxygen desaturation index (ODI) was defined as the total number of episodes of $\geq 4\%$ oxyhemoglobin desaturation during sleep (total sleep time was recorded in hours). The micro-arousal index (MAI) was defined as the average number of arousals per hour of sleep.

Anthropometric Information and Biochemical Measurements

Information was collected on sociodemographic factors, history of chronic disease and medications, and lifestyle-related factors. Trained investigators measured height, body weight, waist circumference (WC), and hip circumference (HC), and the average values of three measurements were used for the analysis. Height and weight were measured with a digital scale, with each participant standing straight wearing light clothing. WC was measured at a point midway between the lowest rib and iliac crest. HC was measured at the largest circumference of the buttocks. BMI was calculated as weight in kilograms divided by height in meters squared (kg/m^2). The WHR was calculated as WC/HC . For each patient, high-density lipoprotein (HDL-C), low-density lipoprotein (LDL-C), total cholesterol (TC), triglycerides (TG), and fasting blood glucose (FBG) levels were measured in the hospital laboratory using an autoanalyzer (H-7600; Hitachi, Tokyo, Japan). Serum fasting insulin (FIN) was measured using a human insulin-specific radioimmunoassay (Linco Research, St. Charles, MO, USA).

Selection of Genetic Loci, Genotyping, and Genetic Risk Score Construction

The Affymetrix Genome-Wide Human SNP Array 6.0 (SNP6.0) and Affymetrix Axiom™ Genome-Wide CHB Array Plates (CHB) were used for genotyping. Genotypes were then generated by Axiom Genotyping Algorithm v1 (Axiom GT1) and constitute our genetic database, which was described previously.²³ We selected previously reported BMI- and WHR-associated SNPs from a large-scale GWAS that had been replicated in East Asian populations.^{24–27} Some studies perform the analysis with the largest WHR data from the UK Biobank²⁸ and found over 941 variants for BMI.²⁹ However, a World Health Organization (WHO) expert consultation suggested that the associations among BMI, body fat percentage, and health risks differ between Asian and European populations.³⁰ Therefore, BMI thresholds must be tailored for Asian populations because they show markedly different obesity-related characteristics from non-Asian populations.³¹ Therefore, this study used SNPs demonstrated to be relevant in East Asian populations. These SNPs were described in our previous report.³² A total of 32 BMI-associated SNPs and 13 WHR-associated SNPs were included in the analysis. SNPs with a high missing genotype call rate ($> 5\%$) or low minor allele frequency (< 0.01) were excluded, along with those out of Hardy–Weinberg equilibrium (HWE). After filtering variants in our genomic database in linkage disequilibrium with each other in the same regions ($r^2 > 0.8$), we focused on 29 independent BMI-associated and 11 WHR-associated SNPs for the case group. For the control group, the SNPs were genotyped using a MassARRAY Compact Analyzer (Sequenom, San Diego, CA, USA). Finally, BMI SNPs SEC16B rs574367, TNNI3K rs1514175, PTBP2 rs1555543, NEGR1 rs2568958, RBJ rs713586, TMEM18 rs6548238, ITIH4-AS1 rs2535633, ETV5 rs7647305, GNPDA2 rs10938397, PCSK1 rs261967, POC5 rs2112347, TFAP2B rs987237, CDKAL1 rs9356744, KLF9 rs11142387, LRRN6C-LINGO2 rs10968576, NT5C2 rs11191580, BDNF rs6265, MTCH2 rs3817334, RPL27A rs4929949, ALDH2 rs671, FAIM2 rs7138803, MTIF3 rs4771122, MAP2K5 rs2241423, FTO rs1558902, SH2B1 rs7498665, GP2 rs12597579, MC4R rs17782313, KCTD15 rs29941, TMEM160 rs3810291 and WHR SNPs TBX15 rs984222, LYPLAL1 rs4846567, GRB14 rs10195252, VEGFA rs6905288, RREB1 rs6931262, NFE2L3 rs1055144, MSC rs12679556, ABCA1 rs10991437, SFXN2 rs7917772, CMIP rs2925979, GDF5 rs224333 were included.

For GRS construction, we used an additive genetic model for each variant, applying linear weighing of 0, 1, and 2 to genotypes containing 0, 1, and 2 risk alleles, respectively. The weighted GRS was calculated by weighting each risk allele according to the effect size, and then adding the scores (the effect size of the SNP after increasing BMI and WHR, determined based on previous Asian studies on obesity).

Statistical Analysis

MATLAB 8.1 (MathWorks, Natick, MA, USA), SPSS 21.0 (IBM Corp., Armonk, NY, USA), GraphPad Prism 7.0 (GraphPad Software Inc., La Jolla, CA, USA), PLINK (<http://zzz.bwh.harvard.edu/plink/ld.shtml>), and R (R

Development Core Team, Vienna, Austria) software were used for database management and statistical analysis. The general characteristics of the participants are provided as mean \pm SD for continuous variables and frequency (%), n) for categorical variables. A multiple linear regression model adjusted for age, sex, and BMI was used to test for associations among BMI-GRS, WHR-GRS, and clinical characteristics. BMI-GRS and WHR-GRS were modelled as continuous variables, and a general linear regression model was applied to test the associations with quantitative traits.

In MR analysis, we used BMI-GRS and WHR-GRS as instrumental variables to measure the strength of the causal relationship between obesity and OSA. The odds ratios (ORs) for instrumental variables were derived using the Wald-type estimator.³³ Linear associations of BMI-GRS, WHR-GRS and obesity were assessed using multivariable linear regression models (adjusted for age and sex when focusing on BMI, and for age, sex, and BMI when focusing on WHR). Multivariable logistic regression models were used to assess the associations of obesity and obesity-related GRS with the risk of OSA. The β values of the regressions were used to calculate causal effect estimates (β_e) between obesity and OSA, as follows: $\beta_e = \beta_{\text{GRS-OSA}}/\beta_{\text{GRS-BMI/WHR}}$. OR_e was calculated as $\exp(\beta_e)$. Multivariable logistic regression models were used to assess the associations of BMI-GRS and WHR-GRS with AHI, ODI, and MAI. β_e was calculated as $\beta_{\text{GRS-AHI/ODI/MAI}}/\beta_{\text{GRS-BMI/WHR}}$. P_e was determined using the t-statistic. The inverse variance method was applied for Egger regression, using a formula described in detail previously.³⁴

Mendelian randomization R package were used to perform sensitivity analysis and pleiotropy. Power calculations were computed with online tool: <https://shiny.cnsgenomics.com/mRnd/>.

Results

General Characteristics

The general characteristics of the 7134 participants in this study (4335 patients with moderate-to-severe OSA and 2799 community-based control subjects) are presented in Table 1. Participants with OSA were more obese and had worse dyslipidemia than the controls ($P < 0.05$). The OSA group had a higher proportion of men than the control group (85.3%

Table 1 Basic Characteristics of the Enrolled Subjects

	Control (N=2799)	Case (N=4335)	P
Age (years)	52 \pm 7	45 \pm 12	<0.001
Male (%)	1280 (45.7%)	3714 (85.3%)	<0.001
Height (m)	1.63 \pm 0.08	1.71 \pm 0.07	<0.001
Weight (Kg)	65.3 \pm 11.4	81.5 \pm 14.0	<0.001
BMI (Kg/m ²)	24.4 \pm 3.4	27.9 \pm 4.0	<0.001
WC (cm)	83.5 \pm 10.2	99.4 \pm 10.5	<0.001
HC, (cm)	94.4 \pm 7.3	103.3 \pm 8.4	<0.001
WHR	0.88 \pm 0.07	0.96 \pm 0.06	<0.001
FBG (mmol/L)	5.55 \pm 1.55	5.69 \pm 1.30	<0.001
FIN (uU/mL)	10.49 \pm 6.61	15.18 \pm 12.66	<0.001
TC (mmol/L)	5.30 \pm 1.35	4.89 \pm 1.00	<0.001
TG (mmol/L)	1.81 \pm 1.64	2.23 \pm 1.95	<0.001
HDL-C (mmol/L)	1.38 \pm 0.37	1.04 \pm 0.24	<0.001
LDL-C (mmol/L)	2.97 \pm 1.02	3.06 \pm 0.83	<0.001
AHI	–	49.23 \pm 21.58	–
ODI	–	50.00 \pm 23.83	–
MAI	–	36.33 \pm 22.60	–

Notes: The data are presented as means and standard deviation and categorical data as the number (percentage). Differences in the baseline characteristics between the two groups were examined using t-test and Chi-square test.

Abbreviations: BMI, body mass index; WC, waist circumference; HC, hip circumference; WHR, waist/hip ratio; FBG, fasting blood glucose; FIN, fasting serum insulin; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein; cholesterol; AHI, apnoea-hypopnea index; ODI, oxygen desaturation index; MAI, micro-arousal index.

vs 45.7%, $P < 0.05$). The descriptive statistics for males and females separately were shown in [Table S1](#). The 29 BMI- and 11 WHR-associated SNPs selected for GRS construction are shown in [Table 2](#), respectively. The data for the SNPs, including gene, chromosome, position, minor alleles, major alleles, risk alleles, and effect sizes, are listed. None of the SNPs failed quality control, with minor allele frequencies were < 0.5 and $P_{HWE} > 0.05$.

Table 2 Characteristics of BMI- and WHR- Associated SNPs

SNP	CHR	Gene	Position	Minor Allele	Major Allele	Risk Allele	MAF	Effect Size	P_{H-E}
BMI SNPS									
rs574367	1	SEC16B	177873210	T	G	T	0.196	0.059	0.625
rs1514175	1	TNNI3K	74991644	C	T	T	0.231	0.029	0.868
rs1555543	1	PTBP2	96944797	A	C	C	0.124	0.005	0.785
rs2568958	1	NEGR1	72765116	G	A	A	0.077	0.023	0.455
rs713586	2	RBJ	25158008	C	T	C	0.464	0.022	0.090
rs6548238	2	TMEM18	634905	T	C	C	0.084	0.063	0.878
rs2535633	3	ITIH4-AS1	52859630	G	C	C	0.404	0.029	0.980
rs7647305	3	ETV5	185834290	T	C	C	0.053	0.026	0.723
rs10938397	4	GNPDA2	45182527	G	A	G	0.305	0.037	0.675
rs261967	5	PCSK1	95850250	G	T	G	0.420	0.038	0.662
rs2112347	5	POC5	75015242	T	G	T	0.424	0.018	0.731
rs987237	6	TFAP2B	50803050	G	A	G	0.165	0.029	0.667
rs9356744	6	CDKALI	20685486	C	T	T	0.392	0.034	0.106
rs11142387	9	KLF9	72998332	C	A	C	0.321	0.04	0.276
rs10968576	9	LRRN6C-LINGO2	28414339	G	A	G	0.211	0.009	0.775
rs11191580	10	NT5C2	104906211	C	T	C	0.291	0.03	0.909
rs6265	11	BDNF	27679916	A	G	G	0.471	0.05	0.191
rs3817334	11	MTCH2	47650993	T	C	T	0.320	0.024	0.073
rs4929949	11	RPL27A	8604593	C	T	T	0.416	0.018	0.130
rs671	12	ALDH2	112241766	A	G	G	0.209	0.038	0.123
rs7138803	12	FAIM2	50247468	A	G	A	0.280	0.02	0.977
rs4771122	13	MTIF3	28020180	G	A	G	0.184	0.005	0.527
rs2241423	15	MAP2K5	68086838	G	A	G	0.402	0.031	0.237
rs1558902	16	FTO	53803574	A	T	A	0.127	0.076	0.239
rs7498665	16	SH2B1	28883241	G	A	G	0.125	0.031	0.044
rs12597579	16	GP2	20257867	T	C	C	0.269	0.041	0.856
rs17782313	18	MC4R	57851097	C	T	C	0.219	0.055	0.729
rs29941	19	KCTD15	34309532	C	T	C	0.242	0.007	0.270
rs3810291	19	TMEM160	47569003	A	G	A	0.290	0.042	0.013
WHR SNPS									
rs984222	1	TBX15	119503843	C	G	G	0.413	0.025	0.463
rs4846567	1	LYPLALI	219750717	T	G	G	0.293	0.021	0.753
rs10195252	2	GRB14	165513091	C	T	T	0.099	0.022	0.690
rs6905288	6	VEGFA	43758873	G	A	A	0.266	0.025	0.094
rs6931262	6	RREB1	7217517	T	C	T	0.196	0.021	0.792
rs1055144	7	NFE2L3	25871109	A	G	A	0.431	0.012	0.809
rs12679556	8	MSC	72514228	T	G	G	0.245	0.021	0.479
rs10991437	9	ABCA1	107735920	A	C	A	0.363	0.023	0.125
rs7917772	10	SFXN2	104487443	A	G	A	0.480	0.02	0.306
rs2925979	16	CMIP	81534790	A	G	A	0.410	0.02	1
rs224333	20	GDF5	34023962	A	G	A	0.271	0.029	0.021

Abbreviations: SNP, single nucleotide polymorphism; CHR, Chromosome; MAF, Minor allele frequency; P_{H-E} , P value for Hardy–Weinberg equilibrium.

Associations of SNPs with Clinical Traits and OSA

The linear associations of BMI- and WHR-associated SNPs with the clinical traits of all subjects and OSA are listed in [Table 3](#). Of all subjects, we found BMI-related SNPs rs574367, rs6548238, rs7647305, rs10938397, rs261967, rs2112347, rs206936, rs10968576, rs6265, rs7138803, rs1558902, rs17782313, rs3810291, rs11671664 were significantly correlated with BMI ($p < 0.05$), rs2568958 and rs4771122 were correlated with TC ($\beta = -0.08$, $p = 0.013$; $\beta = -0.045$, $p = 0.043$; respectively), rs671, rs7138803 and rs4771122 were associated with TG (all $p < 0.05$), rs12597579 was associated with LDL ($\beta = 0.036$, $p = 0.038$), rs574367, rs6548238, rs9356744, rs6265, rs2237892, rs1558902, rs12597579 and rs17782313 were associated with FBG (all $p < 0.05$), rs574367, rs6548238, rs7647305, rs9356744, rs6265, rs2237892, rs671, rs7138803, rs1558902 were associated with FIN (all $p < 0.05$), when adjusted for age and sex. For WHR SNPs, rs984222 was associated with WHR ($\beta = -0.004$, $p = 1.40 \times 10^{-5}$), rs4846567 and rs10195252 were associated with FIN ($\beta = -0.52$, $p = 5.3 \times 10^{-4}$; $\beta = -0.52$, $p = 0.025$, respectively), rs6905288 was associated with TG and HDL ($\beta = -0.14$, $p = 6.4 \times 10^{-5}$; $\beta = 0.018$, $p = 0.002$, respectively), rs6931262 was associated with WHR and LDL ($\beta = 0.002$, $p = 0.046$; $\beta = 0.041$, $p = 0.032$; respectively), rs1055144 was associated with FIN ($\beta = 0.28$, $p = 0.04$), rs10991437 was associated with WHR ($\beta = 0.002$, $p = 0.014$); rs7917772 was associated with LDL and FBG ($\beta = 0.030$, $p = 0.045$; $\beta = 0.055$, $p = 0.014$, respectively) when adjusted for age, sex and BMI.

Fewer BMI- and WHR-associated SNPs were related to clinical traits in participants with OSA ([Tables S2](#) and [S3](#)). The associations of the BMI- and WHR-associated SNPs with OSA risk are shown as forest plots in [Figures S1](#) and [S2](#). BMI-SNPs rs713586, rs10938397, rs2112347, rs2241423 and rs1558902 increased the risk of OSA (OR=1.085, 95% confidence interval [CI]:1.006–1.171, $p = 0.0347$; OR=1.129, 95% CI:1.039–1.227, $p = 0.0043$; OR= 1.113, 95% CI:1.030–1.204, $p = 0.0071$; OR=1.087, 95% CI:1.005–1.176, $p = 0.038$; OR=1.172, 95% CI:1.044–1.316, $p = 0.0073$, respectively) ([Figure S1](#)). WHR-SNPs rs4846567 and rs10195252 decreased the risk of OSA (OR= 0.856, 95% CI:0.782–0.936, $p = 6.67 \times 10^{-4}$; OR=0.850, 95% CI:0.742–0.974, $p = 0.019$, respectively) ([Figure S2](#)).

Associations of BMI and WHR with OSA: MR Analysis

Linear regressions showed 7.2% variance for the association between the BMI GRS and the exposure variable (BMI) after adjustment for age and sex. The distributions of BMI and BMI-GRS are shown in [Figure S3](#). The correlations between GRS and clinical traits are shown in [Table S4](#). BMI-GRS was associated with FIN ($\beta = 0.071$, $p = 0.045$) and BMI ($\beta = 0.55$, $p = 2.7 \times 10^{-5}$). [Figure 1A](#) compares the associations of BMI GRS, as an observed and instrumental variable, with OSA after adjustment for age and sex. The association was also studied in men ([Figure 1B](#)) and women separately ([Figure 1C](#)). In all subjects, BMI was significantly associated with OSA (OR = 1.279, 95% CI: 1.256–1.302, $p = 1.17 \times 10^{-153}$) after adjusting for age and sex. MR analysis showed a significant association between BMI-GRS and OSA risk (OR = 1.64, 95% CI: 1.148–2.349, $p = 0.0066$) ([Figure 1A](#)). The p -value of the Egger regression was 0.042. The risk of OSA was higher in men than in all subjects (OR = 2.21, 95% CI: 1.622–3.018, $p = 5.57 \times 10^{-7}$) ([Figure 1B](#)). BMI-GRS was not associated with BMI in the MR analysis of women ($\beta = -0.051$, $p = 0.07$) ([Figure 1C](#)).

Linear regressions showed 46.5% variance for the association between the WHR GRS and the exposure variable (WHR) after adjustment for age, sex and BMI. The distributions of WHR and WHR-GRS are shown in [Figure S4](#). The MR analysis of WHR and OSA in all subjects, men and women, respectively were shown [Figure 1D](#), [Figure 1E](#) and [F](#). We found no causal relationships between WHR and OSA (OR = 2.257, 95% CI: 0.450–11.329, $p = 0.3226$) ([Figure 1D](#)). In the observational analysis, WHR was significantly associated with OSA (OR = 3.001, 95% CI: 2.730–3.298, $p = 1.06 \times 10^{-114}$) for all subjects after adjustment for age, sex, and BMI ([Figure 1D](#)); OR = 2.669, 95% CI: 2.360–3.019, $p = 4.75 \times 10^{-55}$ in men after adjustment for age and BMI ([Figure 1E](#)); OR = 3.236, 95% CI: 2.781–3.766, $p = 4.05 \times 10^{-52}$ in women after adjustment for age and BMI ([Figure 1F](#)).

Associations of BMI and WHR with OSA Quantitative Traits: MR Analysis

The associations of BMI with OSA quantitative traits, ie, AHI, ODI, and MAI, were analyzed ([Figure 2](#)). For all subjects, BMI was significantly associated with AHI ([Figure 2A](#)), ODI ([Figure 2B](#)), and MAI ([Figure 2C](#)) ($\beta = 1.723$, $p = 7.07 \times 10^{-106}$; $\beta = 2.206$, $p = 2.68 \times 10^{-140}$; $\beta = 0.862$, $p = 2.88 \times 10^{-22}$). In MR analysis, each 1 SD increase in BMI-GRS (4.0 kg/m²) was

Table 3 The Linear Associations Between BMI- and WHR- Associated SNPs with Related Clinical Characteristics

SNP	BMI/WHR		TC		TG		HDL		LDL		FBG		FIN	
	β	ρ	β	ρ	β	ρ	β	ρ	β	ρ	β	ρ	β	ρ
BMI- associated SNPs*														
rs574367	0.33	1.2×10^{-5}	-0.01	0.64	0.057	0.14	-0.005	0.48	-0.011	0.56	0.062	0.033	0.41	0.038
rs1514175	0.017	0.83	0.0085	0.68	0.0097	0.79	0.005	0.44	0.011	0.56	0.022	0.43	0.3	0.1
rs1555543	-0.1	0.31	0.015	0.57	-0.044	0.35	0.017	0.028	0.005	0.83	-0.034	0.33	-0.43	0.068
rs2568958	-0.14	0.26	-0.08	0.013	-0.11	0.08	0.008	0.42	-0.051	0.074	-0.045	0.3	-0.38	0.18
rs713586	0.085	0.2	-0.017	0.34	-0.022	0.49	-0.004	0.44	0.012	0.44	0.018	0.43	0.017	0.91
rs6548238	-0.52	2.0×10^{-5}	0.0004	0.99	-0.003	0.96	0.011	0.25	1.8×10^{-4}	0.1	-0.085	0.041	-0.57	0.038
rs2535633	0.11	0.12	0.014	0.43	-0.01	0.76	-0.0005	0.92	0.017	0.29	-0.003	0.9	0.23	0.15
rs7647305	-0.35	0.021	-0.015	0.7	-0.01	0.15	0.022	0.057	-0.036	0.3	-0.037	0.48	-0.67	0.047
rs10938397	0.19	0.01	-0.016	0.4	-0.006	0.85	-0.013	0.025	-0.031	0.059	-0.027	0.29	-0.16	0.35
rs261967	0.26	1.3×10^{-5}	-0.009	0.6	0.033	0.29	-0.014	0.007	0.002	0.92	0.018	0.44	0.23	0.13
rs2112347	0.19	0.005	-0.03	0.09	-0.004	0.89	-0.004	0.45	-0.016	0.3	0.012	0.6	0.13	0.4
rs206936	-0.15	0.023	0.022	0.21	-0.042	0.17	0.013	0.013	0.021	0.17	-0.012	0.61	0.18	0.24
rs987237	0.18	0.051	0.015	0.53	-0.004	0.92	-0.005	0.46	0.024	0.24	0.029	0.36	0.25	0.23
rs9356744	-0.049	0.48	-0.025	0.16	-0.005	0.87	-0.003	0.53	-0.015	0.34	0.089	1.9×10^{-4}	-0.37	0.02
rs11142387	-0.068	0.35	0.021	0.27	0.012	0.72	0.002	0.78	0.021	0.2	0.0006	0.98	-0.18	0.29
rs10968576	0.18	0.032	-0.027	0.2	0.032	0.4	-0.007	0.28	-0.006	0.76	0.033	0.24	0.3	0.11
rs11191580	-0.05	0.5	-0.029	0.13	-0.016	0.63	-0.002	0.73	-0.018	0.28	-0.047	0.062	0.049	0.77
rs6265	-0.19	0.0047	0.011	0.51	-0.04	0.2	0.01	0.051	0.01	0.52	-0.08	4.4×10^{-4}	-0.33	0.033
rs2237892	0.073	0.318	-0.017	0.35	-0.004	0.9	-0.005	0.34	-0.025	0.13	-0.14	4.0×10^{-8}	0.43	0.01
rs3817334	0.036	0.62	0.012	0.51	0.005	0.89	0.001	0.8	0.002	0.91	-0.011	0.66	0.09	0.59
rs4929949	0.066	0.33	0.0024	0.89	0.007	0.83	-0.008	0.11	0.007	0.63	0.014	0.55	0.013	0.93
rs671	-0.16	0.052	-0.028	0.18	-0.1	0.007	-0.005	0.44	0.02	0.29	-0.021	0.46	0.38	0.043
rs7138803	0.31	2.8×10^{-5}	0.017	0.38	0.082	0.017	-0.015	0.01	0.002	0.9	0.022	0.4	0.46	0.008
rs4771122	0.084	0.34	-0.045	0.043	-0.094	0.02	0.003	0.61	-0.023	0.24	0.003	0.92	0.2	0.32
rs2241423	0.12	0.084	0.032	0.074	-0.023	0.46	0.002	0.73	0.018	0.25	0.031	0.2	0.11	0.5
rs1558902	0.43	1.7×10^{-5}	0.033	0.21	0.03	0.52	-0.006	0.46	0.019	0.4	0.089	0.01	0.66	0.004
rs7498665	0.068	0.51	0.035	0.19	0.011	0.81	-0.011	0.19	0.016	0.48	0.037	0.3	-0.053	0.83
rs12597579	0.042	0.59	0.011	0.58	-0.025	0.47	0.0004	0.94	0.036	0.038	-0.055	0.034	-0.17	0.34
rs17782313	0.27	8.6×10^{-4}	0.002	0.93	0	0.81	-0.002	0.8	-0.006	0.76	0.063	0.026	-0.036	0.85
rs29941	0.06	0.45	-0.031	0.13	-0.015	0.69	-0.001	0.86	-0.023	0.2	-0.016	0.56	0.15	0.42
rs3810291	0.23	0.0021	0.012	0.54	0.014	0.68	-0.002	0.68	-0.016	0.36	-0.0004	0.99	0.11	0.53
rs11671664	-0.21	0.0024	0.032	0.074	0.026	0.41	0.008	0.13	0.009	0.56	-0.004	0.87	0.073	0.64

(Continued)

Table 3 (Continued).

SNP	BMI/WHR		TC		TG		HDL		LDL		FBG		FIN	
	β	ρ	β	ρ	β	ρ	β	ρ	β	ρ	β	ρ	β	ρ
WHR- associated SNPs [#]														
rs984222	-0.004	1.4×10^{-5}	0.002	0.9	-0.044	0.16	0.005	0.3	0.011	0.48	0.017	0.46	0.061	0.66
rs4846567	-0.001	0.21	-0.001	0.97	0.047	0.16	0.004	0.45	-0.024	0.15	-0.006	0.8	-0.52	5.3×10^{-4}
rs10195252	-0.003	0.077	0.014	0.63	0.049	0.34	0.004	0.67	-0.02	0.44	-0.06	0.11	-0.52	0.025
rs6905288	-0.0001	0.91	0.019	0.35	-0.14	6.4×10^{-5}	0.018	0.002	0.03	0.09	-0.022	0.4	-0.24	0.14
rs6931262	0.002	0.046	0.015	0.49	0.012	0.75	-0.012	0.05	0.041	0.032	0.022	0.44	0.25	0.14
rs1055144	0	0.95	0.006	0.73	-0.003	0.92	0.007	0.13	0.017	0.26	0.021	0.35	0.28	0.04
rs12679556	-0.0005	0.6	0.012	0.57	-0.036	0.32	0.004	0.49	0.013	0.46	-0.041	0.12	-0.088	0.59
rs10991437	0.002	0.014	0.026	0.16	0.044	0.17	-0.008	0.14	-0.014	0.38	-0.022	0.36	0.034	0.81
rs7917772	0.0009	0.31	0.018	0.31	-0.037	0.22	0	1	0.03	0.045	0.055	0.014	0.1473	0.28
rs2925979	0.0006	0.5	-0.019	0.29	0.023	0.46	-0.009	0.09	-0.021	0.18	-0.027	0.24	-0.23	0.1
rs224333	0	0.98	-0.007	0.72	0.061	0.083	-0.011	0.06	0.009	0.6	0.028	0.28	-0.28	0.073

Notes: *Adjust for age, gender. [#]Adjust for age, gender, BMI.

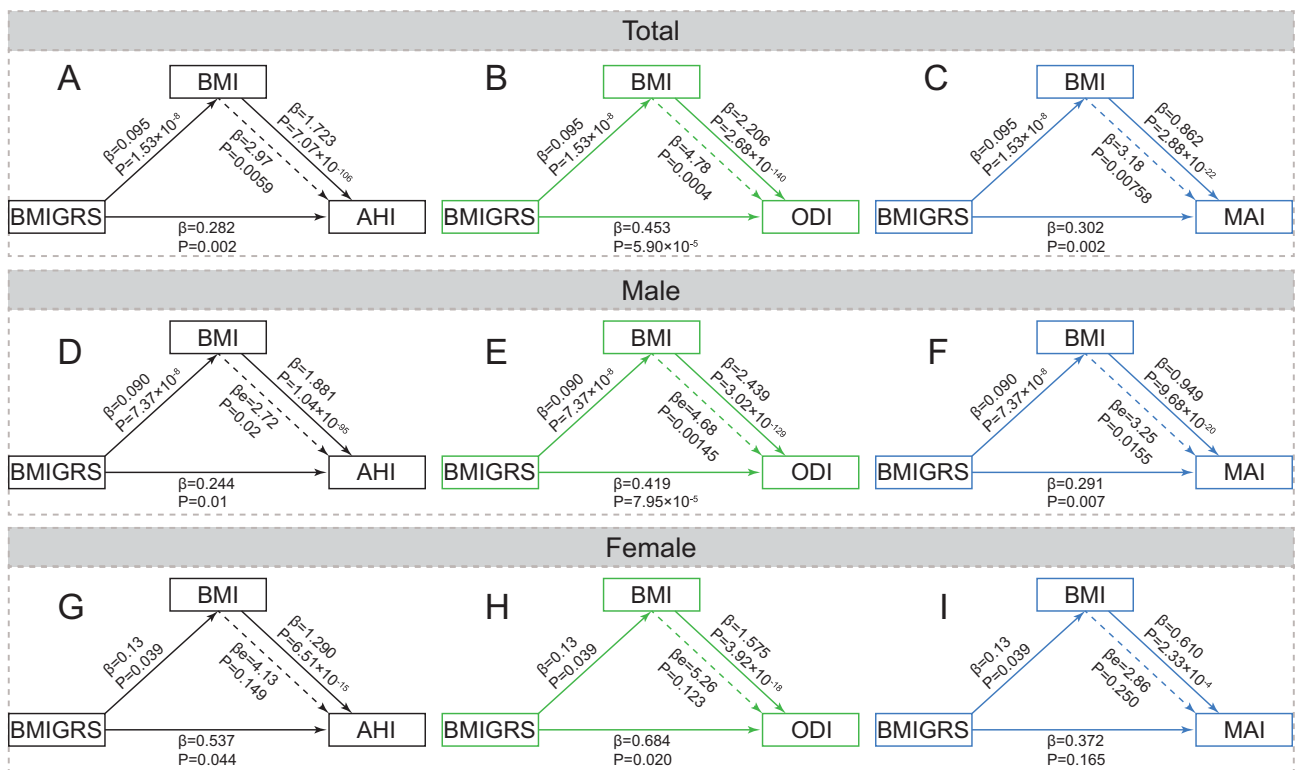
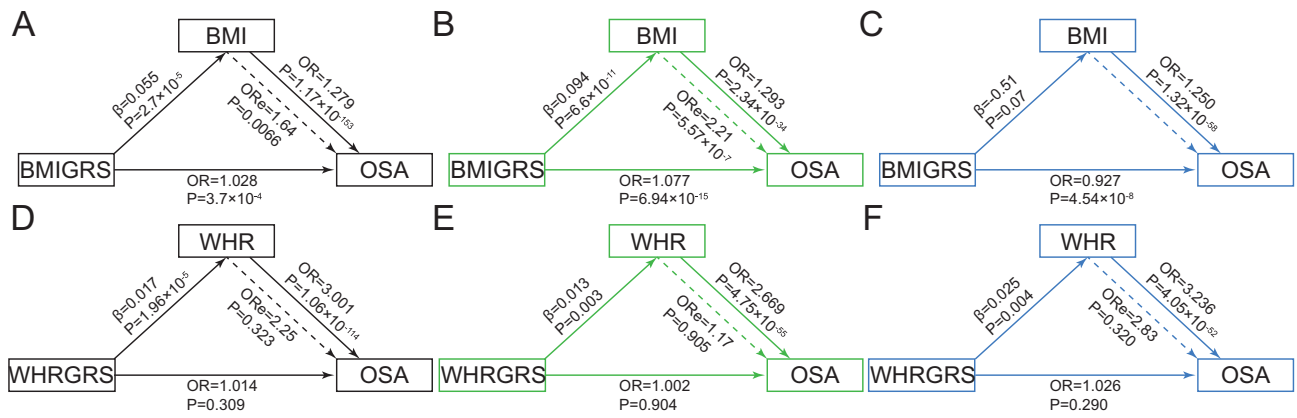


Figure 2 Mendelian randomization analysis for the association of BMI GRS and OSA quantitative traits. (A) BMI GRS and AHI for total population; (B) BMI GRS and ODI for total population; (C) BMI GRS and MAI for total population; (D) BMI GRS and AHI for men; (E) BMI GRS and ODI for men; (F) BMI GRS and MAI for men; (G) BMI GRS and AHI for women; (H) BMI GRS and ODI for women; (I) BMI GRS and MAI for women.

associated with an increased risk of OSA, based on the AHI ($\beta = 2.973$, standard error of the mean [SEM] = 1.079, $\rho = 0.00588$) (Figure 2A), ODI ($\beta = 4.779$, SEM = 1.349, $\rho = 0.0004$) (Figure 2B), and MAI ($\beta = 3.180$, SEM = 1.191, $\rho = 0.00758$) (Figure 2C). For men, an increase in BMI-GRS was also associated with increased OSA, based on the AHI ($\beta = 2.723$, SEM = 1.171, $\rho = 0.020$) (Figure 2D), ODI ($\beta = 4.677$, SEM = 1.467, $\rho = 0.00145$) (Figure 2E), and MAI ($\beta = 3.245$, SEM = 1.340, $\rho = 0.0155$) (Figure 2F). However, no associations were found between BMI and AHI (Figure 2G), ODI (Figure 2H), or MAI (Figure 2I) in women ($\rho > 0.05$) when adjusted for age. There is a stronger association between BMI, BMI-GRS with ODI compared to AHI. However, no associations were found between WHR-GRS with AHI, ODI, and MAI

in all subjects ([Figure S5A–C](#)), men ([Figure S5D–F](#)) and women ([Figure S5G–I](#)) as the instrumental variables (WHR- GRS) did not met the MR assumptions.

Egger results and Power Calculations

The MR-egger results of BMI, WHR SNPs and OSA, OSA related traits were shown in [Table S5](#). The power calculations BMI-GRS, WHR GRS and OSA, OSA related traits were shown in [Table S6](#).

Discussion

In this study, we demonstrated that general obesity is a genetic risk factor for OSA, especially in men. Central obesity was not causally related to OSA in women or men.

As an instrumental rather than exposure variable, GRS has frequently been used to predict outcomes.¹⁴ A number of studies have used the obesity GRS to predict the risk of various diseases, however, there have been fewer studies on the causal relationship between obesity and OSA. In a GWAS of OSA including 16,761 OSA patients from the FinnGen Study dataset, which used 64 independent BMI-associated SNPs as instrumental variables to predict OSA, Strausz et al discovered that BMI was a strong predictor of OSA,⁵ consistent with our results. However, their study identified OSA patients from nationwide health registries, rather than through standard PSG. In the present study, we used laboratory-based PSG and relatively complete obesity phenotype data to perform MR analyses.

Some observational studies have suggested that WHR is associated with OSA.^{35,36} It has been reported that the visceral adiposity index is a good marker of metabolic syndrome, but not of OSA.³⁷ Meanwhile, decreases in end-expiratory lung volume appear to be related to increased overall chest wall fat, rather than to increased fat in any particular region of the chest wall.³⁸ Obesity is characterized by fatty deposits around the neck; this promotes pharyngeal collapse, which is independently associated with AHI and may be a determinant of the severity of OSA.^{39,40} Weight loss reduces pharyngeal fat pads and can improve symptoms of OSA.³⁹ Results showing that overall obesity, rather than abdominal obesity, may be associated with OSA, consistent with our conclusions. Further studies are required to validate the lack of a causal relationship between abdominal obesity and OSA.

We also found that the associations between BMI, BMI-GRS with ODI were stronger than AHI. There were multiple studies showing that ODI was a more sensitive and valuable predictor to detect OSA^{41,42} which was consistent with our results. Oxygen desaturation parameters were better markers for cardiovascular disease⁴³ and OSA associated morbidity and mortality compared to the AHI.^{44,45} In turn, it was reported that BMI influences the accuracy of ODI for OSA diagnosis.⁴⁶ Obesity influences the severity of blood oxygen desaturation during apnea and hypopnea events.⁴⁷ Therefore, more attention should be paid to the causal relationship between hypoxia and obesity, and the corresponding mechanism is worth exploring.

There are sex differences in the manifestations and progression of OSA, men have a two- or three fold higher risk of OSA compared to women, and the underlying mechanisms of these differences are complex.^{3,48} There may be sex differences in anatomical and physiological features of the upper airways, especially with respect to the modulatory effects of sex hormones on breathing control, as well as sex differences in fat distribution, upper airway size and craniofacial morphology.^{48,49} In women, fat tends to be preferentially deposited around the abdomen rather than the neck.⁵⁰ Also, women have more stable and less mobile upper airway structures than men, providing protection against severe forms of OSA.⁵¹ Women with polycystic ovary syndrome are at increased risk of developing OSA due to their higher free testosterone levels.⁵² Among menopausal women, there is a higher prevalence, but not severity, of OSA.⁵³ Several studies have suggested a role of sex hormones in sleep modulation, and in the progression and severity of OSA.^{48,54} These studies suggested that, in contrast to men, obesity was not the main cause of OSA in women. In addition, OSA severity is not dependent on WHR or neck circumference in women.⁵⁵ In our previous interventional study, OSA patients who underwent Roux-en-Y gastric bypass surgery showed significant improvements in sleep parameters and obesity indices, which indirectly confirmed the causal relationship between obesity and OSA.⁵⁶

Limitations

This was the first study of the causal relationships of overall and abdominal obesity with OSA and its quantitative traits. We used individual-level data from the genomic database of our GWAS, and confirmed OSA by standard PSG in all cases; nevertheless, this study had some limitations. First, not all SNPs relevant to BMI and WHR were included. Second, the SNPs in the control group were obtained with a DNA extraction kit and analyzed using a MassARRAY Compact Analyzer, which was not consistent with the OSA group. Third, the male/female ratio was different between the OSA and control groups, which may explain the failure to identify a causal relationship between obesity and OSA in women. Fourth, the control group was recruited from the community, and PSG was not performed as standard. In addition, interactions among the phenotype-related SNPs were not taken into consideration. Finally, bidirectional MR analyses of OSA and obesity were not performed, as there have been no GWAS of OSA in Asian populations. Our genomic database was built to explore the genetic background of OSA, with the aim of aiding its diagnosis and treatment in the future.

Conclusions

Our MR study demonstrated that BMI, but not WHR, is causally related to OSA in men. In contrast, obesity may not be a causal factor of OSA in women. These results suggest that greater attention should be paid to weight management in men, to reduce OSA risk.

Abbreviations

OSA, obstructive sleep apnea; MR, Mendelian randomization; SNP, single nucleotide polymorphism; GRS, genetic risk score; LD, linkage disequilibrium; BMI, body mass index; WHR, waist hip ratio; CHR, Chromosome; MAF, Minor allele frequency; H-E, Hardy–Weinberg equilibrium; IV, instrumental variable; OR, odds ratio; AHI, apnea-hypopnea index; ODI, oxygen desaturation index; MAI, Micro-arousal index.

Data Sharing Statement

All data generated or analyzed during this study are included in this published article.

Ethics Approval and Consent to Participate

The ethics committee of Shanghai Sixth People's Hospital approved this study according to Helsinki Declaration II. All the participants have given the informed consent before taking part in the study.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for the contents of the work.

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Disclosure

The authors declare that they have no competing interests in this work.

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