

World Journal of *Clinical Cases*

World J Clin Cases 2022 November 6; 10(31): 11214-11664



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ABOUT COVER

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RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Xu Guo*; Production Department Director: *Xiang Li*; Editorial Office Director: *Jin-Lei Wang*.

NAME OF JOURNAL

World Journal of Clinical Cases

ISSN

ISSN 2307-8960 (online)

LAUNCH DATE

April 16, 2013

FREQUENCY

Thrice Monthly

EDITORS-IN-CHIEF

Bao-Gan Peng, Jerzy Tadeusz Chudek, George Kontogeorgos, Maurizio Serati, Ja Hyeon Ku

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/2307-8960/editorialboard.htm>

PUBLICATION DATE

November 6, 2022

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INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjgnet.com/bpg/GerInfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>



Observational Study

Relationship between lipids and sleep apnea: Mendelian randomization analysis

Lian-Peng Zhang, Xiao-Xia Zhang

Specialty type: Respiratory system

Provenance and peer review:

Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): D, D
Grade E (Poor): 0

P-Reviewer: Dziegielewska-Gesiak S, Poland; Papadopoulos VP, Greece

Received: May 8, 2022

Peer-review started: May 8, 2022

First decision: July 12, 2022

Revised: July 26, 2022

Accepted: September 20, 2022

Article in press: September 20, 2022

Published online: November 6, 2022



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Abstract

BACKGROUND

Lipids increase the risk of sleep apnea; however, the causality between them is still inconclusive.

AIM

To explore the causal relationship between serum lipids and sleep apnea using 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 188578 individuals of European ancestry. Additionally, sleep apnea-related SNP data were collected from the United Kingdom Biobank study, which comprised 463005 individuals of European ancestry. 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 suggests that genetically predicted serum lipids are not risk factors of sleep apnea.

Key Words: Lipid; Sleep apnea; Mendelian randomization; Single nucleotide polymorphism; Risk factor

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Core Tip: This study had a couple of key advantages. 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 genome-wide association studies, which can greatly improve the statistical ability to detect small effects of complex phenotypes. Second, the study excluded more confounding factors, heterogeneity and level pleiotropy, and conducted sensitivity tests to make our results more convincing.

Citation: Zhang LP, Zhang XX. Relationship between lipids and sleep apnea: Mendelian randomization analysis. *World J Clin Cases* 2022; 10(31): 11403-11410

URL: <https://www.wjgnet.com/2307-8960/full/v10/i31/11403.htm>

DOI: <https://dx.doi.org/10.12998/wjcc.v10.i31.11403>

INTRODUCTION

Snoring during sleep is accompanied by apnea and shallow breathing, 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 than without SA[1-5]. As reported, SA can lead to dyslipidemia, obesity, and metabolic syndrome[6].

Traditional studies believe that SA is mainly linked to the anatomical structure of the upper airway [7]. Recent epidemiological studies have demonstrated that male and obesity are the main risk factors for SA[6]. In the past, there has been discussion about how SA affects serum lipids, and several studies have shown 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)[8-10]. 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 assumed that there is a correlation between them and analyzed 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 [11,12].

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 ($n = 1730820$), HDL ($n = 187167$), TG ($n = 177861$), and TC ($n = 187365$) were obtained from the Global Lipids Genetics Consortium study that summarized 45 studies and incorporated 188578 individuals of European ancestry[13]. The outcome data for genetically predicted SA ($n = 463010$) were harvested from the United Kingdom Biobank 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

To select appropriate instrumental variables, assumption 1 that instrumental variables are strongly correlated with exposure was first satisfied according to our experimental design. Subsequent to

Table 1 Detailed data of Mendelian randomization

Variable	Consortium	PMID	Population	Sex
Sleep apnea	UKB	-	European	Males and females
LDL-C	GLGC	24097068	European	Males and females
HDL-C	GLGC	24097068	European	Males and females
TG	GLGC	24097068	European	Males and females
TC	GLGC	24097068	European	Males and females

GLGC: Global Lipid Genetics Consortium; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; TC: Total cholesterol; TG: Triglyceride; UKB: United Kingdom Biobank.

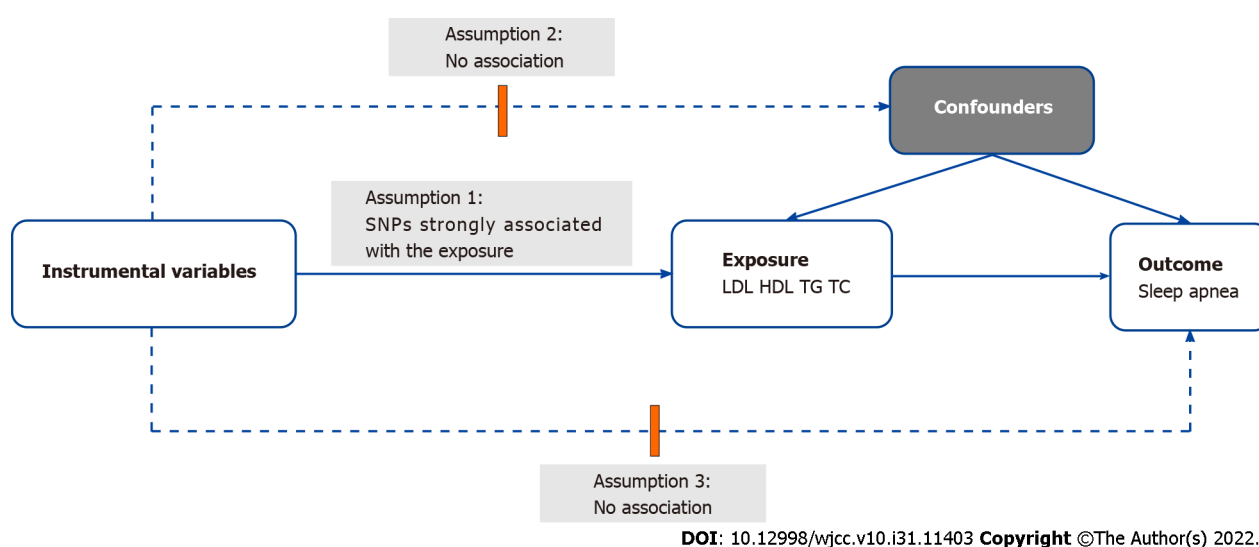


Figure 1 Overall design of Mendelian randomization analysis in this study. LDL: Low-density lipoprotein; HDL: High-density lipoprotein; TG: Triglyceride; TC: Total cholesterol.

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 = 10000 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 sex, 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 analyses

An inverse variance weighted (IVW) meta-analysis was carried out to obtain an MR estimate. 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, were also 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 **Supplementary Figures 1-4**. The package "two-sample-MR" (version 0.5.6; Bristol, United Kingdom) 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 was observed. The detailed results are displayed in Tables 2 and 3. There was no evidence of heterogeneity in the IVW analysis as demonstrated by funnel plots (Supplementary Figures 5-8). The effect size of SNPs on exposure (serum lipids) and outcome (SA) was found in scatter plots (Supplementary Figures 9-12). The effect of every single SNP on the outcomes is manifested in forest plots (Supplementary Figures 13-16).

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 [43 cm], female neck circumference greater than 15 inches [38 cm], male sex, age over 50 years, and smoking[15]). MR analysis showed 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. Can *et al*[20] showed the higher levels of TC, LDL, TG, and apolipoprotein B in the OSA group than in the control group. A study of Japanese working men elucidated a positive correlation between the respiratory disorder index and TG[21]. Tan *et al*[22] noted that HDL was diminished and oxidized LDL was elevated in patients with OSA. 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 revealed 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*[30] 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 and OSA. 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.

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

This study also has limitations. First, the sample population included in our study was 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 unknown whether other biomarkers are causally related to SA.

Table 2 Results from two sample Mendelian randomization analysis

Lipid	Method	Number of SNPs	P value	OR	95%CI
LDL and Sleep apnea	MR Egger	42	0.58	0.99	0.99-1.00
	Weighted median	42	0.97	0.99	0.99-1.00
	Inverse variance weighted	42	0.85	1.00	0.99-1.00
	Simple mode	42	0.31	1.00	0.99-1.00
	Weighted mode	42	0.74	0.99	0.99-1.00
HDL and sleep apnea	MR Egger	55	0.91	0.99	0.99-1.00
	Weighted median	55	0.35	1.00	0.99-1.00
	Inverse variance weighted	55	0.29	1.00	0.99-1.00
	Simple mode	55	0.22	1.00	0.99-1.00
	Weighted mode	55	0.33	1.00	0.99-1.00
TG and Sleep apnea	MR Egger	35	0.92	1.00	0.99-1.00
	Weighted median	35	0.82	0.99	0.99-1.00
	Inverse variance weighted	35	0.57	1.00	0.99-1.00
	Simple mode	35	0.59	0.99	0.99-1.00
	Weighted mode	35	0.94	1.00	0.99-1.00
TC and Sleep apnea	MR Egger	51	0.33	0.99	0.99-1.00
	Weighted median	51	0.68	0.99	0.99-1.00
	Inverse variance weighted	51	0.82	1.00	0.99-1.00
	Simple mode	51	0.20	1.00	0.99-1.00
	Weighted mode	51	0.70	1.00	0.99-1.00

HDL: High-density lipoprotein; LDL: Low-density lipoprotein; MR: Mendelian randomization; OR: Odds ratio; SNPs: Single nucleotide polymorphisms; TC: Total cholesterol; TG: Triglyceride.

Table 3 Heterogeneity test and level pleiotropy test

Lipid	Heterogeneity test, inverse variance weighted			Level pleiotropy test
	Q	df	P value	P value
LDL	33.04	41	0.807	0.459
HDL	67.98	54	0.096	0.408
TG	34.87	34	0.427	0.823
TC	48.34	50	0.540	0.247

HDL: High-density lipoprotein; LDL: Low-density lipoprotein; TC: Total cholesterol; TG: Triglyceride.

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

Obstructive sleep apnea (OSA) has a negative effect on serum lipids, but the relationship between serum lipids and OSA is still uncertain.

Research motivation

We explored 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 genome-wide association studies, 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 Mendelian randomization, the inverse variance weighted method manifested that the level of serum lipids including 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, $P = 0.33$) was not causally associated with sleep apnea (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.

FOOTNOTES

Author contributions: Zhang LP contributed to conceptualization, methodology, software, writing-review, and editing; Zhang XX contributed to formal analysis, writing-review, and editing.

Institutional review board statement: The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). All data base were from public research. No patients were participated in the design or study. Thus, ethical approval was not needed for our study.

Informed consent statement: Since this study does not involve human participation, it is not necessary to sign an informed document.

Conflict-of-interest statement: All authors have no conflicts of interest to declare.

Data sharing statement: The data used in this study are all from published materials, dataset available from <https://gwas.mrcieu.ac.uk/>.

STROBE statement: The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

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S-Editor: Liu JH

L-Editor: Filipodia

P-Editor: Liu JH

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