Novel Susceptibility Genes and Biomarkers for Obstructive Sleep Apnea:

Insights from Genetic and Inflammatory Proteins

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Abstract

Study Objectives: Numerous observational studies link obstructive sleep apnea (OSA) to inflammatory proteins, yet the directionality of these associations remains ambiguous. Therefore, we aimed to clarify the potential associations of gene-predicted inflammatory proteins with OSA.

Methods: Based on genome-wide association study data, we applied Mendelian randomization (MR) to explore potential connections between circulating inflammatory proteins and OSA, primarily using the inverse variance weighting method for robustness. Cochran's Q test, MR–Egger intercept test, MR-PRESSO, and leave-one-out method were used to perform sensitivity tests for pleiotropy and heterogeneity. Replication analyses and meta-analyses were performed using other independent data. Steiger tests and multivariate MR assessed the independent effects of exposure factors, and the functional mapping and annotation (FUMA) platform was used to identify key genes to enhance the understanding of genetics.

Results: Our investigation revealed 21 circulating inflammatory proteins significantly associated with OSA-related phenotypes. Notably, IL-10RA, IL-18R1, TNFSF14, CCL23, ADA, and SLAMF1 had significant effects on multiple phenotypes. After FDR correction, IL-18R1, SLAMF1, IL-10RA, and IL-17C were identified as important candidates for OSA, and multivariate MR analysis strengthened the independent heritability of 20 inflammatory factors. The FUMA platform revealed seven overlapping genes: ROBO1, PRIM1, NACA, SHBG, HSD17B6, RBMS2, and WWOX. All reverse MR analyses and sensitivity analyses confirmed the robustness of these associations.
Conclusions: Our results underscore crucial associations between inflammatory proteins and OSA pathogenesis, revealing new correlates and susceptibility genes. These findings advance biomarker identification for OSA risk and highlight the importance of genetic and inflammatory profiles in OSA management.

Keywords: Obstructive sleep apnea; Snoring; Apnea–hypopnea index; Inflammatory proteins; Mendelian randomization.
Graphical abstract

**Background**

**Data Sources**
- **Inflammation proteins**
  - **Primary analyses**
    - Plasma proteins N = 14,824
  - **Replication analyses**
    - Plasma proteins N = 6,293

**Sleep apnea syndrome**
- **Primary endpoint**
  - FinnGen N= 410,385
  - Meta-Analysis N=476,853
  - UK Biobank N=420,473
- **Associated endpoint**
  - N =21,245
  - Apnea-Hypopnea Index Minimum, Average SpO2, Average Desaturation, Percent under 90% SpO2

**Methods**
- **The Forward MR analyses**
  - **Confounders**
    - Removal of confounding SNPs that independently affect OSA
  - **Instrumental variables**
    - SNP related to Inflammatory proteins
  - **Exposure/Outcome**
    - Inflammatory proteins

**The Reverse MR analyses**
- **Instrumental variables**
  - SNP related to OSA
- **Outcome/Exposure**
  - Sleep apnea syndrome (OSA)

**Results**
- Twenty-one inflammatory proteins showed significant results, with MVMR analysis reinforcing the independent heritability of 20 inflammatory factors. The FUMA platform also identified seven overlapping genes.

**Conclusions:** Our results underscore the pivotal causative influence of inflammatory proteins on OSA pathogenesis, revealing new correlates and susceptibility genes.
Statement of Significance

Obstructive sleep apnea (OSA) is intricately linked to severe health issues, including cardiovascular and neurodegenerative diseases. Despite the widespread prevalence of OSA and its myriad of associated health risks, the inflammatory genetic underpinnings of this condition have yet to be fully elucidated. In this study, we conducted Mendelian randomization and meta-analysis using data from a multiphenotype genome-wide association study to delve deeper into the genetic and inflammatory mechanisms underlying OSA and to identify key biomarkers and risk genes associated with OSA. Considering the significant health risks and societal burdens of OSA, our findings enhance the etiological understanding and offer novel perspectives for the development of targeted therapeutic strategies and the improvement of the clinical management of OSA patients.
1 Introduction

Obstructive sleep apnea (OSA) is a common sleep-related breathing disorder (SBD) that has become a serious public health problem. Its typical feature is the repeated contraction or collapse of the upper airway during sleep, leading to intermittent airway obstruction, followed by hypoxia and hypercapnia in the body, and finally awakening from sleep due to respiratory events. OSA is considered a complex polygenic hereditary disease with complex pathological and physiological mechanisms involving sympathetic nervous system activity, oxidative stress and systemic inflammatory responses. It can cause multiorgan and multisystem damage and is an independent risk factor for chronic conditions, including hypertension, coronary heart disease, and stroke. In both clinical practice and everyday scenarios, the diagnosis and management of OSA present significant challenges. Typically, polysomnography is used for diagnosis, and noninvasive ventilators or medications are used to improve symptoms. However, these methods are not only expensive but also do not fundamentally solve this problem. Thus, the early identification of biomarkers and potential risk factors for OSA is paramount. This information has profound implications for elucidating the underlying mechanisms; advancing early detection, prevention, and treatment strategies; and enhancing long-term disease management of OSA.

Cytokines are important messengers of the immune system. The majority of these proteins are synthesized and secreted by immune cells and some nonimmune cells and play a special role in intercellular interactions and communication. Previous research has established a robust association between OSA and inflammatory markers, notably TNF-α, IL-6, and IL-17, as the levels of these factors are elevated in patients with OSA and their genetic polymorphisms are also associated with OSA susceptibility. The results from animal models and observational clinical studies suggest that chronic, systemic inflammatory changes can exacerbate respiratory events in patients with OSA, cause metabolic and rhythm disturbances in the body, and lead to serious consequences such as neurodegeneration. The study of the roles of these inflammatory proteins in the pathogenesis of OSA will contribute to a...
deeper understanding of the pathogenesis of OSA and help in the exploration of new therapeutic approaches.

Mendelian randomization (MR) is an emerging research method for determining whether an exposure is associated with the occurrence of a disease. The relationship between exposure and disease is estimated using genetic variation as an instrumental variable (IV) for the exposure in question\textsuperscript{17,18}. Since genetic variation is already randomly distributed due to inheritance, MR methods can eliminate the effects of external environmental influences and reduce or minimize contamination and bias due to reverse inference\textsuperscript{19}. To date, no MR studies of inflammatory biomarkers targeting multiple phenotypes of OSA have been published. The aim of this study was to elucidate the associations between inflammatory protein biomarkers and OSA through MR analysis utilizing IV tools, providing fresh insights into OSA pathogenesis and pioneering approaches for its prediction and treatment.

2 Methods

2.1 Study Design

We crafted a flowchart (Figure 1) that presents the comprehensive research framework to provide an intuitive understanding of our study design. In this investigation, we employed bidirectional MR analysis to delineate the dynamics and characteristics of the relationship between inflammatory proteins and OSA. Ninety-one inflammatory proteins in plasma served as the exposure variables, while two sets of OSA data from both the GWAS catalog and the FinnGen study constituted the outcomes. Moreover, we conducted an extended analysis employing snoring data from the GWAS catalog as an endpoint. In addition, given the differences in the pathological and physiological mechanisms of OSA at different stages, we selected five OSA-related indicators as alternate endpoints for the validation analysis. Finally, the effects were replicated using inflammatory factor data from independent sources. This MR study adheres to three foundational assumptions: (1) IVs exhibit a significant correlation with exposure; (2) IVs remain unlinked to confounding factors; and (3) IVs influence outcomes solely through exposure\textsuperscript{20}. By utilizing the public
GWAS database, this research, which has already been ethically approved, obviates the necessity for additional informed consent or ethical endorsement.

2.2 Participants and Data Sources

GWAS summary data for plasma proteins were obtained from a newly published large meta-analysis involving 14,824 European participants across 11 cohorts for 91 plasma proteins. The OSA data from different databases were first analyzed in the FinnGen study and then extended to the UK Biobank cohort. FinnGen data were obtained from the R10 research project, with an exclusively European target group. Disease classification was in accordance with the ICD-10 criteria. After adjusting for the principal components of age, sex, genetic correlation, and genotyping batch, the analysis included a total of 43,901 patients, 366,484 control participants, and 21,306,328 SNPs. The extended cohort data on OSA originate from a recent publication by Sakaue S et al. This study represents a cross-ethnic genetic association analysis involving 220 trait cohorts utilizing genetic data derived from European populations. Snoring phenotypic data were sourced from the UK Biobank, an expansive epidemiological study that included approximately 500,000 individuals aged 40-69 years from various UK regions between 2006 and 2010. A total of 391,531 UK Biobank participants of European descent were included in this study. The participants provided detailed demographic, sociopsychological, and medical information. The genetic data of all participants were subjected to standardized quality control protocols. The five OSA association indicators originated from a cross-ethnic study by Cade et al., incorporating 21,245 samples across 10 cohorts and four ethnic groups, adjusted for principal factors such as body mass index, sex, and genetic correlation. For the European population, selected indicators included the apnea–hypopnea index (AHI), minimum SpO2 (Min SpO2), average SpO2 (Avg SpO2), sleep time below a 90% SpO2 percentage (Per90), and average desaturation (Avg Desat). The replication analysis used inflammatory factors from a meta-analysis involving 8,293 European subjects. Comprehensive details on the phenotypes are presented in Table 1.
We adhered to stringent selection criteria for our IVs to guarantee the validity and accuracy of the inference between inflammatory plasma proteins and OSA: (1) SNPs with phenotypic links were prioritized at \( p < 5 \times 10^{-6} \), given that GWAS loci for plasma proteins rarely meet the standard significance of \( p < 5 \times 10^{-8} \); (2) all IVs underwent linkage disequilibrium (LD) checks (\( R^2 < 0.001 \) within a 10 MB window); and (3) SNPs possessing a minor allele frequency \( \leq 0.01 \) were consistently excluded. The reliability of each SNP was assessed through the F-statistic; instruments with an F-statistic \( \geq 10 \) were considered strong IVs and included in the analysis. The PhenoScanner website was used to validate the SNPs and remove potentially confounding variants with possible causal links to OSA.

2.3 Statistical Analysis

2.3.1 Mendelian Randomization Analysis

In this study, we attempted to elucidate the associations between plasma inflammatory proteins and OSA using MR methods, namely, the inverse-variance weighting (IVW), weighted mode, MR-Egger regression, weighted median estimator (WME) and simple mode methods. The IVW method is pivotal for evaluating the potential connections between plasma inflammatory proteins and OSA, utilizing the principle of random assignment to simulate randomized controlled trials and address endogeneity issues. Additional methods provide a thorough examination, ensuring a comprehensive evaluation of foundational assumptions.

2.3.2 Sensitivity Analysis

A detailed sensitivity analysis was performed, covering heterogeneity, pleiotropy, and leave-one-out tests, to ensure that the MR findings were reliable and stable and to address biases in IVW testing. In the two-sample MR approach, Cochran’s Q statistics were used to evaluate instrument heterogeneity, with \( p > 0.05 \) indicating homogeneous results. Managing this heterogeneity is essential for maintaining the accuracy of MR estimates and minimizing biases. MR-PRESSO was utilized to identify horizontal pleiotropy, a known potential bias in MR studies. After detecting the presence of horizontal
pleiotropy, we provided estimates of the outlier correction. A leave-one-out sensitivity analysis was performed to verify the validity of our conclusions 36. Finally, the MR Steiger directionality test was employed to validate the direction of the overarching effect37. The Benjamini–Hochberg procedure was utilized to adjust for multiple tests, and $P$ values corrected for the false discovery rate (FDR) were derived. A raw $P$ value less than 0.05 with an FDR-corrected $P$ value < 0.1 was considered to indicate a significant association, while an FDR-corrected $P$ value > 0.1 was considered to indicate a possible association between the exposure and outcome. These results were also included in our analysis38-40.

2.3.3 Reverse MR and Meta-analysis

In the reverse MR analysis, we applied the same research principles as in our forward studies, with IVW as our primary method. We adhered to rigorous standards during the selection of IVs for direct and alternative outcomes. A meta-analysis of consistent positive results for inflammatory cytokines across different databases was performed to validate the reliability of our findings. An $I^2$ less than 40% was considered to indicate low heterogeneity, whereas values greater than 75% were considered to indicate significant heterogeneity. For heterogeneity greater than 50% or $p=0.05$, a random-effects model was used, while for lower heterogeneity, a fixed-effects model was used41.

2.3.4 Replication MR Analysis

All reported markers of significance must be powered in additional analyses to assess the reliability of the results. In repeated analyses, we used independent sources of inflammatory factor data to test their significance with respect to OSA and the associated phenotypes. We performed a two-way MR analysis, and the IVW analysis results were regarded as the main reference. The criteria for all MR results and sensitivity analyses were consistent with those of the primary analysis.
2.3.5 Multivariable MR analyses

In this study, despite our efforts to exclude IVs with potentially confounding properties, we recognize that the pathophysiology of OSA is affected by multiple risk factors, and appropriate risk factor correction is necessary to ensure the independence of the results. In addition to the potential risk factors that we excluded, recent studies have indicated that fatty acid homeostasis in innate immune cells is a key regulatory node in the control of pathological inflammation. Considering the close correlation between OSA and inflammation, we used the MVMR to further adjust for the impact of fatty acid factors on the results to verify the independent association of inflammatory factors with OSA. Five MVMR analysis methods, namely, Robust, IVW, Egger, Median and LASSO, were used to verify the results. When at least one of the methods provided significant results, the results were considered robust.

2.3.6 Post-GWAS Gene Analysis

We utilized functional mapping and annotation (FUMA) for the analytical assessment complemented by an enrichment analysis targeting SNP-based phenotype-related specificity to explore the intersections between inflammatory markers and sleep apnea gene sets. Utilizing the described methodology, we analyzed summary statistics for six inflammatory proteins and eight outcome datasets, pinpointing genomic loci associated with the potential risk. The analysis focused solely on protein-coding genes. The R package SuperExactTest was used to evaluate overlaps between genes across two GWAS datasets. SNP2GENE facilitated positional mapping within a 10 kb range. SNP2GENE was utilized with the default settings, with FDR adjustments made to tailor the gene set enrichment analysis for multiple testing scenarios.
3 Results

3.1 IV Selection and Characteristics

Based on IV-specific selection criteria, we utilized a comprehensive suite of 14,456 SNPs as IVs for analyzing 91 inflammatory proteins in plasma. Detailed information regarding these selected IVs is available in Table S1. In an exhaustive epidemiological analysis, specific SNPs emerged as potential confounders through an extensive literature review, including the SNPs rs11039216, rs117888068, and rs3184504, which are associated with body mass index; SNP rs597808, which is associated with smoking status; and SNPs rs34790908 and rs579459, which are associated with hypertension. Comprehensive details on all confounding SNPs are cataloged in Table S7.

3.2 Main MR Results

The results of the study are detailed as the corresponding odds ratios (ORs) and their 95% confidence intervals (CIs), elucidating the associations of individual plasma inflammatory proteins with the risk of developing OSA and its characteristics.

3.2.1 Effect of Inflammatory Proteins in Plasma on OSA/Snoring

The OSA and snoring data were analyzed independently across various databases, with comprehensive MR findings cataloged in Table S2. We first ensured the consistency of the directionality of all results, primarily employing the IVW method for analysis and adopting forest plots for an enhanced descriptive visualization of the outcomes. Initially, 14 inflammatory proteins were identified as significant, with further detailed sensitivity analyses pinpointing 7 proteins with a potential link to OSA, as depicted in Figure 2 and Table S3. Specifically, CCL11 (OR 0.967, 95% CI 0.936–0.999; p = 0.046) and TNFSF14 (OR 0.969, 95% CI 0.941–0.997; p = 0.030) were identified as protective factors against OSA. Conversely, IL-18R1 (OR 1.088, 95% CI 1.023–1.157; p = 0.007), IL-10RA (OR 1.155, 95% CI 1.042–1.282; p = 0.006), SLAMF1 (OR 1.06, 95% CI 1.015–1.107; p = 0.008), CD5 (OR 1.06, 95% CI 1.009–1.113; p = 0.021), and IL-5 (OR 1.059, 95% CI 1.007–1.115; p = 0.026) emerged as risk factors for
OSA. Following comprehensive FDR adjustment for multiple testing, none of the uniform tests for inflammatory proteins met the significance threshold of 0.1, except for IL-18R1 ($P_{FDR}=0.0340$) and SLAMF1 ($P_{FDR}=0.0789$), which were significant in categorical adjustments.

### 3.2.2 Effect of Inflammatory Cytokines on OSA Characteristics

Five characteristic OSA-related indicators were selected as alternative endpoints for analysis: AHI, Min SpO$_2$, Avg SpO$_2$, Per90, and Avg Desat. These indicators are intricately linked to sleep-related breathing events and nocturnal hypoxemia. The initial analysis yielded 4, 6, 5, 4, and 5 positive findings, respectively, culminating in a total of 21 significant results following the comprehensive sensitivity analysis. The complete research findings are detailed in Figure 3 and Table S4. Importantly, traditionally, the relationship between exposure and effect was assessed using OR or beta values. In this investigation, five association indicators served as alternative endpoints, and their varying trends have distinct clinical implications for OSA. For OSA as a direct endpoint, lower Per90 values and higher Min SpO$_2$ and Avg SpO$_2$ values are considered to indicate improved conditions. Based on the actual effect of the direct endpoint, protective effects were observed for the following proteins on the respective endpoints: IL-2 (beta=-2.318, $p=0.038$) on the AHI; CXCL10 (beta=0.198, $p=0.017$) and IL-18R1 (beta=0.213, $p=0.0006$) on Avg Desat; ARTN on Avg SpO$_2$ (beta=0.243, $p=0.047$); IL-17C on Min SpO$_2$ (beta=1.381, $p=0.003$); and TNFSF12 (beta=-1.183, $p=0.018$) and IL-10RB (beta=-0.690, $p=0.032$) on Per90. Conversely, the following proteins had negative effects on the respective endpoints: IL-12B (beta=0.988, $p=0.011$) and IL-10RA (beta=3.715, $p=0.001$) on the AHI; TNFSF14 (beta=-0.249, $p=0.035$), TNFRSF9 (beta=-0.224, $p=0.017$), and CXCL11 (beta=-0.211, $p=0.015$) on Avg Desat; IL-10RA (beta=-0.424, $p=0.004$), CCL23 (beta=-0.150, $p=0.024$), and ADA (beta=-0.134, $p=0.022$) on Avg SpO$_2$; IL-10RA (beta=-1.473, $p=0.002$), IL-10 (beta=-0.860, $p=0.029$), MMP1 (beta=-0.764, $p=0.017$), LIF-R (beta=-0.648, $p=0.021$), and CD6 (beta=-0.439, $p=0.015$) on Min SpO$_2$; and SLAMF1 (beta=1.035, $p=0.030$) and IL-10RA (beta=2.273, $p=0.004$) on Per90. Notably, IL-10RA exhibited significant expression across all phenotypes, excluding Avg Desat. After adjusting for multiple testing...
using a comprehensive FDR method, the effect of IL-18R1 on Avg Desat ($P_{FDR}=0.0382$) was significant, while the effects of IL-10RA on AHI ($P_{FDR}=0.0382$), IL-17C on Min SpO$_2$ ($P_{FDR}=0.0489$), IL-10RA on Min SpO$_2$ ($P_{FDR}=0.0489$) and IL-10RA on Per 90 ($P_{FDR}=0.0981$) were significant when adjusting for the classification. Furthermore, the significant findings associated with IL-18R1, IL-10RA, SLAMF1, and TNFSF14, which overlap with OSA/snoring, underscore their potential pivotal roles in OSA onset and progression, warranting greater attention.

### 3.3 Examination of Outliers and Heterogeneity

Scatter plots (Figure 4), funnel plots (Figure S1), and leave-one-out plots (Figure S2) were generated to assess heterogeneity and identify potential outliers in our preliminary findings. The analysis revealed no outliers. Figures 2 and 3, alongside Tables S5-6, detail the conclusive outcomes from heterogeneity tests, horizontal pleiotropy assessments, and Steiger tests. The MR-PRESSO global test indicated that all significant results consistently had $p$ values greater than 0.05, suggesting no significant horizontal pleiotropy. MR–Egger regression further confirmed the consistency of the findings. Moreover, the Steiger test results, with $p$ values significantly less than 0.05, indicated a strong connection between the IVs and plasma inflammatory proteins. These findings confirmed the precise directionality of associations, strengthening the robustness of the MR results regarding the link between inflammatory cytokines and OSA.

### 3.4 Reverse MR and Meta-analysis

The reverse MR analysis was conducted using the same methodological principles as the forward MR analysis to guarantee the consistency and strength of the findings. The IVW method was used as the primary analytical approach. Following the exclusion of LD, a total of 130 SNPs across eight datasets were identified, all closely linked to OSA and its associated indicators. The F values for all identified SNPs exceeded 10. As depicted in Figure 2 and Tables 2 and S8, no inflammatory factors exhibited a significant inverse association with OSA within these eight outcome datasets. We conducted a
comprehensive meta-analysis on the consistent outcomes of specific inflammatory factors identified across several databases to minimize bias originating from diverse data sources. Following the principle of effect consistency, we identified six key inflammatory proteins: IL-10RA, IL-18R1, TNFSF14, CCL23, ADA, and SLAMF1. The results are depicted in forest plots for a clear visual representation (Figure 5).

3.5 Replication MR Analysis

In the replication analysis, we reported a total of 20 pairs of inflammatory factors with significant associations with 8 outcome phenotypes, including 9 pairs of inflammatory factors with protective associations and 11 pairs of inflammatory factors with deleterious associations. All the results were subjected to rigorous sensitivity analysis, and reverse association was not observed. However, due to differences in the number and categories of inflammatory factors included in different databases, we did not report significant results that were completely consistent and reproducible with the preliminary analysis. The detailed results are shown in Tables S9-10.

3.6 Multivariable MR analyses

The MVMR analysis of candidate inflammatory factors revealed that several inflammatory factors were significantly associated with OSA, and the strength and direction of these associations were affected by different fatty acid factors. For example, for the six key candidate metabolites, the results for ADA, IL-18R1, TNFSF14, and IL-10RA remained stable in association with OSA after adjusting for all nine fatty acid factors. SLAMF1 was no longer significant after adjusting for the influence of docosahexaenoic acid, and the correlation between CCL23 and OSA was weakened after adjusting the ratio of omega-6 fatty acids to omega-3 fatty acids. Other previously reported inflammatory factors were also affected to varying degrees. After adjusting for any fatty acid factors, the associations involving IL-2 were no longer significant, and only 2 results for ARTN and CCL11 showed weak associations, indicating that the independent influence of these inflammatory factors was weak and likely to be affected by the interaction of fatty acid factors. For individual fatty acid factors, linoleic acid and saturated fatty acids had the
greatest impact. After adjustment, the associations with 5 inflammatory factors lost significance. Omega-6 fatty acids, polyunsaturated fatty acids and total fatty acids also affected 4 types of inflammatory factors. All the results are shown in Figure 6 and Table S11.

3.7 Post-GWAS Gene Analysis

FUMA was used to precisely map the summary statistics of the seven significant inflammatory proteins identified in the previously mentioned GWASs. Figure 7 presents the Manhattan plot showing the input GWAS summary statistics and gene-based test results as analyzed using MAGMA. We identified 303 lead SNPs and 9488 candidate SNPs in LD with the lead SNPs, in addition to 759 independent significant SNPs across 146 genomic risk loci, as detailed in Tables S12-14. The SuperExactTest R package was used to evaluate a total of 18,517 genes in the genome. Similarly, we identified 910 significant independent SNPs, 514 lead SNPs, and 433 genomic risk loci associated with OSA and its related indicators, as detailed in Tables S15-17. Within this dataset, a total of seven genes were pinpointed for inflammatory proteins and their endpoint outcomes. Specifically, the ROBO1, PRIM1, and NACA genes were downregulated, while the SHBG, HSD17B6, RBMS2, and WWOX genes were upregulated, as shown in Table S18.

4 Discussion

The relationship between inflammation and sleep has always been a popular research topic, and as one of the more prevalent sleep disorders, OSA has a major impact on human health. A deeper understanding of the risk factors for its development is essential for the development of new strategies for disease prevention and treatment. To our knowledge, this study is the first to comprehensively assess the associations between inflammatory factors and OSA and its characteristics using MR methods. In this study, we combined MR, META, MVMR and FUMA analyses to determine the associations between OSA and inflammatory proteins. A total of 21 inflammatory proteins had significant effects on different features of OSA, and all the results passed rigorous sensitivity tests. Among them, IL-18R1, IL-10Ra,
SLAMF1, CD5, IL-5, IL-12B, TNFSF14, TNFRSF9, CXCL11, CCL23, ADA, MMP1, LIF-R, and CD6 were identified as risk factors for the development of OSA. Several of these findings are consistent with those of previous observational studies, but numerous proteins have never been reported to be associated with OSA pathophysiology or severity\textsuperscript{25,44,45}. In particular, we observed that IL-10Rα, TNFSF14, SLAMF1, and IL-18R1 showed consistently significant associations with multiple endpoint outcomes, especially indicators relevant to nocturnal hypoxemia. This finding confirms the potential associations between inflammatory proteins and sleep characteristics and provides a new perspective for exploring the underlying mechanisms involved.

As a key immunomodulatory cytokine, IL-10 binds to the receptors IL-10Rα and IL-10Rb and mediates a variety of biological effects\textsuperscript{46-48}. Previous research predominantly indicates that IL-10 can activate its signaling pathway through increased IL-10Rα, promoting an anti-inflammatory response and reducing the OSA incidence\textsuperscript{49}. Interestingly, this result seems contrary to the conclusion of the present study. We found that IL-10 and IL-10Rα may be risk factors for the development of OSA, whereas the opposite is true for IL-10Rb, and this differential effect between the different receptors may result from the lower affinity of IL-10 for IL-10Rb\textsuperscript{48}. Animal experiments have shown that hypoxia reduces inflammatory gene expression, confirming the impact of hypoxia on inflammatory processes\textsuperscript{50}. A study conducted by Dace et al.\textsuperscript{51} further supported that IL-10 expression was suppressed with higher levels of nocturnal hypoxia. These studies are consistent with the conclusion obtained here that hypoxia affects inflammatory protein expression and repair in vivo, masking positive anti-inflammatory processes. In fact, circadian rhythm disorders and intermittent hypoxia, common stressors, jointly trigger and aggravate the inflammatory response in patients with OSA. In particular, HIF-1α mediates the activation of NF-κB and the NLRP3 inflammasome, promoting the secretion of proinflammatory cytokines such as IL-1β and IL-18\textsuperscript{52}. IL-1β is a multifunctional cytokine that participates in the initiation and regulation of neuroinflammation and is overexpressed in diseases such as PD, AD, and OSA. In this study, we found no evidence of a significant association between IL-1β and OSA, a finding consistent with previously
published studies\textsuperscript{52,53}. Compared to the significant results from observational studies, the heterogeneity of the data resulting from differences in hypoxia exposure between different groups based on databases may be strong evidence for the inconsistent results.

Previous studies have documented the pleiotropic effects of IL18R1\textsuperscript{54,55}. A recent study revealed that the concentrations of IL18R1, ADA, and CCL23 in cerebrospinal fluid are linked to neurodegenerative diseases such as Parkinson's disease and Alzheimer's disease\textsuperscript{56}. Additionally, notable increases in the levels of IL-18 signaling components have been detected in patients with severe psychiatric disorders\textsuperscript{57}. Notably, patients with neurodegenerative and psychiatric disorders frequently experience sleep disturbances, which may serve as both risk factors and early indicators for these conditions\textsuperscript{58-60}. Our study included additional samples and data, confirming the associations between IL18R1, ADA, and CCL23 with OSA\textsuperscript{61-63}. A well-known link exists between OSA and neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease, and sleep disorders such as nocturnal hypoxia and RBD often appear as early symptoms of these diseases. Etiological hypotheses for neuroinflammation deepen this association and highlight the potential of targeting inflammatory pathways as a therapeutic approach\textsuperscript{64,65}. Our study highlights the association between OSA and specific inflammatory proteins, corroborated by a meta-analysis. As no single neuroinflammatory marker is disease-specific, our findings emphasize the nuanced role of inflammation in OSA and related conditions\textsuperscript{66,67}.

FUMA revealed seven genetic risk loci, namely, ROBO1, PRIM1, NACA, SHBG, HSD17B6, RBMS2, and WWOX, associated with inflammatory proteins and sleep apnea outcomes, suggesting a common pathophysiological mechanism. ROBO1 encodes a receptor protein that is crucial for neuronal growth, and its misexpression impairs neural and brain function and is correlated with shortened craniofacial development\textsuperscript{68,69}. PRIM1 is genetically pleiotropic and is associated with sleep apnea, major depression, and limited lung function caused by immune pathways\textsuperscript{70-72}. Like HSD17B6, NACA, SHBG, RBMS2, and WWOX are implicated in cell proliferation and differentiation, tumor suppression, nervous system development, and metabolic regulation. However, their potential effects on OSA remain uncertain.
This study provides insights for future research into their potential roles in shared genetic underpinnings and disease etiology.

In conclusion, our findings suggest that inflammatory factors play a potential pathogenic role in OSA. In contrast to traditional GWASs, we used the MR method to identify inflammatory protein markers that may be related to OSA, exploited the "natural randomization" characteristics of gene variation, used specific IVs to infer potential associations, focused on specific factors or mechanisms, and effectively weakened the influence of confounding factors, such as environment and lifestyle. Sensitivity analyses further avoided the masking effect of reverse associations and ensured clear association inferences over time.

This study provides an important reference for the early diagnosis of OSA, prognosis, and development of new therapeutic strategies. The pathogenesis of OSA is multifaceted and shaped by genetics and environmental factors, with diverse inflammatory factors contributing to its clinical diversity. This finding suggests that a single therapeutic approach might not suffice. Thus, understanding the dynamics of inflammatory proteins in OSA patients and their interactions with chronic hypoxia and immune adaptation is crucial for advancing research in this field. Despite the achievements of this study, some limitations exist. First, we relied on the largest available inflammatory factor signature and OSA-related GWAS datasets. Differences in the quality control of phenotypic data and population selection in these studies may lead to IV selection errors. Second, even with FDR correction for multiple testing, the limited sample size may still allow false-positive results. Moreover, all reported inflammatory factors must be validated in additional cohorts, which is a necessary step to confirm the efficiency of novel biomarkers. Therefore, these findings need to be further verified by more comprehensive basic experimental studies to elucidate the mechanisms underlying the associations between inflammatory factors and OSA risk.
5 Conclusion

Our findings elucidate the important roles of specific circulating inflammatory proteins in the pathogenesis of OSA while also identifying the key genetic underpinnings that contribute to its complexity. The discovery of key genes with increased expression deepens the understanding of the molecular mechanisms of OSA and emphasizes the importance of integrating genetic and molecular insights into clinical practice, providing potential avenues for innovative therapeutic targets and strategies.
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Data Availability

The datasets supporting this study are available from the website of GWAS Catalog database (https://www.ebi.ac.uk/gwas) and FinnGen consortium (https://www.finngen.fi). The online tool of PhenoScanner can be accessed from http://www.phenoscanner.medschl.cam.ac.uk/.

Financial Disclosure

None

Non-financial Disclosure

None
References
16. Li C, Shi S. Gut microbiota and metabolic profiles in chronic intermittent hypoxia-induced rats:


41. von Hippel PT. The heterogeneity statistic I(2) can be biased in small meta-analyses. BMC Med Res Methodol. 2015; 15: 35.
47. de Oliveira Cardoso JM, de Brito RCF, Costa AFP, et al. IL-10 receptor blockade controls the in vitro infectivity of Leishmania infantum and promotes a Th1 activation in PBMC of dogs with visceral leishmaniasis. Mol Immunol. 2021; 137: 20-27.
research: the journal of laboratory and clinical medicine. 2022; 242: 93-104.


Figure Legends

**Figure 1.** Schematic representation of the MR analysis in this study. (A) Illustration of the foundational assumptions of Mendelian randomization. (B) Depiction of the structured flowchart guiding this MR study. GWAS, genome-wide association study; IV, instrumental variable; SNP, single-nucleotide polymorphism; MR, Mendelian randomization; IVW, inverse variance weighting; WM, weighted median; UKB, UK Biobank; FinnGen, FinnGen study (Created with BioRender.com).

**Figure 2.** Associations between sleep apnea and OSA/snoring via Mendelian randomization. SNP, single-nucleotide polymorphism; OR, odds ratio; CI, confidence interval.

**Figure 3.** Mendelian randomization analysis of OSA characteristics. SNP, single-nucleotide polymorphism; OR, odds ratio; CI, confidence interval.

**Figure 4.** Scatter plot illustrating the results of the horizontal pleiotropy analysis of Inflammatory Proteins associated linked to OSA and its characteristics. In our assessment of the impacts of inflammatory proteins on OSA, we excluded findings with significant heterogeneity and horizontal pleiotropy, identifying 28 inflammatory cytokines as eligible for inclusion.

**Figure 5.** Forest plot of the meta-analysis results. Meta-analysis was used for the associations of plasma inflammatory proteins, OSA, and their associated indicators to assess the presence of positive or potentially positive outcomes and their reliability. The analysis was predominantly focused on the results obtained via the IVW method and the chosen effects models. (A) Meta-analysis of ADA; (B) meta-
analysis of CCL23; (C) meta-analysis of IL-18R1; (D) meta-analysis of SLAMF1; (E) meta-analysis of TNFSF14; and (F) meta-analysis of IL-10RA.

Figure 6. Associations of the MVMR with inflammatory factors and OSA. For each MVMR analysis, we added each genetic confounder separately. Abbreviations: IVW: inverse variance weighted; LASSO: least absolute shrinkage and selection operator; Median: weighted median; OR: odds ratio; * P value < 0.05.

Figure 7. Manhattan plot illustrating GWAS summary statistics and functionally annotated candidate SNPs. Red lines signify thresholds of genome-wide significance (−log10 P values). The key inflammatory proteins included IL-10RA (A, G), TNFSF14 (B, H), IL-18R1 (C, I), CCL23 (D, J), ADA (E, K), and SLAMF1 (F, L).
**Table 1 Characteristics of the data source used for the Mendelian randomization study**

<table>
<thead>
<tr>
<th>Trait</th>
<th>Data sources</th>
<th>Sample size</th>
<th>Ancestry</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Inflammatory cytokine</td>
<td>Zhao et al.</td>
<td>14824</td>
<td>European</td>
<td>Circulating inflammatory proteins</td>
</tr>
<tr>
<td>Inflammatory cytokine</td>
<td>Ahola-Olli et al.</td>
<td>8293</td>
<td>European</td>
<td>Circulating levels</td>
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<td>OSA</td>
<td>FinnGen</td>
<td>410385</td>
<td>European</td>
<td>ICD-10</td>
</tr>
<tr>
<td>OSA</td>
<td>Sakaue S et al.</td>
<td>476853</td>
<td>European</td>
<td>ICD-10</td>
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<tr>
<td>Snoring</td>
<td>UK Biobank</td>
<td>420473</td>
<td>European</td>
<td>Questionnaire: Being told by a partner, close relative or friend that you snore at night</td>
</tr>
<tr>
<td>AHI</td>
<td>Cade et al.</td>
<td>21245</td>
<td>European</td>
<td>The severity of sleep apnea by counting the number of apneas and hypopneas during sleep</td>
</tr>
<tr>
<td>Min SpO$_2$</td>
<td>Cade et al.</td>
<td>21245</td>
<td>European</td>
<td>Minimum blood oxygen saturation during nighttime sleep</td>
</tr>
<tr>
<td>Avg SpO$_2$</td>
<td>Cade et al.</td>
<td>21245</td>
<td>European</td>
<td>Average blood oxygen saturation during night sleep</td>
</tr>
<tr>
<td>Per 90</td>
<td>Cade et al.</td>
<td>21245</td>
<td>European</td>
<td>The percentage of cumulative time with oxygen saturation below 90% in total sleep time</td>
</tr>
<tr>
<td>Avg Desat</td>
<td>Cade et al.</td>
<td>21245</td>
<td>European</td>
<td>Initial SatO$_2$ minus final SatO$_2$</td>
</tr>
</tbody>
</table>

**Abbreviations:** OSA, obstructive sleep apnea; AHI, apnea-hypopnea index; Min SpO$_2$, minimum SpO$_2$; Avg SpO$_2$, average SpO$_2$; Per90, percentage of sleep time below 90% SpO$_2$; Avg Desat, average desaturation.
Table 2 MR analysis of reverse associations between inflammatory proteins and OSA, including their characteristics

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>nSNPs</th>
<th>OR (95%CI)</th>
<th>pval</th>
<th>Heterogeneity analysis</th>
<th>Horizontal pleiotropy</th>
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</thead>
<tbody>
<tr>
<td></td>
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<tr>
<td>AHI</td>
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<tr>
<td>IL-2</td>
<td>13</td>
<td>0.998 (0.992-1.005)</td>
<td>0.613</td>
<td>7.728 0.806</td>
<td>0.00638536 0.612</td>
</tr>
<tr>
<td>IL-12B</td>
<td>14</td>
<td>0.999 (0.993-1.004)</td>
<td>0.705</td>
<td>5.970 0.947</td>
<td>-0.009364972 0.405</td>
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<tr>
<td>IL-10RA</td>
<td>13</td>
<td>0.998 (0.992-1.005)</td>
<td>0.606</td>
<td>11.399 0.495</td>
<td>0.009752496 0.444</td>
</tr>
<tr>
<td>Avg Desat</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CXCL10</td>
<td>6</td>
<td>0.949 (0.875 to 1.030)</td>
<td>0.211</td>
<td>0.628 0.987</td>
<td>0.000971913 0.965</td>
</tr>
<tr>
<td>IL-18R1</td>
<td>6</td>
<td>1.390 (0.724 to 2.668)</td>
<td>0.322</td>
<td>325.089 0.000</td>
<td>0.042796885 0.832</td>
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<tr>
<td>TNFSF14</td>
<td>6</td>
<td>1.053 (0.961 to 1.153)</td>
<td>0.272</td>
<td>2.811 0.729</td>
<td>-0.032013888 0.252</td>
</tr>
<tr>
<td>CXCL11</td>
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<td>1.014 (0.925 to 1.111)</td>
<td>0.774</td>
<td>6.347 0.274</td>
<td>-0.032146166 0.206</td>
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<tr>
<td>Avg SpO2</td>
<td></td>
<td></td>
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<tr>
<td>ARTN</td>
<td>10</td>
<td>1.011 (0.921 to 1.111)</td>
<td>0.811</td>
<td>21.194 0.007</td>
<td>0.006500736 0.814</td>
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<tr>
<td>IL-10RA</td>
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<td>1.023 (0.963 to 1.087)</td>
<td>0.463</td>
<td>5.435 0.795</td>
<td>0.000517173 0.976</td>
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<tr>
<td>CCL23</td>
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<td>9.373 0.404</td>
<td>0.009387388 0.560</td>
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<tr>
<td>ADA</td>
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<td>11.621 0.235</td>
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<td>Min SpO2</td>
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<tr>
<td>IL-1C</td>
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<td>1.004 (0.988 to 1.021)</td>
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<td>IL-10</td>
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<tr>
<td>MMP1</td>
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<td>0.270</td>
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<td>LIF-R</td>
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<td>Per 90</td>
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<td>1.001 (0.992 to 1.011)</td>
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<td>10.990 0.612</td>
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<td>0.385</td>
<td>8.602 0.802</td>
<td>0.015302736 0.260</td>
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</tbody>
</table>

**Abbreviations:** AHI, apnea–hypopnea index; Min SpO2, minimum SpO2; Avg SpO2, average SpO2; Per90, percentage of sleep time below 90% SpO2; Avg Desat, average desaturation.
Figure 1

A

MR II Genetic instruments are not influenced by confounding variables

Confounders

Genetic Instruments
GWAS Summary Data

MR I Genetic instruments are associated with risk factors

Exposure
91 inflammation-related proteins

MR analysis
Bidirectional MR evaluation
Sensitivity analysis

Outcome
Sleep apnea syndrome and its characteristics
OSA
Snoring
Average SpO2
Minimum SpO2
Average desaturation
Apnea hypopnea index
Percent under 90% SpO2

Meta-Analysis
from Code

MR III Genetic instruments only affect outcomes through associated risk factors

Pleio effect

B

Exposure
91 inflammation-related proteins
\( N=14824 \) cohorts=11
1. IV selection (\( P<5e-6 \))
2. LD clumping (r2<0.001, window size=10000kb)
3. Exclude IVs associated with confounders and outcomes
4. Remove weak SNPs (F<10)

Outcome
Sleep apnea syndrome and its characteristics
OSA from Meta-Analysis (N=476,853)
Snoring from UK Biobank (N=420,473)
Apnea-Hypopnea Index (N=21,245)
Average Desaturation (N=21,245)
Average SpO2 (N=21,245)
Minimum SpO2 (N=21,245)
Percent under 90% SpO2 (N=21,245)

MR Analysis
Inverse Variance Weighted
MR-Egger Regression
Weighted Median
Simple Mode
Weighted Mode

Sensitivity Analysis
MR-PRESSO Global Test
MR-Egger Intercept Test
Heterogeneity Test
Leave-One-Out Analysis
Cochrane’s Q Test
Steiger Test

Genetic Independence Test
Reverse MR Analysis
Replication MR Analysis
Meta Analysis
Multivariable MR analyses
Post-GWAS Gene Analysis

1. Harmonize effect size and alleles of SNPs on the exposure and outcome
2. Remove confounding SNPs by Phenoscanner and replication MR analyses
## Figure 2

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Outcome</th>
<th>Gwas</th>
<th>nSNP</th>
<th>OR [95% CI]</th>
<th>Pval</th>
<th>Cochran’s Q TEST</th>
<th>MRregger pval</th>
<th>Steiger pval</th>
<th>MRPRESSO GLOBAL pval</th>
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<td>IL-18R1</td>
<td>OSA</td>
<td>Sakaue S et al. 18</td>
<td></td>
<td>1.088(1.023 to 1.157)</td>
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<td>0.606</td>
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<td>OSA</td>
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<td>OSA</td>
<td>Finningen 21</td>
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<td>1.080(1.015 to 1.107)</td>
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<td>OSA</td>
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<td>0.470</td>
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<td>0.967(0.936 to 0.999)</td>
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<td>Snoring</td>
<td>UK Biobank 23</td>
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<td>Snoring</td>
<td>UK Biobank 9</td>
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<tr>
<td>OSA</td>
<td>IL-18R1</td>
<td>Sakaue S et al. 29</td>
<td></td>
<td>1.042(0.965 to 1.124)</td>
<td>0.293</td>
<td>0.132</td>
<td>0.044</td>
<td>0.033</td>
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<tr>
<td>OSA</td>
<td>IL-10RA</td>
<td>Sakaue S et al. 29</td>
<td></td>
<td>1.080(0.985 to 1.142)</td>
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<td>0.673</td>
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<td>SLAMF1</td>
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<tr>
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<td>CD5</td>
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<td></td>
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<td>CCL11</td>
<td>UK Biobank 25</td>
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<td>0.943(0.810 to 1.099)</td>
<td>0.452</td>
<td>0.239</td>
<td>0.297</td>
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<td>0.960(0.818 to 1.126)</td>
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<td>0.463</td>
<td>0.250</td>
<td>0.582</td>
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<tr>
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<td>IL-5</td>
<td>UK Biobank 25</td>
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<td>0.978(0.832 to 1.150)</td>
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<td>0.419</td>
<td>0.644</td>
<td>0.605</td>
<td>0.426</td>
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*P<0.05 was considered statistically significant*
**Figure 3**

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Outcome</th>
<th>nSNP</th>
<th>OR(95%CI)</th>
<th>Pval</th>
<th>Cochrans Q TEST</th>
<th>MRegger Global pval</th>
<th>Steiger Global pval</th>
<th>MRPRESSO GLOBAL pval</th>
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<tr>
<td>IL-2</td>
<td>Apnea hypopnea index</td>
<td>11</td>
<td>0.099(0.011 to 0.877)</td>
<td>0.0378</td>
<td>0.7433</td>
<td>0.9725</td>
<td>1.51e-14</td>
<td>0.736</td>
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<tr>
<td>IL-12B</td>
<td>Apnea hypopnea index</td>
<td>23</td>
<td>2.686(1.260 to 5.728)</td>
<td>0.0105</td>
<td>0.3526</td>
<td>0.5515</td>
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<td>IL-10RA</td>
<td>Apnea hypopnea index</td>
<td>9</td>
<td>4.194(2.214 to 399.811)</td>
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<td>Average desaturation</td>
<td>12</td>
<td>1.218(1.035 to 1.433)</td>
<td>0.0169</td>
<td>0.9681</td>
<td>0.2329</td>
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<td>1.238(1.055 to 1.399)</td>
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<td>1.275(1.004 to 1.619)</td>
<td>0.0466</td>
<td>0.4018</td>
<td>0.4136</td>
<td>6.00e-18</td>
<td>0.395</td>
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<tr>
<td>IL-10RA</td>
<td>Average SpO2</td>
<td>9</td>
<td>0.654(0.461 to 0.871)</td>
<td>0.0037</td>
<td>0.4544</td>
<td>0.9646</td>
<td>2.35e-10</td>
<td>0.499</td>
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<tr>
<td>COL23</td>
<td>Average SpO2</td>
<td>20</td>
<td>0.960(0.755 to 0.980)</td>
<td>0.0266</td>
<td>0.9275</td>
<td>0.9223</td>
<td>9.81e-95</td>
<td>0.959</td>
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<tr>
<td>ADA</td>
<td>Average SpO2</td>
<td>12</td>
<td>0.974(0.779 to 0.951)</td>
<td>0.0218</td>
<td>0.6986</td>
<td>0.8932</td>
<td>4.96e-11</td>
<td>0.739</td>
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<tr>
<td>IL-17C</td>
<td>Minimum SpO2</td>
<td>13</td>
<td>3.977(1.566 to 9.974)</td>
<td>0.0033</td>
<td>1.0840</td>
<td>0.4906</td>
<td>2.23e-14</td>
<td>0.154</td>
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<tr>
<td>IL-10RA</td>
<td>Minimum SpO2</td>
<td>9</td>
<td>0.229(0.080 to 0.583)</td>
<td>0.0020</td>
<td>0.7947</td>
<td>0.7837</td>
<td>6.64e-11</td>
<td>0.832</td>
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<tr>
<td>IL-10</td>
<td>Minimum SpO2</td>
<td>14</td>
<td>0.423(0.195 to 0.916)</td>
<td>0.2921</td>
<td>0.3475</td>
<td>0.0791</td>
<td>5.21e-20</td>
<td>0.406</td>
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<tr>
<td>MMP1</td>
<td>Minimum SpO2</td>
<td>14</td>
<td>0.466(0.249 to 0.871)</td>
<td>0.0166</td>
<td>0.9911</td>
<td>0.8679</td>
<td>4.98e-33</td>
<td>0.859</td>
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<tr>
<td>LIF-R</td>
<td>Minimum SpO2</td>
<td>14</td>
<td>0.523(0.301 to 0.909)</td>
<td>0.2125</td>
<td>0.9195</td>
<td>0.9964</td>
<td>2.43e-46</td>
<td>0.691</td>
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<tr>
<td>CD6</td>
<td>Minimum SpO2</td>
<td>14</td>
<td>0.644(0.482 to 0.820)</td>
<td>0.0154</td>
<td>0.6757</td>
<td>0.3538</td>
<td>1.74e-129</td>
<td>0.560</td>
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<tr>
<td>TNFSF12</td>
<td>Percent under 90% SpO2</td>
<td>18</td>
<td>0.396(0.115 to 0.818)</td>
<td>0.0182</td>
<td>0.4878</td>
<td>0.6929</td>
<td>4.10e-36</td>
<td>0.525</td>
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<tr>
<td>IL-10RI</td>
<td>Percent under 90% SpO2</td>
<td>17</td>
<td>0.502(0.267 to 0.941)</td>
<td>0.0316</td>
<td>0.9576</td>
<td>0.7425</td>
<td>1.19e-112</td>
<td>0.941</td>
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<tr>
<td>SLAMF1</td>
<td>Percent under 90% SpO2</td>
<td>22</td>
<td>2.814(1.103 to 7.181)</td>
<td>0.0304</td>
<td>0.6956</td>
<td>0.6784</td>
<td>6.91e-40</td>
<td>0.690</td>
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<tr>
<td>IL-10RA</td>
<td>Percent under 90% SpO2</td>
<td>9</td>
<td>9.708(2.101 to 44.861)</td>
<td>0.0036</td>
<td>0.8968</td>
<td>0.9019</td>
<td>1.33e-11</td>
<td>0.866</td>
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</tbody>
</table>

*P*<0.05 was considered statistically significant
Figure 4

- CD5 on OSA FlinnGen
- SLAMF1 on OSA FlinnGen
- IL-18R1 on OSA FlinnGen
- IL-10RA on OSA FlinnGen
- IL-5 on Snoring
- CCL11 on Snoring
- TNFSF14 on Snoring
- IL-10RA on AHI
- IL-12B on AHI
- IL-2 on AHI
- CXCL11 on Avg Desat
- IL-18R1 on Avg Desat
- TNFSF14 on Avg Desat
- CXCL10 on Avg Desat
- CCL23 on Avg SpO₂
- ADA on Avg SpO₂
- ARTN on Avg SpO₂
- IL-10RA on Avg SpO₂
- CD6 on Min SpO₂
- IL-10 on Min SpO₂
- IL-17C on Min SpO₂
- LIF-R on Min SpO₂
- MMP1 on Min SpO₂
- IL-10RA on Min SpO₂
- IL-10RB on Per 90
- SLAMF1 on Per 90
- TNFSF12 on Per 90
- IL-10RA on Per 90

Legend:
- MR Egger
- Simple mode
- Weighted mode
- Weighted median
- Inverse variance weighted
### Figure 5

#### A

<table>
<thead>
<tr>
<th>Study</th>
<th>logOR SE(logOR)</th>
<th>Odds Ratio</th>
<th>OR (95%CI (common); (random))</th>
<th>Weight (common)</th>
<th>Weight (random)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avg SpO2</td>
<td>0.1349 0.0595</td>
<td>0.87 [0.75; 0.98]</td>
<td>0.1% 41.1%</td>
<td>41.1%</td>
<td>41.1%</td>
</tr>
<tr>
<td>Average &amp; 24/7</td>
<td>-0.527 0.1201</td>
<td>-1.09 [0.50; 2.31]</td>
<td>99.9% 58.6%</td>
<td>99.9%</td>
<td>58.6%</td>
</tr>
<tr>
<td>Common effect model</td>
<td>1.00 [1.00; 1.00]</td>
<td>100.2%</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Random effects model</td>
<td>0.99 [0.98; 1.00]</td>
<td>---</td>
<td>100.0%</td>
<td>---</td>
<td>---</td>
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</tbody>
</table>

Heterogeneity: $I^2 = 92.9%$, $Q = 0.0076, p = 0.00$

#### B

<table>
<thead>
<tr>
<th>Study</th>
<th>logOR SE(logOR)</th>
<th>Odds Ratio</th>
<th>OR (95%CI (common); (random))</th>
<th>Weight (common)</th>
<th>Weight (random)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avg SpO2</td>
<td>-1.1965 0.0886</td>
<td>0.36 [0.27; 0.46]</td>
<td>0.2% 39.9%</td>
<td>39.9%</td>
<td>39.9%</td>
</tr>
<tr>
<td>Average &amp; 24/7</td>
<td>-0.0983 0.0252</td>
<td>0.99 [0.98; 1.00]</td>
<td>99.9% 91.1%</td>
<td>99.9%</td>
<td>91.1%</td>
</tr>
<tr>
<td>Common effect model</td>
<td>0.90 [0.81; 1.00]</td>
<td>100.0%</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Random effects model</td>
<td>0.84 [0.82; 1.00]</td>
<td>---</td>
<td>100.0%</td>
<td>---</td>
<td>---</td>
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</tbody>
</table>

Heterogeneity: $I^2 = 98.1%$, $Q = 0.0076, p = 0.00$

#### C

<table>
<thead>
<tr>
<th>Study</th>
<th>logOR SE(logOR)</th>
<th>Odds Ratio</th>
<th>OR (95%CI (common); (random))</th>
<th>Weight (common)</th>
<th>Weight (random)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avg IRI</td>
<td>0.2134 0.0922</td>
<td>1.25 [1.10; 1.40]</td>
<td>20.3% 41.2%</td>
<td>20.3%</td>
<td>41.2%</td>
</tr>
<tr>
<td>OSA from Salazar et al.</td>
<td>0.3949 0.0712</td>
<td>1.24 [1.12; 1.34]</td>
<td>74.7% 56.4%</td>
<td>74.7%</td>
<td>56.4%</td>
</tr>
<tr>
<td>Common effect model</td>
<td>1.19 [1.01; 1.40]</td>
<td>100.0%</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Random effects model</td>
<td>1.15 [1.01; 1.31]</td>
<td>---</td>
<td>100.0%</td>
<td>---</td>
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</tr>
</tbody>
</table>

Heterogeneity: $I^2 = 77.5%$, $Q = 0.0089, p = 0.00$

#### D

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<tr>
<th>Study</th>
<th>logOR SE(logOR)</th>
<th>Odds Ratio</th>
<th>OR (95%CI (common); (random))</th>
<th>Weight (common)</th>
<th>Weight (random)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Per 50</td>
<td>1.5345 0.4780</td>
<td>2.30 [1.70; 3.40]</td>
<td>0.2% 39.3%</td>
<td>39.3%</td>
<td>39.3%</td>
</tr>
<tr>
<td>OSA from FinGuy</td>
<td>0.2582 0.0631</td>
<td>1.05 [1.02; 1.10]</td>
<td>55.6% 43.2%</td>
<td>55.6%</td>
<td>43.2%</td>
</tr>
<tr>
<td>Common effect model</td>
<td>1.95 [1.82; 2.11]</td>
<td>160.0%</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Random effects model</td>
<td>1.54 [1.41; 1.70]</td>
<td>---</td>
<td>160.0%</td>
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</table>

Heterogeneity: $I^2 = 77.6%$, $Q = 0.0012, p = 0.04$

#### E

<table>
<thead>
<tr>
<th>Study</th>
<th>logOR SE(logOR)</th>
<th>Odds Ratio</th>
<th>OR (95%CI (common); (random))</th>
<th>Weight (common)</th>
<th>Weight (random)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avg IRI</td>
<td>-0.2495 0.1359</td>
<td>0.78 [0.62; 0.98]</td>
<td>0.1% 39.1%</td>
<td>39.1%</td>
<td>39.1%</td>
</tr>
<tr>
<td>Average &amp; 24/7</td>
<td>0.9544 0.0328</td>
<td>1.01 [0.89; 1.13]</td>
<td>99.9% 67.7%</td>
<td>99.9%</td>
<td>67.7%</td>
</tr>
<tr>
<td>Common effect model</td>
<td>1.61 [1.38; 1.88]</td>
<td>100.0%</td>
<td>---</td>
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</tr>
<tr>
<td>Random effects model</td>
<td>0.91 [0.771; 1.05]</td>
<td>---</td>
<td>100.3%</td>
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</tbody>
</table>

Heterogeneity: $I^2 = 79.0%$, $Q = 0.0000, p = 0.00$

#### F

<table>
<thead>
<tr>
<th>Study</th>
<th>logOR SE(logOR)</th>
<th>Odds Ratio</th>
<th>OR (95%CI (common); (random))</th>
<th>Weight (common)</th>
<th>Weight (random)</th>
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<tr>
<td>AHI</td>
<td>3.7474 1.0014</td>
<td>4.18 [2.39; 7.38]</td>
<td>0.2% 15.0%</td>
<td>15.0%</td>
<td>15.0%</td>
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<tr>
<td>Avg SpO2</td>
<td>4.2073 1.1959</td>
<td>1.08 [0.92; 1.27]</td>
<td>4.4% 36.7%</td>
<td>4.4%</td>
<td>36.7%</td>
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<tr>
<td>SNR</td>
<td>4.7247 1.0763</td>
<td>1.04 [0.80; 1.35]</td>
<td>2.1% 20.9%</td>
<td>2.1%</td>
<td>20.9%</td>
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<tr>
<td>Salazar</td>
<td>-0.0760 0.0109</td>
<td>-0.97 [0.88; 1.07]</td>
<td>9.1% 35.4%</td>
<td>9.1%</td>
<td>35.4%</td>
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<tr>
<td>OSA from Salazar et al.</td>
<td>0.1440 0.0529</td>
<td>1.00 [0.81; 1.24]</td>
<td>99.9% 23.3%</td>
<td>99.9%</td>
<td>23.3%</td>
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<tr>
<td>Common effect model</td>
<td>1.09 [0.88; 1.33]</td>
<td>100.0%</td>
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<td>---</td>
</tr>
<tr>
<td>Random effects model</td>
<td>1.02 [0.81; 1.29]</td>
<td>---</td>
<td>100.0%</td>
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</table>

Heterogeneity: $I^2 = 68.1%$, $Q = 3.2973, p = 0.01$

Exposure = IL-16R1
Exposure = SLAMF1
Exposure = TNFSF14
Exposure = IL-16α
Figure 6

<table>
<thead>
<tr>
<th>LIF-R</th>
<th>MMP1</th>
<th>SLAMF1</th>
<th>TNFSF12</th>
<th>TNFSF14</th>
<th>ADA</th>
<th>ARTN</th>
<th>CCL1</th>
<th>CCL23</th>
<th>CD5</th>
<th>CD6</th>
<th>CXCL10</th>
<th>CXCL11</th>
<th>IL-2</th>
<th>IL-5</th>
<th>IL-18R1</th>
<th>IL-17C</th>
<th>IL-12B</th>
<th>IL-10R8</th>
<th>IL-10R8</th>
<th>Deoxymethionine</th>
<th>Linoleic acid</th>
<th>Monounsaturated fatty acids</th>
<th>Omega-3 fatty acids</th>
<th>Omega-6 fatty acids</th>
<th>Polyunsaturated fatty acids</th>
<th>Ratio of omega-6 fatty acids to omega-3 fatty acids</th>
<th>Saturated fatty acids</th>
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