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Observational Study

Relationship between lipids and sleep apnea: based on Mendelian randomization analysis

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Abstract

BACKGROUND

Lipids have been reported to increase the risk of sleep apnea. However, the causality between them is still inconclusive.

AIM

Our study explored the causal relationship between serum lipids and sleep apnea using the two-sample Mendelian randomization (MR) analysis.

METHODS

Single nucleotide polymorphism (SNP) data related to serum lipids were obtained from the Global Lipids Genetics Consortium study, which included 188,578 individuals of European ancestry[1]. Additionally, sleep apnea-related SNP data were collected from the UK Biobank study, which comprised 463,005 individuals of European ancestry. A two-sample MR analysis was performed to assess the causality between serum lipids and sleep apnea based on the above public data.

RESULTS

Genetically predicted low-density lipoprotein (odds ratio [OR] = 0.99, 95% confidence interval [CI] = 0.99 to 1.00, *P* = 0.58), high-density lipoprotein (OR = 0.99, 95%CI = 0.99 to 1.00, *P* = 0.91), triglyceride (OR = 1.00, 95%CI = 0.99 to 1.00, *P* = 0.92), and total cholesterol (OR = 0.99, 95%CI = 0.99 to 1.00, *P* = 0.33) were causally unrelated to sleep apnea.

CONCLUSION

Our MR analysis suggested that genetically predicted serum lipids were not the risk factors of sleep apnea.

INTRODUCTION

Snoring during sleep is accompanied by apnea and shallow breathing, therefore resulting in intermittent hypoxemia. Sleep apnea (SA) is a complex disease complicated by cardiovascular diseases, such as coronary syndrome, hypertension, congestive heart failure, arrhythmia, and pulmonary hypertension, and neuropsychiatric dysfunction, such as inattention, memory, and cognitive impairment. In addition, the incidence of insulin resistance and metabolic disorder is also higher in patients with SA than in patients without SA[2-6]. As reported, SA can lead to dyslipidemia, obesity, and metabolic syndrome[7].

Traditional studies believe that SA is mainly linked to the anatomical structure of the upper airway[8]. Recent epidemiological studies have demonstrated that male and obesity are the main risk factors for SA[7]. In the past, there has been discussion about how SA affects serum lipids, and several studies have exhibited that the levels of dyslipidemia, including low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglyceride (TG), and total cholesterol (TC), increase in patients with obstructive SA (OSA)[9-11]. Nevertheless, it is rarely discussed whether serum lipids can be risk factors for SA. Understanding the effect of serum lipids on SA may assist in reducing relevant risk factors and providing novel ideas for the intervention of SA.

The critical risk factors of OSA are obesity and high body mass index (BMI), which are both associated with abnormal lipid metabolism. However, it remains unclear whether lipids may be directly correlated with OSA. We assume that there is a correlation between them and analyze their correlation using the Mendelian randomization (MR) method. MR, a newly developed research method, uses genetic variants as instrumental variables to investigate whether a risk factor causally afflicts a health outcome and is possible to avoid confounding factors in observational studies and clinical trials[12, 13]. In our research, LDL, HDL, TG, and TC were utilized as representative lipid markers to probe the causal relationship between lipids and SA.

MATERIALS AND METHODS

Data resources and study design

Our data were sourced from published data. The statistical data for genetically predicted LDL (N = 173,0820), HDL (N = 187,167), TG (*n* = 177,861), and TC (*n* = 187,365) were obtained from the Global Lipids Genetics Consortium (GLGC) study that summarized 45 studies and incorporated 188,578 individuals of European ancestry[1]. The outcome data for genetically predicted SA (*n* = 463,010) were harvested from the UK Biobank (UKB) study (Table 1). Afterwards, a two-sample MR analysis was conducted to investigate the causal relationship of serum lipids with SA. The complete experimental design is shown in Figure 1.

Selection of genetic instrumental variables

In order to select appropriate instrumental variables, assumption 1 that instrumental variables were strongly correlated with exposure was first satisfied according to our experimental design. Subsequent to separate extraction of SNPs associated with LDL, HDL, TG, and TC with genome-wide significance ($P < 5 \times 10^{-8}$), the clumping process ($R^2 < 0.001$, window size = 10,000 kb) was conducted to remove the linkage disequilibrium[14]. Second, assumption 2 was fulfilled to ensure no association between the instrumental SNPs and confounding factors (BMI, male gender, and obesity were identified as confounders[15] in this study). SNPs related to confounding

factors were excluded using a website (http://www.phenoscanner.medschl.cam.ac.uk/). Last, SNPs related to outcomes were also eliminated by the aforementioned website to meet assumption 3.

Statistical analysis

An inverse variance weighted (IVW) meta-analysis was carried out to obtain an MR estimate. In order to enable a more reliable IVW approach, there was no evidence of targeted pleiotropy in the selected IVs (MR-Egger, $P > 0.05$)[16, 17]. Other methods, including MR-Egger method, weighted median method, Simple mode method, and weighted mode method, also were conducted to evaluate the stability of the results[18, 19]. The weighted median method has the advantage that the results are consistent even when up to 50% of the information comes from invalid instrumental variables[18].

Sensitivity analysis

The Cochran's Q test was utilized to assess the heterogeneity of individual genetic variability we estimated. *P* value less than 0.05 was regarded as significant heterogeneity. The stability of the results was evaluated using the funnel diagram. Pleiotropy was not found by MR-Egger test. The leave-one-out sensitivity analysis was performed to observe whether the results changed after each SNP was eliminated. The results are presented in Figure S2 to S5.

The package "Two-Sample-MR" (version 0.5.6, Bristol, UK) in R (version 4.1.2, Vienna, Austria) was utilized in our analysis.

RESULTS

Association of serum lipid levels with the risk of SA

In MR, the IVW method manifested that the level of serum lipids including LDL (odds ratio [OR] = 0.99, 95% confidence interval [CI] = 0.99 to 1.00, *P* = 0.58), HDL (OR = 0.99, 95%CI = 0.99 to 1.00, *P* = 0.91), TG (OR = 1.00, 95%CI = 0.99 to 1.00, *P* = 0.92), and TC (OR = 0.99, 95%CI = 0.99 to 1.00, *P* = 0.33) was not causally associated with SA. Another four approaches were also applied including MR Egger, weighted median, Simple mode, and Weighted mode. No obvious heterogeneity and horizontal pleiotropy were

observed. The detailed results are displayed in Table 2 and Table 3. There existed no evidence of heterogeneity in the IVW analysis as demonstrated by funnel plots (Figure S6 to S9). The effect size of SNPs on exposure (serum lipids) and outcome (SA) was found in scatter plots (Figure S10 to Figure S13). The effect of every single SNP on the outcomes is manifested in forest plots (Figure S14 to Figure S17).

DISCUSSION

This study carefully selected SNPs as effective instrumental variables and excluded known risk factors (obesity and high BMI, as well as other known risk factors, including male neck circumference greater than 17 inches [43cm], female neck circumference greater than 15 inches [38cm], male gender, age over 50 years, smoking, and so on[15]). It was found through the MR analysis in the present study that genetically predicted LDL, HDL, TG, and TC had no causal relationship with SA.

Numerous studies have dissected the relationship between serum lipids and SA, but the results have been varied. Murat can *et al* found the higher levels of TC, LDL, TG, and Apolipoprotein B in the OSA group than in the control group[20]. A study of Japanese working men elucidated a positive correlation between the respiratory disorder index and TG[21]. Tan *et al* noted that HDL was diminished and oxidized LDL was elevated in patients with OSA[22]. In a study of patients in eastern China, the authors observed that LDL was independently associated with OSA[23]. The inconsistency of the above results may be related to the small sample size and the involvement of confounding factors.

Our results unraveled that genetically predicted LDL, HDL, TG, and TC were not causally correlated with SA. This result can be explained by the following mechanisms. First, the deposition of excessive fat in the neck may increase airway resistance and resultant susceptibility to SA. Nonetheless, the study comparing the distribution of neck soft tissues and fat between normal men and women by magnetic resonance imaging elaborated that the difference of fat deposition might not substantially damage the anatomical structure of the airway[24]. Second, SA is a complex disease and not simple pathogenesis of mechanical load. The factors involved also consist of the neurohumoral

and metabolic inflammatory environment[25, 26]. Apneas and hypopneas are classified into obstructive or central types[27], with OSA as the most common type. In OSA, airway anatomy is critically implicated in the influence of airway collapsing pressure in patients with the hypotonic airway. However, some evidence illustrated that neuromuscular factors are a pivotal cause of airway collapse during sleep, including upper airway dilator dysfunction, increased chemical sensitivity, and low arousal threshold (premature sleep arousal contributes to unstable ventilation control)[28, 29]. Dong *et al* delved into the relationship between lipid accumulation products (LAPs) and OSA in patients with type 2 diabetes mellitus, which revealed that after the same confounding factors were adjusted, neither TG nor waist circumference, as constituents of LAPs, was signally associated with apnea-hypopnea indexes (AHI) and OSA[30]. BMI, visceral fat, and neck circumference are the principal predictors of clinical expression in OSA. After exclusion of these known risk factors, our calculated results unveiled that genetically predicted lipids did not directly correlate to SA. Multiple studies have concluded lipids as a risk factor for SA, most likely because dyslipidemia metabolism may cause obesity and obesity is the primary risk factor for OSA. However, the direct correlation between lipids and SA was discussed in our study based on big data research, not the real world. For the aforementioned reasons, there might not be a causal relationship between serum lipids and SA.

There are several advantages to this study. First, different from other observational studies, genetic variants can be collected from different samples of individuals, and genetic associations can be attained from large GWAS, which can remarkably improve the statistical ability to detect the small effects of complex phenotypes[31]. Second, the present study excluded more confounding factors, excluded heterogeneity and level pleiotropy, and conducted sensitivity tests to strengthen the conviction of our results.

Of course, our study also has limitations. First of all, the sample population included in our study is all from Europe. In this context, it cannot be confirmed that the same conclusion is obtained from non-European populations. In addition, in terms of the

selection of serum lipid markers, only four markers were included in our research. It remains enigmatic whether other bio-markers are causally related to SA.

CONCLUSION

Genetically predicted LDL, HDL, TG, and TC may not have a causal relationship with SA. More pathogenesis of SA needs to be studied.

ARTICLE HIGHLIGHTS

Research background

OSA has a negative effect on serum lipids, but the relationship between serum lipids and OSA is still uncertain.

Research motivation

Explore the direct effect of serum lipids on OSA.

Research objectives

We observed that lipids are not related to OSA, and we need to further look for other markers to predict OSA in the future.

Research methods

First, compared with other observational studies, the genetic variants can be obtained from different sample of individuals, and genetic associations can be obtained from large GWAS, which can greatly improve the statistical ability to detect small effects of complex phenotypes. Second, the study excluded more confounding factors, excluded heterogeneity and level pleiotropy, and conducted sensitivity tests to make our results more convincing.

Research results

In MR, the IVW method manifested that the level of serum lipids including LDL (odds ratio [OR] = 0.99, 95% confidence interval [CI] = 0.99 to 1.00, P = 0.58), HDL (OR = 0.99, 95%CI = 0.99 to 1.00, P = 0.91), TG (OR = 1.00, 95%CI = 0.99 to 1.00, P = 0.92), and TC (OR = 0.99, 95%CI = 0.99 to 1.00, P = 0.33) was not causally associated with SA.

Research conclusions

Through Mr analysis, this study concludes that serum lipids are not associated with SA.

Research perspectives

We need to find other markers to predict SA in the future.

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1	Bing-Kun Zheng, Xue-Yi Sun, Jie Xian, Peng-Peng Niu. "Maternal Testosterone and Offspring Birth Weight: A Mendelian Randomization Study", The Journal of Clinical Endocrinology & Metabolism, 2022 Crossref	54 words — 3%
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