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ORIGINAL RESEARCH

Obstructive Sleep Apnea Syndrome and Obesity Indicators, Circulating Blood Lipid Levels, and Adipokines Levels: A Bidirectional Two-Sample Mendelian Randomization Study

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Purpose: This investigation sought to elucidate the genetic underpinnings that connect obesity indicators, circulating blood lipid levels, adipokines levels and obstructive sleep apnea syndrome (OSAS), employing a bidirectional two-sample Mendelian randomization (MR) analysis that utilizes data derived from extensive genome-wide association studies (GWAS).

Methods: We harnessed genetic datasets of OSAS available from the FinnGen consortium and summary data of four obesity indices (including neck circumference), seven blood lipid (including triglycerides) and eleven adipokines (including leptin) from the IEU OpenGWAS database. We primarily utilized inverse variance weighted (IVW), weighted median, and MR-Egger methods, alongside MR-PRESSO and Cochran's Q tests, to validate and assess the diversity and heterogeneity of our findings.

Results: After applying the Bonferroni correction, we identified significant correlations between OSAS and increased neck circumference (Odds Ratio [OR]: 3.472, 95% Confidence Interval [CI]: 1.954–6.169, P= 2.201E-05) and decreased high-density lipoprotein (HDL) cholesterol levels (OR: 0.904, 95% CI: 0.858–0.952, P= 1.251E-04). Concurrently, OSAS was linked to lower leptin levels (OR: 1.355, 95% CI: 1.069–1.718, P= 0.012) and leptin receptor levels (OR: 0.722, 95% CI: 0.530–0.996, P= 0.047). Sensitivity analyses revealed heterogeneity in HDL cholesterol and leptin indicators, but further multiplicative random effects IVW method analysis confirmed these correlations as significant (P< 0.05) without notable heterogeneity or horizontal pleiotropy in other instrumental variables.

Conclusion: This investigation compellingly supports the hypothesis that OSAS could be a genetic predisposition for elevated neck circumference, dyslipidemia, and adipokine imbalance. These findings unveil potential genetic interactions between OSAS and metabolic syndrome, providing new pathways for research in this domain. Future investigations should aim to delineate the specific biological pathways by which OSAS impacts metabolic syndrome. Understanding these mechanisms is critical for developing targeted prevention and therapeutic strategies.

Keywords: sleep disorders, metabolic syndrome, causal inference, GWAS

Introduction

Obstructive sleep apnea syndrome (OSAS) represents a multifaceted disorder with intricate pathophysiological characteristics. It is principally marked by nocturnal sleep snoring with apnea and daytime somnolence. The pathogenesis of OSAS predominantly involves partial or complete obstruction of the upper airway during sleep, culminating in intermittent hypoxia (IH) and sleep fragmentation.[1] Concurrent with the global rise in obesity rates, the incidence of OSAS has escalated markedly, eliciting considerable public health concern. Empirical evidence suggests that obesity is a principal risk factor for OSAS, with its prevalence in obese cohorts reaching up to 30%, in stark contrast to the 2–4% in the general population. This prevalence escalates to an alarming 50–98% in severely obese individuals.[2]

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Furthermore, OSAS is intricately linked with increased sympathetic nervous activity, systemic inflammation, oxidative stress and endothelial dysfunction. These elements, in conjunction with obesity, synergistically contribute to the pathogenesis and progression of associated complications, including metabolic syndrome and cardiovascular diseases.[3,4] Additionally, obesity-induced disturbances in adipokine metabolism, abnormalities in C-reactive protein (CRP) and an increase in other cardiovascular risk markers, are pivotal in the development and progression of OSAS and its complications. While clinical research has identified associations between obesity, dyslipidemia, adipokines and OSAS, these studies grapple with confounding factors and reverse causality, leading to contentious findings. To mitigate these issues, our study adopts a Mendelian randomization (MR) approach within epidemiological research, utilizing a spectrum of genetic variants as instrumental variables (IVs) for causal inference.[5] MR studies stand out for their potential to diminish confounding influences, thus shedding new light on the potential causal links between these metabolic indicators and OSAS.

The primary objective of this study is to delineate the causal associations between OSAS and obesity, circulating blood lipid concentrations and adipokine levels from a genetic standpoint, employing MR methodologies. Through this investigation, we aim to deepen our comprehension of the pathophysiological underpinnings of OSAS and furnish robust scientific evidence to inform the development of more efficacious prevention and treatment strategies.

Methods

Study Design

The aim of this study was to evaluate the causal interconnections between OSAS and factors such as obesity, blood lipid concentrations, and adipokine levels. This was achieved by performing bidirectional two-sample MR analysis on datasets sourced from genome-wide association studies (GWAS). The datasets utilized in this research are publicly accessible GWAS data, and the corresponding ethical approvals are detailed in the respective original studies. To ensure the robustness of our findings, sensitivity analyses were systematically conducted. The foundational assumptions of our MR analyses are threefold: (1) the IVs are strongly associated with the exposure factors; (2) the IVs are independent of any confounders that might influence the exposure and outcome relationship; (3) the IVs influence the outcome variables exclusively through these exposure factors. The specifics of the MR study design are depicted in Figure 1. To mitigate the risk of false positives arising from multiple comparisons, this study implemented the Bonferroni correction method, setting the threshold for statistical significance at a P value less than 0.0023 (where P= 0.05/22). Results yielding a P value between 0.0023 and 0.05 were deemed as suggestive.

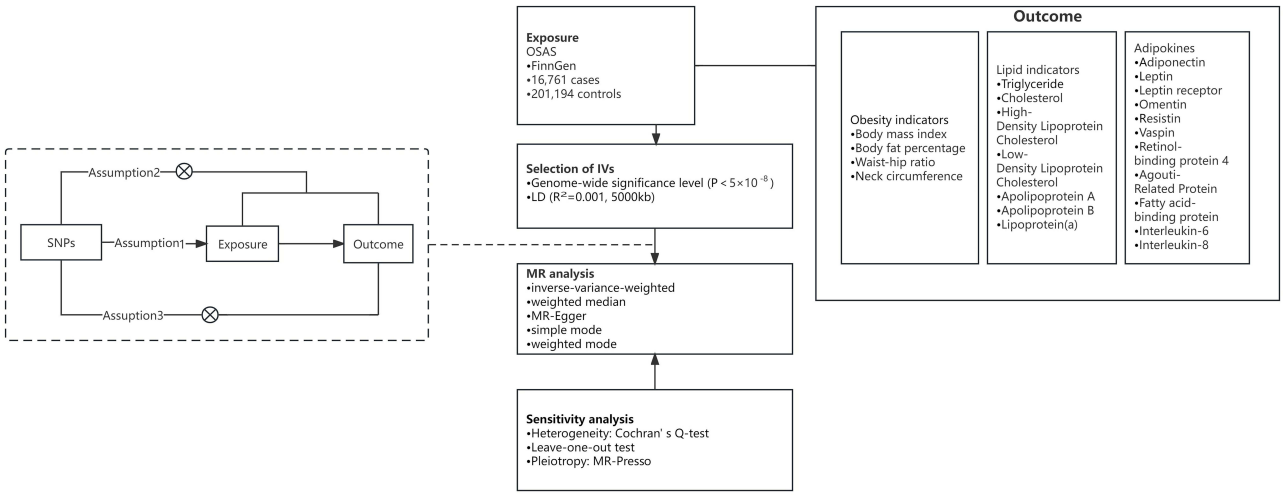

Figure 1 Graphical representation of the MR assumptions.

Data Sources and Instrumental Variables Selection

In the context of this study, we categorized obesity indicators into four primary measurements: body mass index (BMI), body fat percentage (BFP), neck circumference (NC), and waist-hip ratio (WHR). The serum lipid biomarkers under investigation encompass a broad spectrum, comprising triglycerides (TG), total cholesterol (TC), low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, lipoprotein A [Lp(a)], apolipoprotein A (ApoA) and apolipoprotein B (ApoB). Additionally, the study focuses on a range of adipokines, which are crucial in metabolic regulation. These include leptin, adiponectin, leptin receptor, resistin, vaspin, omentin, retinol-binding protein 4 (RBP4), interleukin-6 (IL-6), interleukin-8 (IL-8), agouti-related protein (AGRP) and fatty acid-binding protein (FABP). Each of these biomarkers plays a pivotal role in the metabolic pathways and is hypothesized to contribute to the pathophysiology of OSAS.

The GWAS summary datasets pertaining to obesity indicators, serum lipid biomarkers and adipokines were acquired from the OpenGWAS database, a resource developed by the MRC Integrative Epidemiology Unit (IEU) at the University of Bristol (https://gwas.mrcieu.ac.uk/). These datasets encompass over 450,000 individuals predominantly of European descent. To establish robust associations between genetic variants and the various lipid biomarkers, we meticulously selected genetic variants exceeding the genome-wide significance threshold ($P<5\times10^{-8}$) for our MR analysis. In instances where multiple GWAS datasets were available for a particular factor, preference was given to the dataset containing the largest number of validated genetic instruments. These approaches were adopted to ensure the highest level of precision and reliability in our analysis.

The summary-level data for OSAS were sourced from a recent GWAS. This study encompassed 16,761 OSAS patients and 201,194 control participants, drawn from the Finnish Genetics Study.[6] The diagnosis of OSAS in this cohort adhered to the criteria set forth in the International Classification of Diseases, 10th revision (ICD-10) and 9th revision (ICD-9), specifically under the codes ICD-10: G47.3 and ICD-9: 3472A. Diagnostic criteria were comprehensive, incorporating subjective symptom reports from patients, clinical examinations, and objective measures from sleep recordings. Notably, a threshold of at least five apnea-hypopnea indices or respiratory event indices per hour was employed as a diagnostic benchmark (Table 1).[7]

Instrumental Variable (IV)

In this investigation, we implemented a bifurcated approach to pinpoint IVs linked with OSAS. Initially, single nucleotide polymorphisms (SNPs) exhibiting significant associations with OSAS were identified at the gene level ($P<5.0\times10^{-8}$, $R^2<0.001$, cluster window size = 5,000 kb), with a focus on ensuring these SNPs were not correlated with the study outcome. Subsequently, IVs of insufficient strength were excluded by calculating the F-statistic for each SNP, defined as $F = beta^2/se^2$, where beta denotes the estimate and se denotes the standard error of the allele impacting the exposure.[8] An elevated F-statistic implies that these analyses are less susceptible to weak instrumental bias.[9] Comprehensive details regarding the IVs utilized in this study are available in Supplementary Table S1.

Statistical Analysis

This study is dedicated to exploring the causal links between OSAS and a spectrum of health indicators, including obesity indicators, circulating blood lipid levels, and adipokines levels. To achieve this objective, a suite of methodological tools was employed, each selected for its distinct advantages in evaluating the accuracy and underlying assumptions of the relationship between genetic variants and health outcomes. These tools include inverse variance weighting (IVW), MR-Egger regression, weighted median estimation, simple mode, and weighted mode. The IVW method amalgamates the Wald estimate for each SNP to yield a comprehensive estimate through meta-analysis. This approach is particularly effective in scenarios devoid of horizontal pleiotropy, where genetic variants do not influence other factors, thus providing unbiased results.[10] The MR-Egger method offers dual benefits: it furnishes consistent estimates of causal effects under less stringent assumptions and identifies potential directional pleiotropy exerted by genetic variants.[11] Meanwhile, the weighted median estimation remains reliable even if up to 50% of the genetic variants deviate from MR assumptions.[12]

Table 1 Characteristics of GWAS Consortiums Used for Each Variable

Traits	GWAS Accession Number	Sample Size	Numbers of SNPs	Population	Year
Obesity indicators					
BMI	ieu-b-40	681,275	2,336,260	European	2018
BFP	ukb-b-8909	454,633	9,851,867	European	2018
WHR	ieu-b-4830	85,978	7,908,954	European	2022
NC	ebi-a-GCST90017135	8,732	7,756,629	Mixed	2021
Lipid indicators					
TG	ieu-b-111	441,016	12,321,875	European	2020
CHOL	ebi-a-GCST90025953	437,878	4,232,052	European	2021
HDL-C	ebi-a-GCST90025956	400,754	4,218,934	European	2021
LDL-C	ebi-a-GCST90002412	431,167	16,293,344	European	2020
ApoA	ukb-d-30630_raw	-	13,585,234	European	2018
ApoB	ukb-d-30640_raw	-	13,585,958	European	2018
Lp(a)	ukb-d-30790_raw	-	13,583,854	European	2018
Adipokines					
Interleukin-6	ebi-a-GCST90012005	21,758	11,782,139	European	2020
Interleukin-8	ebi-a-GCST90011994	21,758	12,717,989	European	2020
Adiponectin	ieu-a-1	39,883	2,675,209	Mixed	2012
Leptin	ebi-a-GCST90012076	21,758	13,097,407	European	2020
Leptin receptor	prot-a-1724	3,301	10,534,735	European	2018
Omentin	ebi-a-GCST90085763	400	5,188,525	European	2022
Resistin	ebi-a-GCST90012034	21,758	13,138,697	European	2020
Vaspin	ebi-a-GCST90085786	400	5,188,525	European	2022
RBP4	prot-a-2507	3,301	10,534,735	European	2018
AGRP	ebi-a-GCST90012063	21,758	13,102,571	European	2020
FABP	ebi-a-GCST90012075	21,758	13,138,563	European	2020
OSAS	finn-b-G6_SLEEPAPNO	16,761	16,380,465	European	2021

To mitigate bias stemming from horizontal pleiotropy, we utilized MR-PRESSO and MR-Egger intercept regression for detecting significant horizontal pleiotropy across all outcomes.[13] Additionally, we performed leave-one-out analysis to evaluate the impact of individual SNPs on outcomes. The robustness of our results was further fortified by conducting heterogeneity tests, including Cochran's Q statistic and multiplicative random effects IVW method (IVW-mre), on statistically significant findings, with a P value threshold of less than 0.05. In cases where heterogeneity, rather than horizontal pleiotropy, was observed, a random effects IVW MR analysis was deemed appropriate.

Furthermore, reverse MR analyses were conducted between OSAS and the aforementioned health indicators, adhering to a selection criterion of $P < 5\times10^{-8}$ for SNPs, utilizing the same methods and theoretical framework as in the forward MR analyses. All statistical procedures were executed using two-sample MR and MR-PRESSO within the R software environment.[13,14]

Results

In this investigation, we identified 102 SNPs significantly associated with OSAS as IVs from the GWAS dataset. SNPs that might introduce bias due to continuous imbalance were excluded (Supplementary Table S1). All selected SNPs demonstrated F values exceeding 10, underscoring the robustness of these IVs and mitigating the risk of bias from weak IVs.

Our analyses revealed associations of OSAS with various obesity indicators (notably NC), lipid levels (including TG, HDL cholesterol, LDL cholesterol and ApoB), and adipokines (such as leptin and leptin receptor) in at least one MR method. Specifically, the IVW method (Table 2, Supplementary Figure S1) indicated that OSAS is a risk factor for increased NC (Odds Ratio [OR]: 3.472, 95% Confidence Interval [CI]: 1.954–6.169, P= 2.201E-05), elevated TG levels (OR: 1.029, 95% CI: 1.003–1.056, P= 0.027), decreased HDL cholesterol levels (OR: 0.904, 95% CI: 0.858–0.952, P= 1.251E-04), decreased LDL cholesterol levels (OR: 0.962, 95% CI: 0.936–0.989, P= 6.667E-03), and decreased ApoB levels (OR: 0.987, 95% CI: 0.971–

Table 2 Bidirectional MR Results of Obesity Indicators, Lipid Indicators, Adipokines and OSAS

Exposure	Outcome	No. SNP	IVW or IVW-mre			MR-PRESSO	MR-Egger Intercept Regression	Cochran's Q Statistic
			Beta	P	OR (95% CI)	P	P	P
OSAS	NC	4	1.244	2.201E-05	3.472 (1.954–6.169)	0.39	0.572	0.32
OSAS	HDL-C	5	−0.101	1.252E-04	0.904 (0.858–0.952)	0.059	0.927	0.001
OSAS	Leptin	5	0.304	0.012	1.355(1.069–1.718)	0.066	0.863	0.006
OSAS	Leptin R	5	−0.319	0.047	0.722(0.530–0.996)	0.764	0.670	0.789

0.995, P= 4.245E-3), as well as increased leptin levels (OR: 1.355, 95% CI: 1.069–1.718, P= 0.012) and decreased leptin receptor levels (OR: 0.722, 95% CI: 0.530–0.996, P= 0.047). Furthermore, we employed MR-Egger regression, weighted median estimation and both unadjusted and adjusted models to validate these results. While the IVW method indicated a causal relationship between OSAS and variables such as TG, LDL cholesterol and ApoB, the MR-Egger method suggested a contrasting directionality, thus challenging the causal inference (Supplementary Figure S2). To evaluate the stability of these findings, multiple effects detection was performed using MR-PRESSO and MR-Egger intercept regression, which indicated no significant potential multiple effects. The robustness of our findings was corroborated by leave-one-out sensitivity analyses, demonstrating that no single genetic instrument drove the results (Supplementary Figure S3). Cochran's Q statistic revealed no significant heterogeneity in the effects of SNPs on NC, TG, LDL cholesterol, ApoB and leptin receptor. However, some degree of heterogeneity was noted in HDL cholesterol and leptin, necessitating further analysis using the IVW-mre approach. Funnel plots supported the stability of our methodology (Supplementary Table S2-4 and Supplementary Figure S4).

Multiple tests conducted on these results, applying the Bonferroni correction, affirmed that the occurrence of OSAS is significantly correlated with increased NC and decreased HDL cholesterol levels. While other biomarkers, such as TG, LDL cholesterol, ApoB, leptin and leptin receptor levels, exhibited trends (as indicated by their OR values), they did not reach statistical significance post-Bonferroni correction, with P values exceeding 0.0023. It is critical to note that while these changes in biomarkers may not achieve statistical significance, they could still bear biological or clinical relevance.

In the reverse analysis segment of our study, we explored the causal relationships between obesity metrics, lipid levels, adipokines and OSAS (Supplementary Table S5). Our study identified a significant correlation between elevated levels of BMI (OR: 2.133, 95% CI: 1.935–2.351, P= 2.378E-52), BFP (OR: 2.040, 95% CI: 1.773–2.346, P= 2.074E-23), and TG (OR: 1.077, 95% CI: 1.006–1.153, P= 0.033) and the heightened risk of OSAS. These findings underscore the significant impact of these factors in predicting the likelihood of developing OSAS. However, the application of MR-PRESSO and MR-Egger intercept regression for stability testing revealed potential multiple effects (Supplementary Table S6-8). This finding necessitates a cautious approach in interpreting these associations, particularly regarding their influence on the overall conclusions of our study. The presence of potential multiple effects underscores the complexity of the causal relationships in question and highlights the need for further investigation to fully understand the intricate interplay between these metabolic factors and OSAS.

Discussion

Previous observational studies have established correlations between OSAS and various metabolic parameters, including obesity, lipid levels and adipokine levels.[15–17] However, these studies have been limited in their ability to ascertain the precise nature of the causal relationships involved. To our knowledge, this is the inaugural study employing MR methods at the genetic level to investigate the causal linkage between OSAS and these metabolic factors. By utilizing a spectrum of MR approaches, we have significantly bolstered the stability and reliability of our results, thereby providing a more convincing level of causal evidence compared to traditional observational studies.

Our findings indicate that OSAS plays a substantial role in increasing NC and decreasing HDL cholesterol levels. Additionally, our results suggest potential impacts on the increase in leptin levels, and decrease in leptin receptor levels.

These insights contribute to a deeper understanding of the complex interplay between OSAS and metabolic disturbances, potentially guiding future research and therapeutic strategies.

OSAS and Neck Circumference

This study corroborates the association between an increased risk of NC enlargement and OSAS, thereby aligning with the research conducted by Altan Onat et al and Viktória Molnár et al.[15,18] Altan Onat et al undertook a comprehensive observational study involving 25 patients with severe OSAS (Apnea-Hypopnea Index [AHI] ≥ 30 events per hour) and 19 with non-severe OSAS (AHI < 30 events per hour). Their findings indicated a positive correlation between increased NC and the severity of OSAS.[15] Similarly, Viktória Molnár et al conducted an analysis utilizing magnetic resonance imaging (MRI) to examine the adipose tissue parameters of the upper airways in 36 non-OSA control subjects, 32 patients with mild OSAS, and 32 with moderately-severe OSAS.[18] By applying artificial intelligence techniques to these MRI data, they identified age, percentage of tongue fat, and NC as crucial predictors of OSAS. Their results demonstrated that an increase in NC was positively correlated with OSAS severity and served as an independent predictor of severe OSAS. These collective findings underscore the significance of NC as not only a marker for the presence of OSAS but also as an indicator of its severity. This highlights the importance of including NC measurements in the clinical assessment and risk stratification of patients suspected of having OSAS.

Recent findings have illuminated that increased NC offers greater specificity and sensitivity in diagnosing OSAS when compared to traditional obesity indicators such as BMI, BFP and WHR.[19] This enhanced diagnostic capability can be attributed to the direct correlation between NC and adipose tissue accumulation around the upper airway, which is intimately linked to the pathophysiological mechanisms underlying OSAS. The proliferation of subcutaneous and peripharyngeal fat in the upper airway results in the enlargement of soft tissues. This not only augments neck thickness, leading to increased NC, but also constricts the upper airway. This constriction affects the airway's compliance and heightens the risk of airway collapse during sleep.[20]

Furthermore, increased NC in OSAS patients may be indicative of diminished aerobic capacity, reduced physical activity and fluid retention.[21,22] Prior research has established a connection between upper body subcutaneous fat (excluding abdominal fat) and aerobic capacity.[23] Hormonal fluctuations in OSAS patients, such as elevated cortisol levels, may contribute to fat accumulation in the neck and upper trunk, thereby influencing anthropometric indices.[24] Additionally, Stefania Redolfi et al have shown that increased NC may be a direct consequence of nocturnal fluid shifts from the lower limbs to the upper body in OSAS patients.[25] These insights underscore the significance of NC as a critical risk assessment tool for OSAS. NC is also associated with elevated levels of the prothrombotic factor plasminogen activator inhibitor-1 (PAI-1), which is closely related to the risk of cardiovascular diseases and the pathogenesis of atherosclerosis.[26] Future research may benefit from focusing on interventions aimed at reducing fat accumulation in the neck region, which could potentially mitigate the risk and severity of OSAS.

OSAS and Dyslipidemia

OSAS emerges as a significant risk factor for dyslipidemia. This investigation delineates a substantial association between attenuated HDL cholesterol levels and specific genetic variances, persisting post Bonferroni adjustment. These observations align with the research conducted by Dimitar Karkinski et al and Viseslav Popadic et al.[27,28] Karkinski et al's cross-sectional analysis demonstrated that individuals diagnosed with OSA and a BMI of ≤ 30 kg/m^2 exhibit notably diminished HDL cholesterol levels in comparison to their OSA-negative counterparts.[27] In a retrospective cohort encompassing 328 subjects with OSAS, Popadic and colleagues discerned a heightened propensity for metabolic syndrome in patients with severe OSAS (AHI ≥30 events per hour), marked by significantly reduced HDL cholesterol.[28] Notably, HDL cholesterol levels were found to be inversely related to the severity of OSAS. Prevailing epidemiological studies have substantiated plasma HDL cholesterol concentration as a robust, independent prognosticator of coronary heart disease in the general populace.[28] The cardioprotective role of HDL is underscored by its diverse subfractions; notably, smaller subfractions such as LDL 3-7 and HDL 8-10 contribute to atherosclerotic developments in OSAS patients.[29] Furthermore, the antioxidative capacity of larger HDL subfractions may be compromised due to escalated high-density lipid peroxide (LPO) levels and a decline in serum paraoxonase-1 (PON1) activity, pivotal determinants of

HDL's antioxidative efficacy.[30] This phenomenon potentially elucidates the diminished cardioprotective effect of HDL in OSAS patients, including those with normative HDL concentrations.

The proposed pathogenesis of dyslipidemia in OSAS is intricately linked to oxidative stress and inflammatory responses. The fundamental pathophysiological change in OSAS is IH, a consequence of repeated airway obstruction and reopening. This cycle leads to ATP depletion and subsequent activation of xanthine oxidase, culminating in an overproduction of reactive oxygen species (ROS).[31] Among these, hydroxyl radicals (OH-)—the most potent ROS components—initiate lipid peroxidation upon interacting with susceptible lipids.[32] This process affects lipid membranes, lipoproteins and other lipid-containing molecules. The peroxidative decomposition of unsaturated fatty acids yields LPO end-products such as malondialdehyde (MDA). MDA imparts biological dysfunction to lipid molecules, potentially leading to cell membrane damage and dysfunction. Additionally, MDA can modify the conformation of proteins by reacting with lysine residues, thereby impacting the functionality of enzymes and transport proteins crucial for lipid transport and metabolism.[33,34] Furthermore, MDA can react with proteins and lipids in LDL to form oxidized LDL (oxLDL). OxLDL is a key contributor to atherosclerosis, as it can be taken up by macrophages, transforming them into foam cells.[35]

IH also upregulates key hepatic transcription factors (SREBP-1) and the regulatory enzyme SCD-1, which converts saturated fatty acids into monounsaturated fatty acids.[36] This process enhances the biosynthesis of cholesterol esters and TG, leading to a reduced clearance rate due to lipase activity inhibition and increased mobilization of free fatty acids from adipose tissue.[37] Furthermore, IH may disrupt lipid metabolism by impairing very low-density lipoprotein (VLDL) clearance.[38]

Furthermore, IH in OSAS activates Hypoxia Inducible Factor-1 (HIF-1), a key transcription factor. HIF-1, in turn, initiates pro-inflammatory transcription factors such as nuclear factor kappa B (NF-kB) and activates the NF-kB signaling pathway. This activation leads to an increased mobilization of pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), IL-6, IL-8, CRP and PAI-1. Simultaneously, there is a decrease in anti-inflammatory factors like IL-10 in adipose tissue. This shift towards a pro-inflammatory state alters the metabolic activity of adipose tissue, resulting in metabolic dysfunction.[39,40]

These insights into the inflammatory mechanisms of OSAS underscore a complex interplay between hypoxia, inflammation and metabolic disruption. Future research should delve deeper into these pathways, particularly focusing on how they influence the metabolism or transport of LDL and ApoB. Understanding these mechanisms could be pivotal in unravelling the pathophysiology of OSAS and may pave the way for novel targeted therapeutic strategies.

OSAS and Adipokines

The prevalent co-occurrence of obesity in patients with OSAS has directed researchers' attention towards adipokines, bioactive substances secreted by adipose tissue, known for their intricate roles in endocrine and metabolic processes. Our study aligns with the findings of Shazia Jehan et al, Zuleyha Bingol et al, and a meta-analysis by Xiaoyan Li, showing that OSAS is associated with elevated leptin levels and reduced leptin receptor levels.[17,41–43] Prior research has indicated that plasma leptin levels in OSAS patients increase progressively with the severity of the condition and correlate strongly with the AHI and nocturnal oxygen saturation.[43] It is posited that chronic IH augments leptin signaling in the carotid body, predominantly through the action on the leptin receptor, thereby promoting hypoxic ventilatory responses. This leads to increased minute ventilation, reduced mechanical load on the upper airway, and stimulated compensatory neuromuscular responses.[44]

Elevated leptin levels in OSAS patients have been likened to the hyperleptinemia observed in obesity, marked by a decreased expression of leptin receptors and a blunted response to leptin, indicative of leptin resistance.[45] John Ciriello's animal study confirmed that long-term exposure to IH results in increased leptin levels and decreased leptin receptor expression, which impairs leptin's action on target cells, disrupts sleep architecture, alters sympathetic nerve activity, and diminishes control over the genioglossus and adjacent muscles, crucial in managing upper airway obstruction.[46] Clinical studies have demonstrated that continuous positive airway pressure (CPAP) treatment in OSAS patients with obesity significantly ameliorates metabolic disorders related to leptin resistance, enhancing the body's sensitivity to leptin, decreasing pharyngeal load, and improving pharyngeal ventilation.[47] However, it has also been observed that leptin levels may not significantly differ between OSAS patients and control groups, suggesting that the interplay between OSAS and leptin levels is complex and influenced by multiple factors, warranting further in-depth investigation.[48]

Although the precise biological mechanisms underlying the elevation of leptin levels in OSAS remain elusive, sleep deprivation and hypoxemia are widely acknowledged as critical contributors. Research indicates that IH can lead to increased expression of the suppressor of cytokine signaling 3 protein in the arcuate hypothalamic nucleus. This is accompanied by a decrease in the protein levels of extracellular signal-regulated kinase 1/2 and an increase in the phosphorylation of ERK1/2. These changes collectively inhibit the activation of the leptin receptor signaling cascade, thus impeding the activation of leptin-related pathways (such as pro-opiomelanocortin), culminating in the development of leptin resistance.[47] The intricacies of leptin resistance, particularly the signaling process of the leptin receptor post blood-brain barrier traversal, are yet to be fully elucidated.[49]

Furthermore, the recurrent apneic episodes characteristic of OSAS exacerbate hypoxemia and carbon dioxide accumulation, leading to heightened sympathetic nerve activity and diminished parasympathetic function. This physiological alteration stimulates the renin-angiotensin axis, promoting leptin production and secretion.[46] The resultant systemic leptin resistance contributes to the emergence of obesity, insulin resistance, metabolic syndrome and cardiovascular diseases. Leptin orchestrates the activation of signaling cascades including JAK/STAT, MAPK, IRS/PI3K/Akt pathways, concurrently augmenting the expression of atherogenesis-related cytokines and chemokines, thereby fostering vascular wall inflammation and perturbations in cellular functionality—pivotal elements in the pathogenesis of atherosclerosis.[50] Notwithstanding the prospective advent of central leptin resistance within the milieu of obesity and diabetes, the vascular milieu retains a pronounced or even amplified responsiveness to leptin, culminating in vascular dysfunction and expedited atherogenic progression.[51] Future investigations should focus on unraveling the specific mechanisms behind leptin resistance, evaluating its presentation across diverse populations, and exploring the potential effects of therapeutic interventions in ameliorating leptin resistance in OSAS. Such investigative efforts are crucial for advancing a more holistic comprehension of the pathophysiological intricacies of OSAS and potentially augmenting the effectiveness of its therapeutic approaches.

This study stands out for several notable strengths that enhance its contribution to the existing body of research on OSAS. Firstly, it pioneers the exploration of the causal relationships between OSAS and key health indicators—obesity, lipid levels, and adipokine levels—at the genetic level. Employing a bidirectional MR approach, our study effectively circumvents the confounding factors and measurement biases that are often inherent in observational studies. Secondly, our selection of genetic variants for IVs were informed by the most comprehensive GWAS data available. The chosen IVs, each with an F value exceeding 10, demonstrate a strong association with the exposure, lending credence to the reliability of our estimates and ruling out the influence of weak IVs. Thirdly, the robustness of our findings is further bolstered by a series of sensitivity analyses and thorough assessments for potential pleiotropy. These additional measures were instrumental in minimizing any possible biases in our results. Consequently, our findings provide substantial evidence to support the conclusion that OSAS contributes to an increase in NC, dyslipidemia, and disruptions in adipokine levels. These insights not only advance our understanding of OSAS but also underscore the significance of employing advanced genetic methodologies to unravel the complex interplay between this condition and various metabolic disturbances.

While this study significantly contributes to understanding the genetic correlates of obesity and OSAS, it is crucial to acknowledge its limitations. First and foremost, the absence of extensive GWAS data restricted our ability to conduct subgroup analyses based on variables such as gender, geographical location, and age. This limitation curtails the broader applicability and generalizability of our conclusions. Secondly, the primary reliance on data from European populations limits the extrapolation of our findings to non-European groups, given the known variations in gene expression and genetic predisposition among different ethnicities. The correlation between genetic markers and OSAS could significantly vary across different ethnic groups. Additionally, our study faced constraints due to insufficient SNP data on plasma adipokine levels. This limitation hampered our ability to perform a comprehensive IVW-based MR method analysis or in-depth sensitivity analysis, potentially overlooking certain biases. To address these issues and enhance the robustness of our findings, future studies should incorporate diverse and comprehensive GWAS data that spans various demographics and ethnicities. Such studies would not only validate and broaden our findings but also allow for a more detailed examination of the interactions between genetic predispositions to OSAS and other significant health outcomes, such as cardiovascular diseases. Given recent evidence indicating that obesity significantly elevates cardiovascular risk compared to OSAS, our research underscores the influence of OSAS on obesity-related factors. However, elucidating the subsequent impacts on

cardiovascular health and specific biological pathways remains a critical gap.[4] Future research is essential to intricately analyze these factors and their mechanisms to fully comprehend their contributions to cardiovascular risk.

Conclusion

In conclusion, our study, utilizing MR analysis, has provided compelling genetic evidence establishing a definitive association between OSAS and key metabolic disturbances—namely, increased NC, dyslipidemia, and adipokine imbalances. These findings illuminate the potential genetic interplay between OSAS and metabolic syndrome, offering new avenues for research in this field. The evidence points towards a complex interaction between OSAS and various aspects of metabolic health, underscoring the necessity for further research. Future studies should aim to unravel the specific biological pathways through which OSAS influences metabolic syndrome. A deeper understanding of these mechanisms is crucial for the development of targeted preventive measures and therapeutic strategies.

Data Sharing Statement

The datasets underpinning the conclusions drawn in this article are accessible through the IEU OpenGwas project repository. Interested readers and researchers can access these datasets at (https://gwas.mrcieu.ac.uk/).

Ethics Statement

This study utilizes aggregated data rather than individual-level data. The data involved all originate from publicly published GWAS summary databases, which complies with the conditions for exemption from review as stated in the "Ethical Review Measures for Life Sciences and Medical Research Involving Humans".

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 all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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