Nature and Science of Sleep

Elevate Series

Open Access Full Text Article

ORIGINAL RESEARCH

Causal Relationship Between Childhood Obesity and Sleep Apnea Syndrome: Bidirectional Two-Sample Mendelian Randomization Analysis

Ping Wang*, Shuli Liu*, Ling Min Kong, Nannan Qi

Department of Pediatrics, The Second Affiliated Hospital of Shandong First Medical University, Taian, Shandong, 271000, People's Republic of China

*These authors contributed equally to this work

Correspondence: Nannan Qi, Department of Pediatrics, The Second Affiliated Hospital of Shandong First Medical University, No. 366, Taishan Street, Taian, Shandong, 271000, People's Republic of China, Email 13953851791@163.com

Background: Childhood obesity has become a global pandemic, leading to a range of diseases. Childhood obesity appears to be associated with an increased prevalence of sleep apnea syndrome. Sleep apnea is an inestimable risk factor for thrombosis, hypertension, cardiomyopathy and many other diseases. Therefore, exploring the relationship between childhood obesity and sleep apnea syndrome will help to understand the potential link between the two and provide research directions for future disease prevention and treatment. However, no studies have confirmed whether there is a causal relationship between childhood obesity and sleep apnea syndrome.

Methods: The IEU OpenGWAS project provided the GWAS-aggregated data for childhood obesity and sleep apnea syndrome. Inverse-variance weighted (IVW) was used as the main method to evaluate the causal relationship between childhood obesity and sleep apnea syndrome. Single nucleotide polymorphisms (SNPs) were regarded as instrumental variables, and the screening threshold was $P < 5.0 \times 10^{-6}$. Leave-one-out method was performed to confirm the robustness of the results.

Results: IVW analysis confirmed a causal relationship between genetic susceptibility to childhood obesity and an increased risk of sleep apnea syndrome [odds ratio (OR)=1.12, 95% confidence interval (CI): 1.02–1.23, P=0.016]. However, two-sample MR results also showed no causal relationship between genetic susceptibility to sleep apnea syndrome and an increased risk of childhood obesity (OR=1.50, 95% CI: 0.95–2.38, P=0.083). The intercept of MR-Egger regression was close to 0, which implies that there are no confounding factors in the analysis to affect the results of two-sample MR analysis. The leave-one-out results show that the bidirectional two-sample MR analysis results were robust.

Conclusion: There is a causal relationship between genetic susceptibility to childhood obesity and increased risk of sleep apnea syndrome. People with a history of childhood obesity should pay more attention to physical examination to early prevention and management of sleep apnea syndrome.

Keywords: bidirectional two-sample Mendelian randomization, childhood obesity, sleep apnea syndrome, causal relationship, single nucleotide polymorphisms

Introduction

Childhood obesity has become a global pandemic, leading to a range of diseases and increasing morbidity and mortality.[1,2] Risk factors for childhood obesity include poor diet, genetic factors, short sleep duration, lack of physical activity, and high stress levels.[3,4] Increasing daily physical exercise or optimizing diet are common measures to prevent obesity.[5] The global prevalence of childhood obesity has reached 5.6% for girls and 7.8% for boys.[6] Childhood obesity has the potential to continue into adulthood, which increases the incidence of diabetes, cancer, and cardiovascular disease.[7]

Sleep apnea syndrome is a common respiratory system disorder that affects a wide range of people, including obstructive sleep apnea syndrome (OSAS), central sleep apnea syndrome (CSAS) and mixed sleep apnea syndrome.[8] OSAS is very common in terms of frequency, and it is often considered that sleep apnea syndrome=OSAS in throughout the world.[9] The characteristic of sleep apnea is the intermittent cessation or reduction of airflow during sleep, leading to

Received: 8 May 2024
Accepted: 30 September 2024
Published: 22 October 2024

a decrease in oxygen saturation in the blood.[10] Sleep apnea is an inestimable risk factor for thrombosis, embolism, hypertension, cardiomyopathy, gestational diabetes and many other diseases.[11,12]

Obesity is a major preventable risk factor and disease modifier for some respiratory diseases.[13] Obesity is a major risk factor for sleep apnea syndrome. The prevalence of sleep apnea syndrome is particularly high in mass obesity and visceral obesity.[14] Adipose tissue deposition in the neck and pharyngeal areas can physically compress the airway, increasing the risk of airway obstruction during sleep.[15,16] Additionally, obesity is often associated with inflammation, which may contribute to airway inflammation and further exacerbate the risk of sleep apnea.[17] Previous studies have found a significant correlation between childhood obesity and sleep apnea syndrome.[18–20] The increasing prevalence of childhood obesity seems to be associated with an increased prevalence of sleep apnea syndrome. Moreover, the relief of OSAS is related to the decrease of low density lipoprotein and apolipoprotein B and the increase of high density lipoprotein.[17] Disrupted sleep can affect hormones such as leptin and ghrelin, which regulate appetite.[21] Reduced sleep quality and duration can also lead to decreased physical activity levels and changes in metabolism, which may contribute to weight gain.[22] However, no studies have confirmed whether there is a causal relationship between childhood obesity and sleep apnea syndrome. Based on previous studies, this study hypothesized that there may be a causal relationship between childhood obesity and sleep apnea syndrome, and validated it using bidirectional two-sample Mendelian randomization (MR) analysis. The results of this study clarify the causal relationship between childhood obesity and sleep apnea syndrome, which is helpful for the management of diseases in the future.

MR is a robust analysis method, which is suitable for using genetic variation to solve the causal problem of how modifiable exposure affects different outcomes.[23] Single nucleotide polymorphisms (SNPs) were used as instrumental variables (IVs) in MR analyses to infer causality for observed associations between modifiable exposures and clinically relevant outcomes.[24,25] During meiosis, alleles are randomly separated, so MR can reduce the bias caused by confounding factors.[26] Genome-wide association studies (GWAS) have identified thousands of variations associated with complex exposures, which has pushed the wide application of MR to a climax.[27,28] In this study, a two-sample MR analysis was performed to assess the causal relationship between childhood obesity and the risk of sleep apnea syndrome (Figure 1). In addition, reverse MR was also performed to observe the bidirectional causal effects of sleep apnea syndrome on childhood obesity. The aim of this study was to explore the causal relationship between childhood obesity and sleep apnea syndrome by using bidirectional two-sample Mendelian randomization (MR) analysis.

Materials and Methods

Data Sources

The IEU OpenGWAS project (https://gwas.mrcieu.ac.uk) provided the GWAS-aggregated data for childhood obesity and sleep apnea syndrome (Supplementary Table 1). The GWAS dataset for childhood obesity (GWAS ID: ieu-a-1096, https://gwas.mrcieu.ac.uk/datasets/ieu-a-1096/) included 13848 samples of European ancestry and 2442739 SNPs.[29] This dataset summarizes 14 research cohorts. Total 5530 cases (≥95th percentile of body mass index achieved before the age

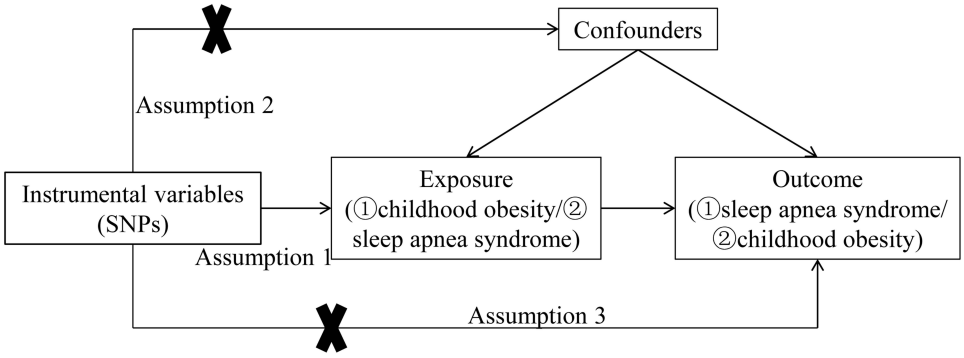

Figure 1 Mendelian randomization model of childhood obesity and sleep respiratory syndrome.
Abbreviation: SNPs, single nucleotide polymorphisms.

of 18 years old) and 8318 controls (relatively conservatively defined as <50th percentile of body mass index consistent throughout all measures during childhood). The GWAS dataset for sleep apnea syndrome (GWAS ID: ebi-a-GCST90018916, https://gwas.mrcieu.ac.uk/datasets/ebi-a-GCST90018916/) included 476853 samples of European ancestry (13818 cases and 463035 controls) and 24183940 SNPs.[30] All statistical data were gathered from the descendants of Europeans, reducing the potential bias due to racial differences. Notably, no overlap was observed, given that samples of childhood obesity and sleep apnea syndrome originated from distinct study groups. The "mRnd" online analysis tool was used to evaluate the statistical power of MR estimates. The power was 0.74 when childhood obesity was the exposure factor and sleep apnea syndrome was the outcome variable. The power was 1 when sleep apnea syndrome was the exposure factor and childhood obesity was the outcome variable. The GWAS dataset of childhood obesity and sleep apnea syndrome used has a relatively large sample size, avoiding the insufficient statistical power caused by limited sample size. Therefore, it has higher reliability.

Selection of IVs

During the initial screening of IVs, a threshold of $P < 5.0\times10^{-8}$ was set to identify statistically significant SNPs. However, the number of SNPs identified at a threshold of $P<5\times10^{-8}$ was limited. To obtain more IVs, the threshold was set to $P<5\times10^{-6}$.[31] Linkage disequilibrium (LD) is mainly measured using two parameters, r^2 and kb. In this study, LD with significant SNPs associated with exposure factors must meet $r^2 < 0.001$ and genetic distance of 10000 kb to avoid LD bias. Subsequently, we removed the palindromic SNPs (ie, AT or G/C) and the SNPs that were not available in the results. In the analysis of causal effects of childhood obesity on sleep apnea syndrome, childhood obesity was the exposure factor and sleep apnea syndrome was the outcome variable. A total of 14 SNPs were selected as IVs. In the analysis of causal effects of sleep apnea syndrome on childhood obesity, sleep apnea syndrome was the exposure factor and childhood obesity was the outcome variable. A total of 13 SNPs were selected as IVs. The strength of association between each IV and exposure factors is usually assessed using the F-statistic. F>10 can effectively avoid the bias caused by weak IVs.[32]

The calculation formula is:[33]

$$F = \left(\beta_{exposure} \Big/ SE_{exposure}\right)^2$$

(Note: $\beta_{exposure}$ and $SE_{exposure}$ represent standard error and effect size of exposure, respectively).

Study Design

MR design was based on three assumptions: (1) IVs must be strongly associated with exposure factors; (2) IVs were not associated with other confounding factors; (3) IVs can affect outcome only through exposure and not through other pathways. The causal relationship between childhood obesity and sleep apnea syndrome was studied by using bidirectional two-sample MR.[34] The schematic overview of our study design is displayed in Figure 1.

Statistical Analysis

Two-sample MR analysis was conducted using weighted median, simple mode, weighted mode, MR-Egger regression and inverse-variance weighted (IVW) methods. Among them, IVW was used as the main method to evaluate the causal relationship between childhood obesity and sleep apnea syndrome. This approach is particularly effective in scenarios devoid of horizontal pleiotropy, where genetic variants do not influence other factors, thus providing unbiased results. A causal effect was presumed to exist if a $P<0.05$ was observed in statistics. The intercept of MR-Egger regression is an indicator of detection horizontal pleiotropy. If the intercept of MR-Egger regression is close to 0, it means that there is no horizontal pleiotropy in IVs. The Cochran's Q (heterogeneity) test was used to analyze the differences between the IVs to quantify the heterogeneity. MR-pleiotropy residual sum and outlier (MR-PRESSO) test was used to detect and correct horizontal pleiotropy through removing the outliers. The leave-one-out sensitivity test was performed to determine whether a single SNP caused significant change in the results by removing the SNP one by one. The difference was considered statistically significant when the test level α was 0.05 ($P < 0.05$). All of the data were analyzed using R (version 4.3.1) software.

Results

The Casual Effect of Childhood Obesity on Sleep Apnea Syndrome

In the analysis of causal effects of childhood obesity on sleep apnea syndrome, childhood obesity was the exposure factor and sleep apnea syndrome was the outcome variable. A total of 14 SNPs were selected as IVs. The F values of all IVs were greater than 10. The intercept of MR-Egger regression was close to 0 (Egger_intercept=−0.0494, P=0.2354) (Table 1), which implies that there is no horizontal pleiotropy in IVs. Meanwhile, this also implies that there are no confounding factors in the analysis to affect the results of two-sample MR analysis.

The two-sample MR results showed a causal relationship between genetic susceptibility to childhood obesity and an increased risk of sleep apnea syndrome (Supplementary Table 2 and Figure 2). In the absence of horizontal pleiotropy of IVs, IVW was the primary method to estimate the causal relationship between genetic susceptibility to childhood obesity and increased risk of sleep apnea syndrome, and the result was the most reliable [odds ratio (OR)=1.12, 95% confidence interval (CI): 1.02–1.23, P=0.016]. The P of the IVW method was less than 0.05 (Supplementary Table 2), indicating a causal relationship between childhood obesity and sleep apnea syndrome. The results of other MR analysis methods were shown in Supplementary Table 2. Although the P of the other four methods were greater than 0.05, it was still considered that there was a causal relationship between childhood obesity and sleep respiratory syndrome, as the IVW result was decisive.

IVW and MR-Egger regression analyses were used for heterogeneity detection. Subsequently, Cochran's *Q* test was used to quantify heterogeneity. The results of Cochran's *Q* test showed that P<0.05, indicating significant heterogeneity. If there was heterogeneity between IVs, the random effects IVW model was used to estimate causal effects.[34,35] The results of IVW (Cochran's Q=55.15, P=3.80E-07) and MR-Egger regression (Cochran's Q=48.81, P=2.26E-06) analyses indicated that there was heterogeneity between the IVs (Table 2 and Figure 3A). Therefore, the random effects IVW model was used to estimate the causal effects between genetic susceptibility to childhood obesity and increased risk of sleep respiratory syndrome (P=0.016). The presence of outlier SNPs was detected using MR-PRESSO, and the causal effect (P=0.043) was estimated after the outlier SNP (rs9941349) was excluded (Table 3). This once again demonstrates a causal relationship between childhood obesity and the risk of sleep apnea syndrome. Sensitivity analysis was performed using the leave-one-out method to evaluate the reliability of MR results. The value of "All" is greater than 0 indicates that the result is reliable. Herein, the leave-one-out results show that the two-sample MR analysis results were robust (Figure 3B). Sensitivity analyses based on maximum likelihood and weighted median were also performed to validate the results, which also showed that the two-sample-MR was robust (Supplementary Figure 1).

The Causal Effect of Sleep Apnea Syndrome on Childhood Obesity (Reverse Two-Sample MR Analysis)

In the analysis of causal effects of sleep apnea syndrome on childhood obesity, sleep apnea syndrome was the exposure factor and childhood obesity was the outcome variable. A total of 13 SNPs were selected as IVs. The F values of all IVs were greater than 10. The intercept of MR-Egger regression was close to 0 (Egger_intercept=−0.0854, P=0.3810) (Table 1), which implies that there is no horizontal pleiotropy in IVs.

Notably, the two-sample MR results showed no causal relationship between genetic susceptibility to sleep apnea syndrome and an increased risk of childhood obesity (OR=1.50, 95% CI: 0.95–2.38, P=0.083) (Supplementary Table 3 and Figure 4A and B). IVW and MR-Egger regression analyses are used for heterogeneity detection. The results of IVW (Cochran's Q=55.15, P=1.70E-07) and MR-Egger regression (Cochran's Q =51.26, P=3.70E-07) analyses indicated that there was heterogeneity between the IVs (Supplementary Table 4 and Figure 4C). Therefore, the random effects IVW model was used to estimate the causal effects between genetic susceptibility to sleep apnea syndrome and increased risk

Table 1 Horizontal Pleiotropy Test

Outcome	Exposure	Egger_Intercept	Standard Error	P Value
Sleep apnea syndrome||id:ebi-a-GCST90018916	Childhood obesity	−0.0494	0.0396	0.2354
Childhood obesity||id:ieu-a-1096	Sleep apnea syndrome	−0.0854	0.0936	0.3810

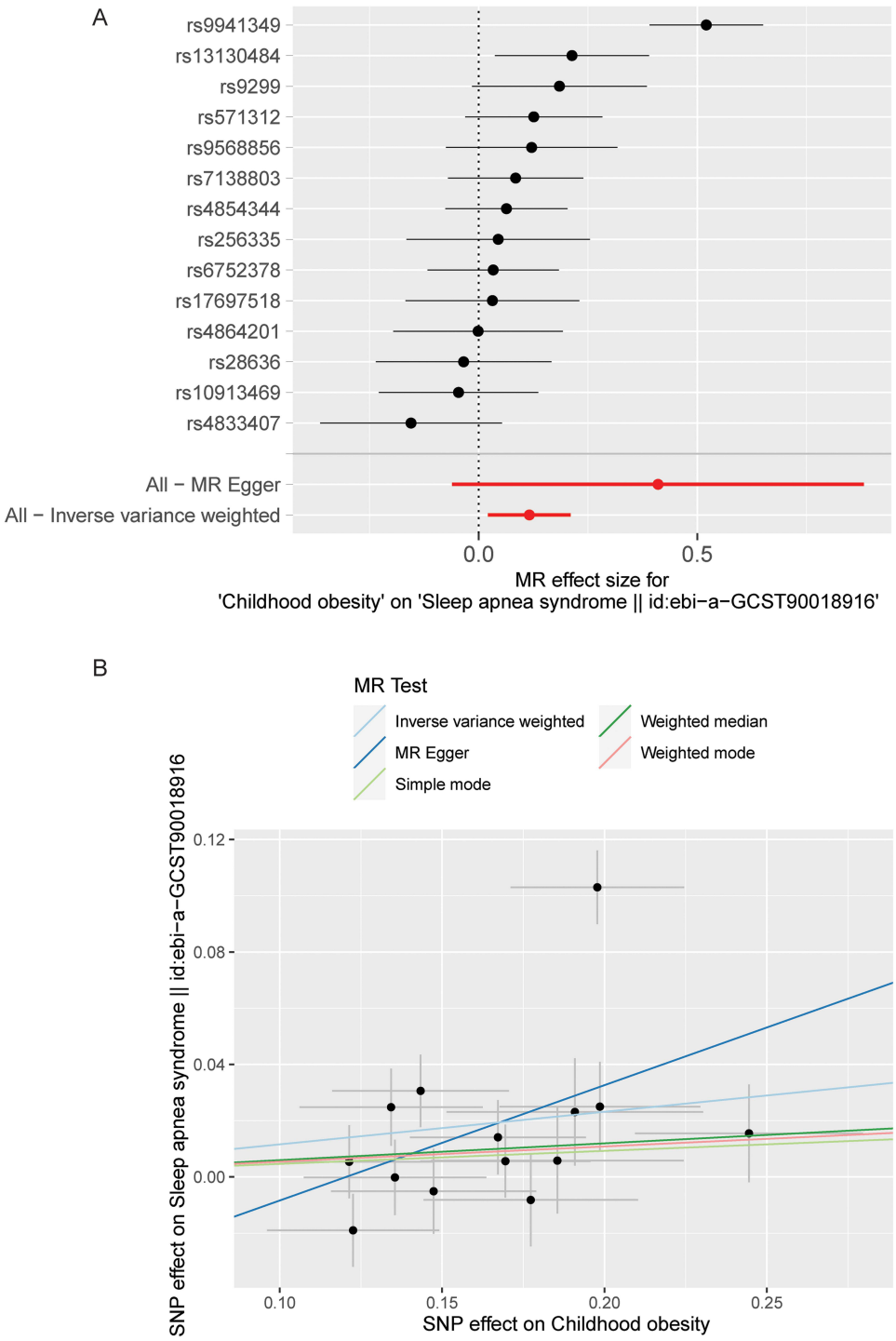

Figure 2 Forest and scatter plots of the impact of childhood obesity on sleep apnea syndrome. (**A**) Forest plot to visualize causal effect of each single SNP on the risk of sleep apnea syndrome; (**B**) Scatter plot to visualize causal effect of childhood obesity on the risk of sleep apnea syndrome.
Abbreviations: SNPs, single nucleotide polymorphisms; MR, Mendelian randomization.

of childhood obesity (P = 0.08). The presence of outlier SNPs was detected using MR-PRESSO, and the causal effect (P=0.55) was estimated after the outlier SNP (rs11075985) was excluded (Supplementary Table 5). This once again indicates that there is no causal relationship between sleep apnea syndrome and the risk of childhood obesity. Sensitivity analysis was performed using the leave-one-out method to evaluate the reliability of MR results. Herein, the leave-one-out results show that the two-sample MR analysis results were robust (Figure 4D).

Table 2 Heterogeneity Test

Outcome	Exposure	Method	Q	Q_df	Q_P Value
Sleep apnea syndrome||id:ebi-a-GCST90018916	Childhood obesity	Inverse variance weighted	55.15307	13	3.80E-07
Sleep apnea syndrome||id:ebi-a-GCST90018916	Childhood obesity	MR Egger	48.80602	12	2.26E-06

Abbreviations: Q, Cochran's *Q* test value; Q_df, degree of freedom of Q statistic; Q_P value, P value of Q statistic.

Discussion

Based on the GWAS dataset, this study used the bidirectional two-sample MR to explore whether there is a bidirectional causal relationship between childhood obesity and sleep apnea syndrome in the European population. Power analysis showed that when childhood obesity was the exposure factor and sleep apnea syndrome was the outcome variable, power was 0.74. When sleep apnea syndrome was the exposure factor and childhood obesity was the outcome variable, power was 1. This avoids the insufficient statistical power caused by limited sample size. Therefore, it has higher reliability. All statistical data were gathered from the descendants of Europeans, reducing the potential bias due to racial differences. Notably, no overlap was observed, given that samples of childhood obesity and sleep apnea syndrome originated from distinct study groups. The analysis results in this study suggest a causal relationship between genetic susceptibility to childhood obesity and an increased risk of sleep apnea syndrome. However, it also suggests that there is no causal relationship between genetic susceptibility to sleep apnea syndrome and an increased risk of childhood obesity. Sensitivity analysis confirmed the robustness of the above results.

Obesity is associated with various diseases, including sleep apnea.[36] Meta-analyses of patients treated with intensive lifestyle interventions or bariatric surgery showed improvements in apnea hypopnea index after treatment.[37,38] Sleep disordered breathing, especially OSAS, is significantly related to overweight and obesity in children.[39,40] Previous report has shown that the occurrence of OSAS in obese children is 13–59%, while the occurrence of OSAS in normal weight children is 1–2%.[41] The incidence of adenotonsillar hypertrophy in obese children is alarming. From the perspective of anatomical factors, adenoid and tonsil hypertrophy is an important cause of OSAS in obese children.[42–44] In addition, altered ventilatory responses and chest wall mechanics, and defective upper airway function in obese children may contribute to their susceptibility to OSAS.[18] Excess weight and fat deposition in the neck and upper airway lead to high airway obstruction during sleep.[45] A MR analysis showed that obesity indicators body mass index, body fat percentage, and triglycerides were significantly associated with an increased risk of OSAS.[46] Herein, The IVW results showed a causal relationship between genetic susceptibility to childhood obesity and an increased risk of sleep apnea syndrome, which is consistent with previous findings. Moreover, the sensitivity analysis implies the robust of the two-sample MR analysis results. Our findings suggest that addressing childhood obesity may have a positive impact on reducing the risk of sleep apnea syndrome. This also implies the necessity of comprehensive screening and intervention plans in pediatric healthcare environments, providing potential exploration directions for the prevention and treatment of sleep apnea syndrome in clinical practice.

Leptin (a type of adipokine) is thought to be one of the reasons for the association between obesity and OSAS. It acts on central chemoreceptors, causing an increase in triggering ventilation, but this mechanism fails because obese patients are resistant to the effects of leptin.[47] Past research has indicated blood leptin levels are positively correlated with the severity of OSAS.[48,49] The relief of OSAS is also related to the decrease of low density lipoprotein and apolipoprotein B and the increase of high density lipoprotein.[17] A MR analysis showed that OSAS was associated with multiple obesity indicators, lipid levels and adipokines.[46] Prior studies have indicated a potential link between insulin sensitivity and OSAS in obese children. Correction of OSAS in obese children is related to improved measures of insulin sensitivity.[50,51] Reduced sleep quality and duration can also lead to decreased physical activity and metabolic changes that affect weight change.[22] Moreover, the interconnected impact of systemic inflammation, oxidative stress, metabolic disturbances, and gut microbiota contributes significantly to the development of obesity and OSAS. This complex relationship between obesity and OSAS underscores the intricate nature of their interaction.[52] There are some errors between the results of this study and the previous observational studies. In this study, the results of reverse two-sample MR analysis did not reveal a causal relationship between genetic susceptibility to sleep apnea syndrome and increased risk of childhood obesity. The leave-one-out method evaluated the reliability of the results, suggesting that the MR analysis results were robust. The reason for this result may be related to the choice of dataset, sample source, etc., and more research is needed in the

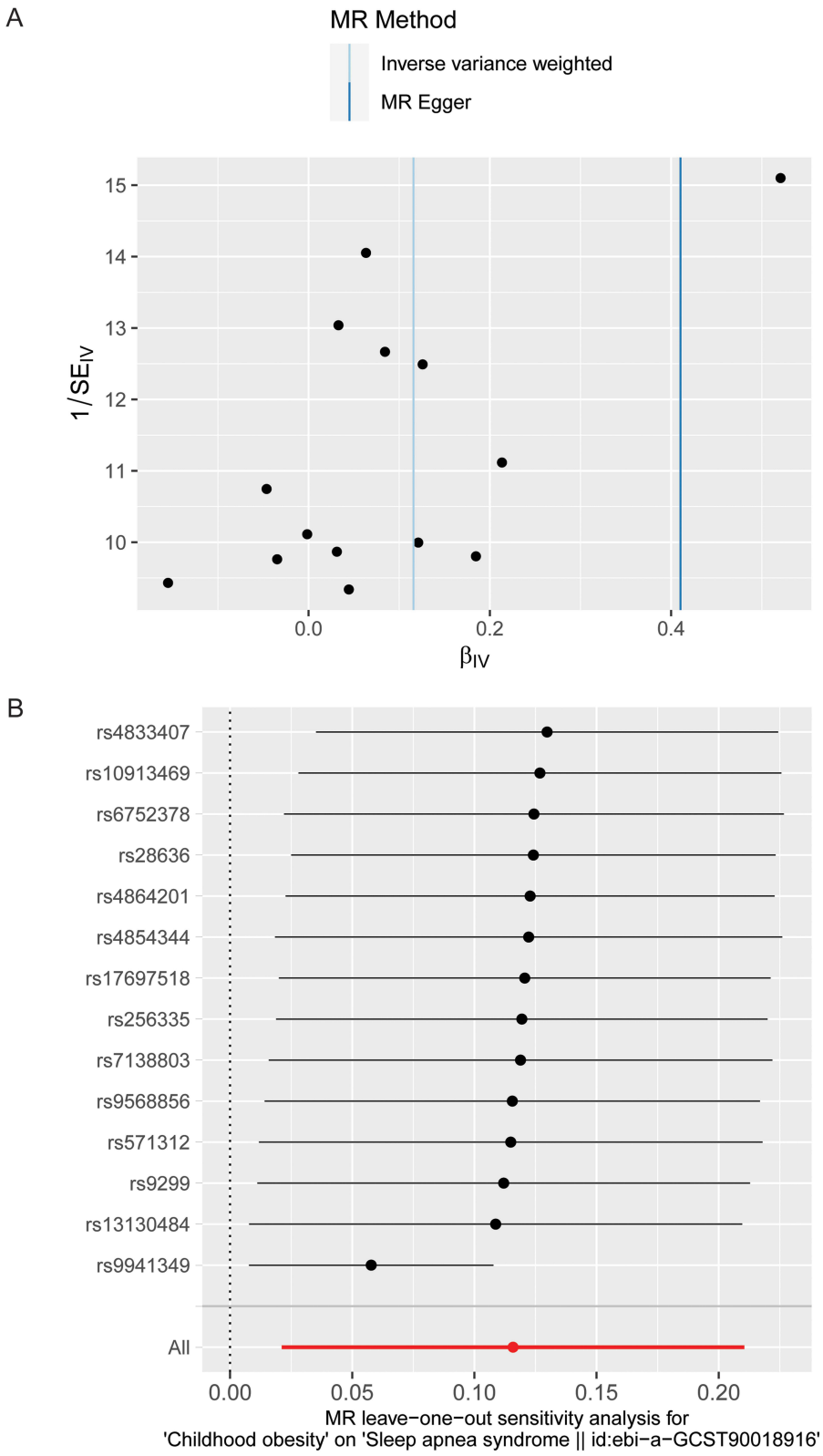

Figure 3 Funnel and leave-one-out plots of the impact of childhood obesity on sleep apnea syndrome. (**A**) Funnel plot to visualize overall heterogeneity of MR estimates for the effect of childhood obesity on the risk of sleep apnea syndrome; (**B**) Leave-one-out plot to visualize causal effect of childhood obesity on the risk of sleep apnea syndrome when leaving one SNP out.

Abbreviations: SNPs, single nucleotide polymorphisms; MR, Mendelian randomization.

Table 3 MR-PRESSO Test of Causal Relationship Between Childhood Obesity and the Risk of Sleep Respiratory Syndrome

Main MR Results	P Value
Causal estimate of raw	0.03222065
Causal estimate of outlier-corrected	0.04285058

Abbreviation: MR, Mendelian randomization.

future. This result also suggests that clinicians should avoid over-reliance on a single factor for diagnosis, and need to explore other possible causes more deeply. At the same time, it also suggests that more rigorous design and methods are needed in the clinical study of the relationship between sleep apnea syndrome and childhood obesity.

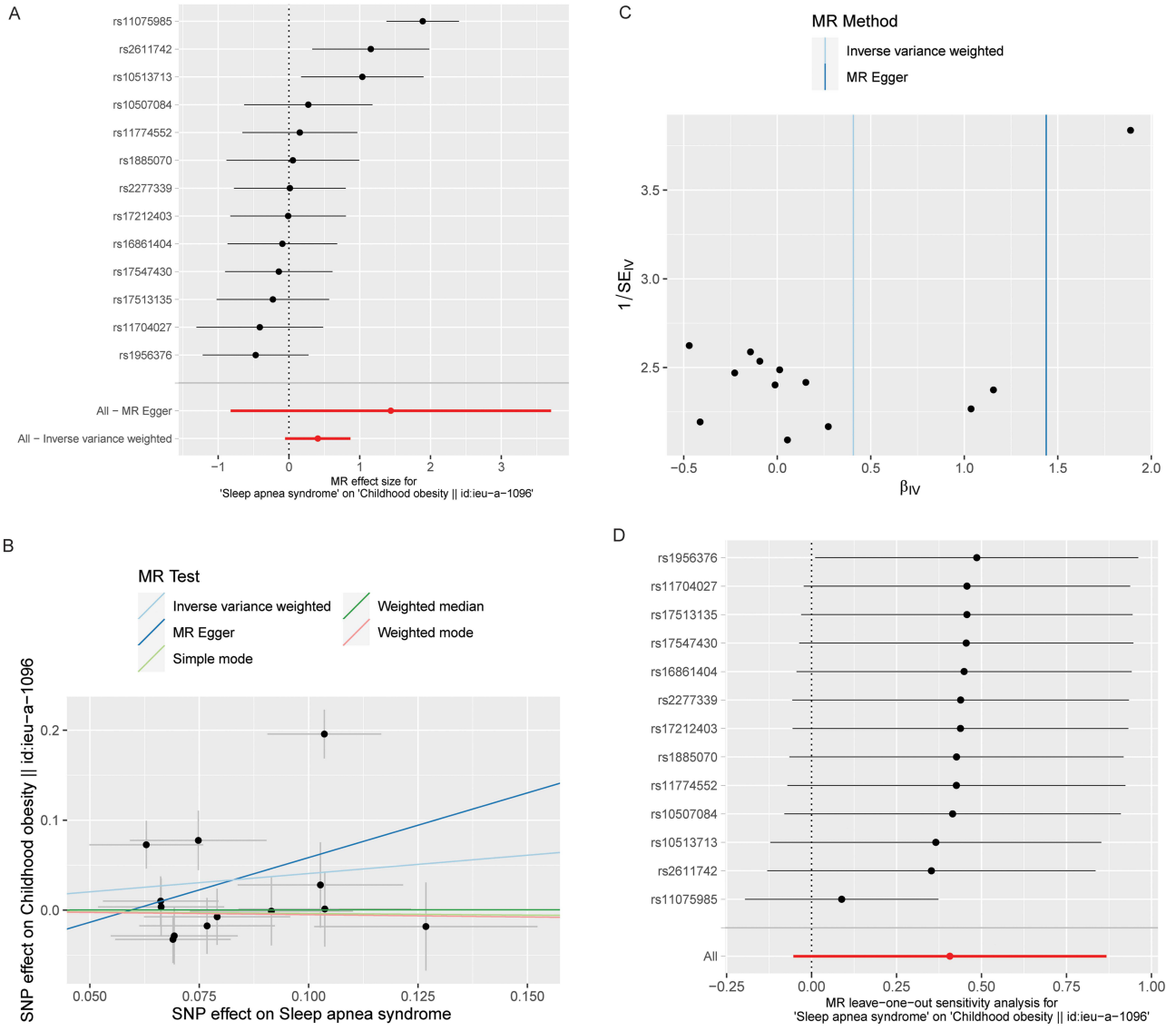

Figure 4 Forest, scatter, funnel and leave-one-out plots of the impact of sleep apnea syndrome on childhood obesity. (**A**) Forest plot to visualize causal effect of each single SNP on the risk of childhood obesity; (**B**) Scatter plot to visualize causal effect of sleep apnea syndrome on the risk of childhood obesity; (**C**) Funnel plot to visualize overall heterogeneity of MR estimates for the effect of sleep apnea syndrome on the risk of childhood obesity; (**D**) Leave-one-out plot to visualize causal effect of effect of sleep apnea on the risk of childhood obesity when leaving one SNP out.
Abbreviations: SNPs, single nucleotide polymorphisms; MR, Mendelian randomization.

Due to the fact that genetic variation is usually unrelated to confounding factors, MR is more effective than traditional observational studies in avoiding reverse causal associations and confounding factors.[53,54] Moreover, due to the high accuracy of the measurement of genetic variation, the regression dilution bias caused by measurement errors can be avoided.[55] In this study, the bidirectional two-sample MR study comprehensively evaluated the causal relationship between childhood obesity and sleep apnea syndrome. MR analysis can provide important support for the causal relationship between childhood obesity and sleep apnea syndrome. In this study, the intercept of MR-Egger regression was close to 0, which implies that there is no horizontal pleiotropy in IVs. Meanwhile, this also implies that there are no confounding factors in the analysis to affect the results of two-sample MR analysis. The IVW results showed a causal relationship between genetic susceptibility to childhood obesity and an increased risk of sleep apnea syndrome. Cochran's *Q* test showed that there was heterogeneity between the IVs. The presence of outlier SNPs was detected using MR-PRESSO, and the causal effect was estimated after the outlier SNP was excluded. This once again demonstrates a causal relationship between childhood obesity and the risk of sleep apnea syndrome. In addition, sensitivity analysis was performed using the leave-one-out method to evaluate the reliability of MR results. Herein, the leave-one-out results also showed that the bidirectional two-sample MR analysis results were robust.

As a health care provider, we should be proactive in the assessment and management of children with obesity. Obesity management includes diet, exercise, and behavioral changes and requires long-term follow-up. The goal of intervention therapy should be lifestyle intervention within the family. The management of overweight or obese children and adolescents should be coordinated with the individual and their families, and parents and guardians should be encouraged to aim primarily at lifestyle changes. Moreover, a support system should be developed with the goal of helping overweight and obese children and their families make lifestyle changes. Decisions about the care of overweight or obese children are made in conjunction with the child and his or her family, and individualized programs are tailored to select interventions that meet the needs of the child and his or her family and are easily accepted. Ensure that interventions that target the lifestyle of overweight or obese children are affordable to their families and society.

There are some limitations in this study. Firstly, this study focused primarily on European populations, and the inference of the results is limited. Therefore, the reliability of the causal associations should be validated in other populations. Secondly, due to the lack of sufficient datasets and sample size, the results of this study were not verified. Therefore, further clinical studies are still needed to confirm our results. Thirdly, stratified analysis, such as the subgroups based on sex, age, order of severity, could not be conducted with aggregated information from the GWAS. Fourthly, there is limited information on the potential differences between exposure and outcome GWAS in the study population. In light of these limitations, further studies with larger MR studies should be undertaken to better confirm the current results.

Conclusion

The results of this study imply a causal relationship between genetic susceptibility to childhood obesity and increased risk of sleep apnea syndrome, but no causal relationship between genetic susceptibility to sleep apnea syndrome and increased risk of childhood obesity. The identification of a causal relationship between childhood obesity and sleep apnea syndrome provides a new basis for exploring potential treatment methods. In addition, people with a history of childhood obesity should pay more attention to physical examination to early prevention and management of sleep apnea syndrome. Moreover, the results of this study may also be valuable for clinical decision-making.

Abbreviations

MR, Mendelian randomization; IVW, Inverse-variance weighted; SNPs, Single nucleotide polymorphisms; OR, odds ratio; CI, confidence interval; OSAS, obstructive sleep apnea syndrome; CSAS, central sleep apnea syndrome; IVs, instrumental variables; GWAS, Genome-wide association studies; LD, Linkage disequilibrium.

Data Sharing Statement

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

Ethical Statement

The present study was approved by the Ethics Committee of the Second Affiliated Hospital of Shandong First Medical University (2023-H-052). This study complied with the Declaration of Helsinki.

Funding

There is no funding to report.

Disclosure

Ping Wang and Shuli Liu contributed equally to this paper, can be considered as co-first authors. The authors declare that they have no conflicts of interest.

References

1. Thomas-Eapen N. Childhood Obesity. *Primary Care*. 2021;48(3):505–515. doi:10.1016/j.pop.2021.04.002
2. Smith JD, Fu E, Kobayashi MA. Prevention and Management of Childhood Obesity and Its Psychological and Health Comorbidities. *Ann Rev Clini Psychol*. 2020;16(1):351–378. doi:10.1146/annurev-clinpsy-100219-060201
3. Weihrauch-Blüher S, Wiegand S. Risk Factors and Implications of Childhood Obesity. *Curr Obes Rep*. 2018;7(4):254–259. doi:10.1007/s13679-018-0320-0
4. Brown CL, Halvorson EE, Cohen GM, Lazorick S, Skelton JA. Addressing Childhood Obesity: opportunities for Prevention. *Pediatr Clin N Am*. 2015;62(5):1241–1261. doi:10.1016/j.pcl.2015.05.013
5. Dabas A, Seth A. Prevention and Management of Childhood Obesity. *Indian J Pediatr*. 2018;85(7):546–553. doi:10.1007/s12098-018-2636-x
6. L Abarca-Gómez. Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128·9 million children, adolescents, and adults. *Lancet*. 2017;390(10113):2627–2642. doi:10.1016/S0140-6736(17)32129-3
7. Horesh A, Tsur AM, Bardugo A, Twig G. Adolescent and Childhood Obesity and Excess Morbidity and Mortality in Young Adulthood-a Systematic Review. *Current Obesity Reports*. 2021;10(3):301–310. doi:10.1007/s13679-021-00439-9
8. Sheng W, Ji G, Zhang L. Management of non-alcoholic fatty liver disease patients with sleep apnea syndrome. *World J Gastroenterol*. 2022;28(43):6099–6108. doi:10.3748/wjg.v28.i43.6099
9. Akashiba T, Inoue Y, Uchimura N, et al. Sleep Apnea Syndrome (SAS) Clinical Practice Guidelines 2020. *Resp Invest*. 2022;60(1):3–32. doi:10.1016/j.resinv.2021.08.010
10. Zhou T, Xie J, Wang X, et al. Causal Association between Whole-Body Water Mass and Sleep Apnea: a Mendelian Randomization Study. *Ann Am Thoracic Soc*. 2022;19(11):1913–1919. doi:10.1513/AnnalsATS.202112-1331OC
11. Hein H. Sleep Apnea as a Risk Factor. *Deutsches Arzteblatt International*. 2022;119(4):57. doi:10.3238/arztebl.m2022.0032
12. Culebras A, Anwar S. Sleep Apnea Is a Risk Factor for Stroke and Vascular Dementia. *Curr Neurol Neurosci Rep*. 2018;18(8):53. doi:10.1007/s11910-018-0855-1
13. Di Palmo E, Filice E. Childhood Obesity and Respiratory Diseases: which Link? *Children (Basel, Switzerland)*. 2021;8(3). doi:10.3390/children8030177
14. Laaban JP. Sleep apnea syndrome and obesity. *Revue Pneumol Clin*. 2002;58(2):91–98.
15. Turnbull CD, Wang SH, Manuel AR, et al. Relationships between MRI fat distributions and sleep apnea and obesity hypoventilation syndrome in very obese patients. *Sleep Breath*. 2018;22(3):673–681. doi:10.1007/s11325-017-1599-x
16. Whittle AT, Marshall I, Mortimore IL, Wraith PK, Sellar RJ, Douglas NJ. Neck soft tissue and fat distribution: comparison between normal men and women by magnetic resonance imaging. *Thorax*. 1999;54(4):323–328. doi:10.1136/thx.54.4.323
17. Bhattacharjee R, Kim J, Kheirandish-Gozal L, Gozal D. Obesity and obstructive sleep apnea syndrome in children: a tale of inflammatory cascades. *Pediatr Pulmonol*. 2011;46(4):313–323. doi:10.1002/ppul.21370
18. Arens R, Muzumdar H. Childhood obesity and obstructive sleep apnea syndrome. *J Appl Physiol*. 2010;108(2):436–444. doi:10.1152/japplphysiol.00689.2009
19. Sánchez-López AM, Noack-Segovia JP, Núñez-Negrillo AM. Childhood Obesity and its Influence on Sleep Disorders: kids-Play Study. *Int J Environ Res Public Health*. 2020;17(21):7948.
20. Kanney ML, Harford KL, Raol N, Leu RM. Obstructive sleep apnea in pediatric obesity and the effects of sleeve gastrectomy. *Semin Pediatr Surg*. 2020;29(1):150887. doi:10.1016/j.sempedsurg.2020.150887
21. Shechter A. Obstructive sleep apnea and energy balance regulation: a systematic review. *Sleep Med Rev*. 2017;34:59–69. doi:10.1016/j.smrv.2016.07.001
22. Papatriantafyllou E, Efthymiou D, Zoumbaneas E, Popescu CA. Sleep Deprivation: effects on Weight Loss and Weight Loss Maintenance. *Nutrients*. 2022;14(8). doi:10.3390/nu14081549
23. Sanderson E, Glymour MM, Holmes MV, et al. Mendelian randomization. *Nat Rev Method Prim*. 2022;2:6.
24. Holmes MV, Ala-Korpela M, Smith GD. Mendelian randomization in cardiometabolic disease: challenges in evaluating causality. *Nat Rev Cardiol*. 2017;14(10):577–590. doi:10.1038/nrcardio.2017.78
25. Xu J, Zhang S, Tian Y, et al. Genetic Causal Association between Iron Status and Osteoarthritis: a Two-Sample Mendelian Randomization. *Nutrients*. 2022;14(18):3683. doi:10.3390/nu14183683
26. Zheng J, Baird D, Borges MC, et al. Recent Developments in Mendelian Randomization Studies. *Curr Epidemiol Rep*. 2017;4(4):330–345. doi:10.1007/s40471-017-0128-6
27. Zhao Q, Chen Y, Wang J, Small DS. Powerful three-sample genome-wide design and robust statistical inference in summary-data Mendelian randomization. *Int J Epidemiol*. 2019;48(5):1478–1492. doi:10.1093/ije/dyz142

28. Porcu E, Rüeger S. Mendelian randomization integrating GWAS and eQTL data reveals genetic determinants of complex and clinical traits. *Nature Communications*. 2019;10(1):3300. doi:10.1038/s41467-019-10936-0
29. Bradfield JP, Taal HR, Timpson NJ, et al. A genome-wide association meta-analysis identifies new childhood obesity loci. *Nature Genet*. 2012;44(5):526–531.
30. Sakaue S, Kanai M. A cross-population atlas of genetic associations for 220 human phenotypes. *Nature Genetics*. 2021;53(10):1415–1424. doi:10.1038/s41588-021-00931-x
31. Hu B, He X, Li F, Sun Y, Sun J, Feng L. Childhood obesity and hypertension in pregnancy: a two-sample Mendelian randomization analysis. *J Hypertens*. 2023;41(7):1152–1158. doi:10.1097/HJH.0000000000003442
32. Pierce BL, Ahsan H, Vanderweele TJ. Power and instrument strength requirements for Mendelian randomization studies using multiple genetic variants. *Int J Epidemiol*. 2011;40(3):740–752. doi:10.1093/ije/dyq151
33. Xie J, Huang H, Liu Z, Li Y, Yu C. The associations between modifiable risk factors and nonalcoholic fatty liver disease: a comprehensive Mendelian randomization study. *Hepatology*. 2023;77(3):949–964. doi:10.1002/hep.32728
34. Guo HY, Wang W, Peng H, Yuan H. Bidirectional two-sample Mendelian randomization study of causality between rheumatoid arthritis and myocardial infarction. *Front Immunol*. 2022;13:1017444. doi:10.3389/fimmu.2022.1017444
35. Zhang K, Jia Y, Wang R, et al. Rheumatoid arthritis and the risk of major cardiometabolic diseases: a Mendelian randomization study. *Scand J Rheumatol*. 2023;52(4):335–341. doi:10.1080/03009742.2022.2070988
36. Fruh SM. Obesity: risk factors, complications, and strategies for sustainable long-term weight management. *J Am Assoc Nurse Practition*. 2017;29 (S1):S3–S14. doi:10.1002/2327-6924.12510
37. Araghi MH, Chen YF, Jagielski A, et al. Effectiveness of lifestyle interventions on obstructive sleep apnea (OSA): systematic review and meta-analysis. *Sleep*. 2013;36(10):1553–1562. doi:10.5665/sleep.3056
38. Greenburg DL, Lettieri CJ, Eliasson AH. Effects of surgical weight loss on measures of obstructive sleep apnea: a meta-analysis. *Am J Med*. 2009;122(6):535–542. doi:10.1016/j.amjmed.2008.10.037
39. Silvestri JM, Weese-Mayer DE, Bass MT, Kenny AS, Hauptman SA, Pearsall SM. Polysomnography in obese children with a history of sleep-associated breathing disorders. *Pediatr Pulmonol*. 1993;16(2):124–129. doi:10.1002/ppul.1950160208
40. Bachrach K, Danis DO. The Relationship Between Obstructive Sleep Apnea and Pediatric Obesity: a Nationwide Analysis. *The Annals of Otology, Rhinology, and Laryngology*. 2022;131(5):520–526. doi:10.1177/00034894211028489
41. Verhulst SL, Van Gaal L, De Backer W, Desager K. The prevalence, anatomical correlates and treatment of sleep-disordered breathing in obese children and adolescents. *Sleep Med Rev*. 2008;12(5):339–346. doi:10.1016/j.smrv.2007.11.002
42. Spector A, Scheid S, Hassink S, Deutsch ES, Reilly JS, Cook SP. Adenotonsillectomy in the morbidly obese child. *Int J Pediatr Otorhinol Yngo*. 2003;67(4):359–364. doi:10.1016/S0165-5876(02)00401-9
43. Verhulst SL, Schrauwen N, Haentjens D, et al. Sleep-disordered breathing in overweight and obese children and adolescents: prevalence, characteristics and the role of fat distribution. *Arch Dischildhood*. 2007;92(3):205–208. doi:10.1136/adc.2006.101089
44. Gordon JE, Hughes MS, Shepherd K, et al. Obstructive sleep apnoea syndrome in morbidly obese children with tibia vara. *J Bone Joint Surg*. 2006;88(1):100–103. doi:10.1302/0301-620X.88B1.16918
45. Cielo CM, Keenan BT. Neck fat and obstructive sleep apnea in obese adolescents. *Sleep*. 2021;44(11):zsab158.
46. Zhang Y, Wang H, Yang J, Wang S, Tong W, Teng B. Obstructive Sleep Apnea Syndrome and Obesity Indicators, Circulating Blood Lipid Levels, and Adipokines Levels: a Bidirectional Two-Sample Mendelian Randomization Study. *Nat Scie Sleep*. 2024;16:573–583.
47. Tauman R, Gozal D. Obesity and obstructive sleep apnea in children. *Paediatr Respirat Rev*. 2006;7(4):247–259. doi:10.1016/j.prrv.2006.08.003
48. Imayama I, Prasad B. Role of Leptin in Obstructive Sleep Apnea. *Ann Am Thoracic Soc*. 2017;14(11):1607–1621. doi:10.1513/AnnalsATS.201702-181FR
49. Ozturk L, Unal M, Tamer L, Celikoglu F. The association of the severity of obstructive sleep apnea with plasma leptin levels. *Archiv Otolaryngol Head Nnec Surg*. 2003;129(5):538–540. doi:10.1001/archotol.129.5.538
50. Gozal D, Capdevila OS, Kheirandish-Gozal L. Metabolic alterations and systemic inflammation in obstructive sleep apnea among nonobese and obese prepubertal children. *Am J Respir Crit Care Med*. 2008;177(10):1142–1149. doi:10.1164/rccm.200711-1670OC
51. Waters KA, Sitha S, O'Brien LM, et al. Follow-up on metabolic markers in children treated for obstructive sleep apnea. *Am J Respir Crit Care Med*. 2006;174(4):455–460. doi:10.1164/rccm.200401-110OC
52. Kuvat N, Tanriverdi H, Armutcu F. The relationship between obstructive sleep apnea syndrome and obesity: a new perspective on the pathogenesis in terms of organ crosstalk. *Clin Rspirator J*. 2020;14(7):595–604.
53. Hu Z, Zhou F. Circulating vitamin C and D concentrations and risk of dental caries and periodontitis: a Mendelian randomization study. *J Clin Periodontol*. 2022;49(4):335–344.
54. Luo S, Li W, Li Q, et al. Causal effects of gut microbiota on the risk of periodontitis: a two-sample Mendelian randomization study. *Front Cell Infect Microbiol*. 2023;13:1160993. doi:10.3389/fcimb.2023.1160993
55. Larsson SC, Michaëlsson K, Burgess S. Mendelian randomization in the bone field. *Bone*. 2019;126:51–58. doi:10.1016/j.bone.2018.10.011