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ORIGINAL RESEARCH

Observational and Genetic Evidence Reveals the Effect of Serum Lipid Levels on COPD Risk

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Background: Disorders of lipid metabolism are linked to an increased risk of various diseases; however, their association with chronic obstructive pulmonary disease (COPD) remains unclear. This study aimed to examine the relationship between serum lipid levels and COPD risk.

Methods: The methods of the National Health and Nutrition Examination Survey (NHANES) and Mendelian randomization (MR) analyses were employed to investigate the relationships between lipids and COPD across multiple populations. Data from 2013 to 2023 were selected for the NHANES study on US population, and weighted multivariable-adjusted logistic regression was employed as the primary statistical method. And data utilized for the MR analysis were derived from genome-wide association studies (GWAS) conducted on European and East Asian populations, with inverse-variance weighted (IVW) method serving as the principal statistical approach.

Results: The NHANES analyses indicated that higher levels of total cholesterol (TC) (OR = 0.85, 95% CI = 0.77–0.93), non-high-density lipoprotein cholesterol (non-HDL-C) (OR = 0.86, 95% CI = 0.78–0.94) and low-density lipoprotein cholesterol (LDL-C) (OR = 0.85, 95% CI = 0.74–0.97) were associated with a reduced risk of COPD in the US population. In the MR analyses, TC (OR = 0.90, 95% CI = 0.84–0.95), non-HDL-C (OR = 0.91, 95% CI = 0.85–0.96), and LDL-C (OR = 0.88, 95% CI = 0.82–0.94) were causally linked to a decreased risk of COPD in the European population. Similar associations were observed in the East Asian population.

Conclusion: Our study identified associations between TC, non-HDL-C, and LDL-C with a reduced risk of COPD. This underscores the importance of monitoring lipid metabolism in patients with COPD and provides supporting evidence for the use of lipid-based therapies in its treatment.

Keywords: lipids, COPD, association, NHANES, Mendelian randomization

Introduction

Chronic obstructive pulmonary disease (COPD) is a condition that poses a significant threat to human health, with a high global incidence. A 2019 study reported a global prevalence of 10.3%, affecting approximately 400 million individuals worldwide.[1] COPD is associated with high rates of disability and mortality, ranking as the third leading cause of disability-adjusted life years (DALYs) and the third leading cause of death globally, with approximately 3.3 million deaths annually attributed to COPD.[2] Smoking and environmental pollution are well-established external risk factors for COPD.[3–5] However, significant variations in COPD prevalence exist among populations exposed to these factors. Notably, fewer than 50% of heavy smokers develop COPD, highlighting differences in individual susceptibility.[6] This variability suggests that intrinsic factors within the human body also play a crucial role in the development of COPD. Therefore, exploring these factors is essential for gaining a deeper understanding of the disease and its underlying mechanisms.

Lipids are a class of compounds that are abundant in the human body and play a crucial role in maintaining normal physiological functions. Previous studies have established strong associations between serum lipid levels and various diseases, particularly cardiovascular and cerebrovascular disorders.[7,8] Recent studies have emphasized the relationship

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between lipids and COPD. Patients with COPD exhibit several lipid metabolism imbalances. Beti Zafirova-Ivanovska et al reported elevated serum low-density lipoprotein cholesterol (LDL-C) levels and decreased high-density lipoprotein cholesterol (HDL-C) levels in COPD patients.[9] A meta-analysis revealed significantly higher serum triglyceride levels in COPD patients compared to healthy individuals.[10] Additionally, serum lipid levels contribute to COPD risk. Robert M. Reed et al identified an association between COPD and elevated HDL-C levels, while Hui Li et al recognized apolipoprotein M (apoM) in HDL-C as a risk factor for COPD development, with its levels increasing progressively with disease severity.[11,12] However, most studies on the lipid-COPD relationship are small-sample observational studies, providing low-level evidence and failing to establish causality. The link between serum lipid levels and COPD risk remains unclear.

The National Health and Nutrition Examination Survey (NHANES) is an ongoing cross-sectional study conducted by the National Center for Health Statistics (NCHS) that collects extensive data on health and disease among the US population. NHANES provides high-quality, large-sample, nationally representative data for assessing the relationships between independent and dependent variables.[13] Mendelian randomization (MR), an emerging method in epidemiological research, serves as an alternative to RCTs and a complement to observational studies. This approach uses genetic variants as instrumental variables (IVs) to mitigate confounding and reverse causality, enabling a genetic assessment of causal relationships between exposures and outcomes.[14]

In this study, we integrated NHANES and MR methodologies to comprehensively evaluate the relationships between serum lipid levels and COPD risk across diverse populations. This approach aimed to assess the impact of lipids on COPD susceptibility and provide evidence for lipid management in COPD patients.

Methods

Study Design

The study design is illustrated in Figure 1. We employed both observational and MR methodologies to evaluate the impact of lipids on COPD. The observational study utilized NHANES data from 2013 to 2023, as this period contained information on COPD. Using these data, we examined the associations between five lipids—total cholesterol (TC), HDL-C, non-HDL-C, LDL-C, and triglycerides—and COPD risk in the US population. NHANES study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[15] The MR study examined the causal relationships between these lipids and COPD risk in European and East Asian populations, respectively. MR study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology-Mendelian Randomization (STROBE-MR) guidelines.[16]

Data Sources

Data for the observational study were obtained from NHANES, which is primarily publicly available and can be accessed at https://wwwn.cdc.gov/nchs/nhanes/. The study included data on the independent variables (five lipids: TC, HDL-C, non-HDL-C, LDL-C, and triglycerides), the dependent variable (COPD), and covariates (age, gender, ethnicity, poverty-to-income ratio [PIR], body mass index [BMI], education level, marital status, smoking status, hypertension, diabetes and coronary heart disease [CHD]) from NHANES 2013–2023. Direct data for non-HDL-C are unavailable in NHANES; non-HDL-C is calculated by subtracting HDL-C from TC. Due to the absence of LDL-C and triglyceride data in NHANES for the years 2020–2023, our analysis of LDL-C and triglycerides was limited to data from 2013–2020.

COPD was diagnosed based on the response to the question, “Ever told you had COPD?”. Smoking status was determined based on the responses to the questions, “Smoked at least 100 cigarettes in your lifetime?” and “Do you now smoke cigarettes?”. Hypertension was characterized based on the ACC/AHA guidelines, which define it as a systolic blood pressure (SBP) of ≥ 130 mmHg or a diastolic blood pressure (DBP) of ≥ 80 mmHg.[17] Moreover, individuals with a history of hypertension or those using antihypertensive medications were classified as hypertensive. Diabetes is defined by the American Diabetes Association (ADA) diagnostic criteria as fasting blood glucose (FBG) ≥7 mmol/l, a 2-hour glucose level during the oral glucose tolerance test (OGTT) ≥11 mmol/l, or an HbA1c level ≥6.5%.[18] Additionally,

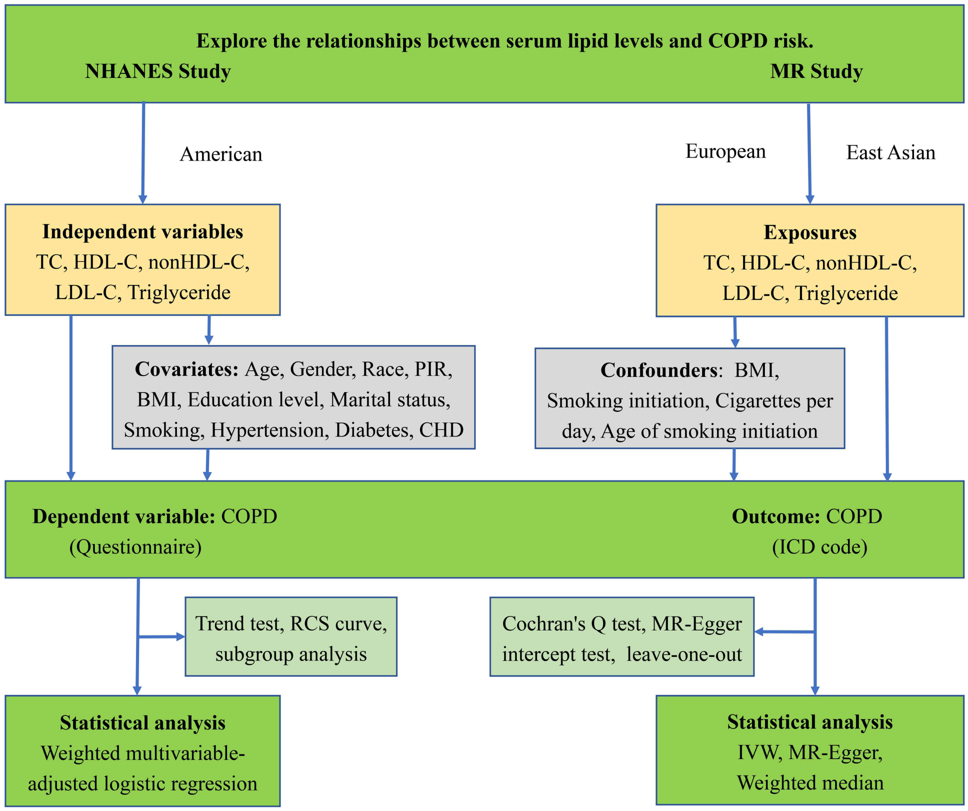

Figure 1 The schematic diagram of this study.

individuals with a history of diabetes or those using insulin or oral hypoglycemic agents are also considered to have diabetes. CHD was determined based on the response to the question, "Ever told you had coronary heart disease?".

The MR analysis used data from large genome-wide association studies (GWAS) databases, with separate data sets for European and East Asian populations. These publicly available data are detailed in Table S1. COPD GWAS data for European populations were obtained from the latest release (version 12) of the FinnGen consortium. FinnGen collects and analyzes genetic data from 500,000 Finnish biobank participants, with COPD diagnosis based on ICD codes. The GWAS data on COPD in the East Asian population were obtained from the Japan Biobank. GWAS data for lipid traits were obtained from the Global Lipids Genetic Consortium (GLGC), a worldwide collaborative initiative dedicated to investigating the genetic underpinnings of lipid traits.[19] This consortium provides the most extensive summary GWAS data available for lipid traits. We selected data on TC, HDL-C, non-HDL-C, LDL-C, and triglycerides from the GLGC, focusing on the European and East Asian populations. To further account for the potential effects of confounding variables, we also acquired GWAS data on smoking and BMI. The smoking data were sourced from GWAS & Sequencing Consortium of Alcohol and Nicotine use (GSCAN), including data for European and East Asian populations.[20] BMI GWAS data for the European population were sourced from the Within Family GWAS Consortium, while data for the East Asian population were obtained from Saori Sakaue et al.[21]

This study is a secondary analysis, with data sourced from the publicly available NHANES and GWAS summary databases. Ethical approval and informed consent for the participants were obtained in the original studies, and thus no additional approval is required for this analysis.

Data Screening

Data were extracted from the NHANES 2013–2023 dataset for study-related variables. The first excluded participants under the age of 20. Additional exclusions were made for individuals with missing data on key variables, including the independent variable (COPD), dependent variables (lipid levels: TC, HDL-C, nonHDL-C, LDL-C, and triglycerides), and

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covariates (education level, marital status, PIR, BMI, and smoking status, hypertension, diabetes, and CHD). The final sample sizes for statistical analysis of lipid levels and COPD risk were as follows: 20,848 participants for TC, HDL-C, and non-HDL-C, 7283 participants for LDL-C, and 7367 participants for triglycerides. Detailed procedures are provided in Figures S1 to S5.

Based on the core assumptions of MR studies and drawing from previous research,[22,23] we established the following criteria for selecting IVs in MR studies: (i) IVs must be strongly associated with the exposure and independent of each other. Single nucleotide polymorphisms (SNPs) that meet a genome-wide significance threshold of $P < 5 \times 10^{-8}$ and a linkage disequilibrium (LD) threshold of $r^2 < 0.001$, with a clumping window of 10,000 kb, were selected. (ii) IVs should not be associated with the outcome; SNPs meeting a genome-wide significance threshold of $P > 5 \times 10^{-8}$ were selected. (iii) Weak IVs were excluded. SNP strength was assessed using the F-statistic, with SNPs considered weak if the F-value was less than 10. (iv) Palindromic SNPs and SNPs with incompatible alleles were removed when harmonizing SNPs between exposure and outcome. The final SNPs selected were utilized as IVs for MR analysis.

Statistical methods

In the NHANES analysis, we used multivariable-adjusted logistic regression to examine the associations between four lipids and COPD. Three models, adjusted for covariates, were evaluated: model 1 (unadjusted), model 2 (adjusted for age, gender, race, education level, marital status, and PIR), and model 3 (adjusted for age, gender, race, education level, marital status, PIR, BMI, smoking status, hypertension, diabetes and CHD). Additionally, to further explore the relationships between lipids and COPD, we conducted a trend test and subgroup analysis. To more accurately reflect the findings in the US population, we incorporated survey weights in the statistical analysis.

In the MR analysis, the inverse-variance weighted (IVW) method with a random effect model was the primary statistical approach, complemented by the MR-Egger regression and weighted median methods.[24–26] When the IVW results reached statistical significance, the findings from MR were deemed significant if both MR-Egger regression and weighted median results were directionally consistent with those of IVW. Several sensitivity analyses were conducted to evaluate the robustness of the results. Cochran's Q test was employed to assess heterogeneity, which did not affect the IVW results.[27] The MR-Egger intercept test was utilized to examine pleiotropy, and a plausible MR result did not indicate the presence of pleiotropy.[25] Leave-one-out analysis was performed to determine whether the MR results were influenced by any single SNP. For the significant results observed in univariable MR in the European population, we further applied multivariable MR to assess the direct causal effects of lipids on COPD by adjusting for the effects of three smoking characteristics (smoking initiation, cigarettes per day, and age of smoking initiation) and BMI.[28] The statistical power of the study was calculated using the online tool available at https://shiny.cnsgenomics.com/mRnd/.[29]

All statistical analyses were performed using R software (version 4.4.2). The "Survey" package was utilized for NHANES analyses. Two-sample MR and sensitivity analyses were conducted using the "TwoSampleMR" package, while multivariable MR analyses were carried out with the "MendelianRandomization" package. Causal effects are presented as odds ratios (OR) with 95% confidence intervals (95% CI). A p-value of less than 0.05 was considered statistically significant.

Results

Tables S2 to S6 provide detailed baseline characteristics of the population included in the NHANES study. These reveal significant differences between the COPD and non-COPD populations in terms of age, race, education level, marital status, PIR, BMI, smoking status, hypertension, diabetes, and CHD, in addition to gender. Overall, COPD patients were older, predominantly non-Hispanic White, had lower education levels, were more likely to be unmarried, had poorer economic status, and exhibited higher rates of obesity, underweight, and smoking, as well as a higher prevalence of hypertension, diabetes, and CHD.

The results of multivariable logistic regression analysis indicated that LDL-C (OR = 0.83, 95% CI = 0.73–0.95, $P = 0.008$), non-HDL-C (OR = 0.89, 95% CI = 0.81–0.97, $P = 0.010$), and TC (OR = 0.85, 95% CI = 0.77–0.93, $P = 0.001$) were associated with a reduced risk of COPD in model 1. In model 2, LDL-C (OR = 0.78, 95% CI = 0.67–0.90, $P = 0.001$), non-HDL-C (OR = 0.83, 95% CI = 0.76–0.91, $P < 0.001$), and TC (OR = 0.79, 95% CI = 0.72–0.87, $P < 0.001$) were also associated with a reduced risk of COPD. These associations remained significant in model 3, where LDL-C (OR = 0.85, 95% CI = 0.74–0.97, P = 0.021), non-HDL-C (OR = 0.86, 95% CI = 0.78–0.94, P = 0.002), and TC (OR = 0.85, 95% CI = 0.77–0.93, P = 0.001) continued to show a reduced risk of COPD. The NHANES analysis did not find an association between HDL-C, triglycerides, and COPD (Table 1). The test for trend revealed a linear relationship between LDL-C, non-HDL-C, TC, and COPD risk reduction across all three models (all P for trend < 0.05). The restricted cubic spline (RCS) curve demonstrates an "L"-shaped relationship between LDL-C and the reduction in COPD risk. Within a certain range, increasing levels of LDL-C are associated with a decreasing risk of COPD. However, after reaching a threshold of 2.8 mmol/l, further increases in LDL-C levels do not result in significant changes in COPD risk (Figure 2). Subgroup analysis revealed a significant interaction between TC and COPD risk based on gender (P = 0.040), education level (P = 0.040), and CHD (P < 0.001). However, no significant subgroup effects were observed for age, race, marital status, PIR, BMI, smoking status, hypertension, and diabetes (all P > 0.05) (Figure S6). A significant subgroup effect was found between LDL-C and COPD risk in the CHD stratification (P < 0.001), but no significant effects were observed in gender, age, race, education level, marital status, PIR, smoking status, hypertension or diabetes stratifications (all P > 0.05) (Figure S7). No subgroup effects were found in the analysis of LDL-C and COPD risk (Figure S8).

A total of 410, 458, 335, 366, and 426 SNPs were selected as IVs for TC, HDL-C, non-HDL-C, LDL-C, and triglycerides, respectively, in the MR analysis of their effects on COPD in the European population. The F-statistics for all SNPs were significantly greater than 10, indicating that none of the IVs were weak (Table S7). The IVW results revealed significant causal relationships between TC (OR = 0.90, 95% CI = 0.84–0.95, $P = 2.99\times10^{-4}$), non-HDL-C (OR = 0.91, 95% CI = 0.85–0.96, $P = 8.57\times10^{-4}$), LDL-C (OR = 0.88, 95% CI = 0.82–0.94, $P = 1.47\times10^{-4}$), and a reduced risk of COPD (Figure 3). The statistical power was 0.97, 0.97, and 0.99, respectively (Table S8). The MR-Egger and weighted median results were consistent with those

Table 1 NHANES Analysis of Five Serum Lipid Levels with the Risk of COPD in US Population

Serum Lipid Levels (mmol/l)	Model 1		Model 2		Model 3	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
HDL-C	0.76(0.57–1.02)	0.063	0.70(0.51–0.96)	0.027	0.92(0.69–1.23)	0.555
Triglyceride	1.05(1.01–1.10)	0.027	1.02(0.96–1.08)	0.509	0.95(0.84–1.07)	0.380
LDL-C	**0.83(0.73–0.95)**	**0.008**	**0.78(0.67–0.90)**	**0.001**	**0.85(0.74–0.97)**	**0.021**
Q1 (<2.41)	Ref.		Ref.		Ref.	
Q2 (2.41–3.16)	0.71(0.52–0.97)	0.031	0.68(0.49–0.93)	0.016	0.79(0.57–1.10)	0.200
Q3 (>3.16)	0.62(0.48–0.80)	<0.001	0.53(0.40–0.71)	<0.001	0.65(0.46–0.92)	0.015
P for trend	<0.001		<0.001		0.015	
Non-HDL-C	**0.89(0.81–0.97)**	**0.010**	**0.83(0.76–0.91)**	**<0.001**	**0.86(0.78–0.94)**	**0.002**
Q1 (<2.97)	Ref.		Ref.		Ref.	
Q2 (2.97–3.83)	0.80(0.66–0.96)	0.018	0.74(0.61–0.91)	0.005	0.84(0.68–1.04)	0.110
Q3 (≥3.83)	0.69(0.56–0.86)	0.001	0.59(0.47–0.74)	<0.001	0.65(0.50–0.84)	0.001
P for trend	0.001		<0.001		0.001	
TC	**0.85(0.77–0.93)**	**0.001**	**0.79(0.72–0.87)**	**<0.001**	**0.85(0.77–0.93)**	**0.001**
Q1 (<4.37)	Ref.		Ref.		Ref.	
Q2 (4.37–5.25)	0.79(0.65–0.96)	0.020	0.74(0.60–0.91)	0.006	0.88(0.71–1.10)	0.200
Q3 (≥5.25)	0.66(0.53–0.81)	<0.001	0.54(0.43–0.68)	<0.001	0.64(0.51–0.82)	<0.001
P for trend	<0.001		<0.001		<0.001	

Notes: model 1 adjusted for: none; model 2 adjusted for: age, gender, race, education level, marital status, and poverty-to-income ratio (PIR); and model 3 adjusted for: age, gender, race, education level, marital status, PIR, body mass index (BMI), smoking status, hypertension, diabetes and coronary heart disease (CHD). Q1, Q2, and Q3 represent the three equally divided levels of LDL-C or TC in the included population, ranging from low to high.
Abbreviations: TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; non-HDL-C, non-high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol. The bold values indicate numerical values with statistical significance.

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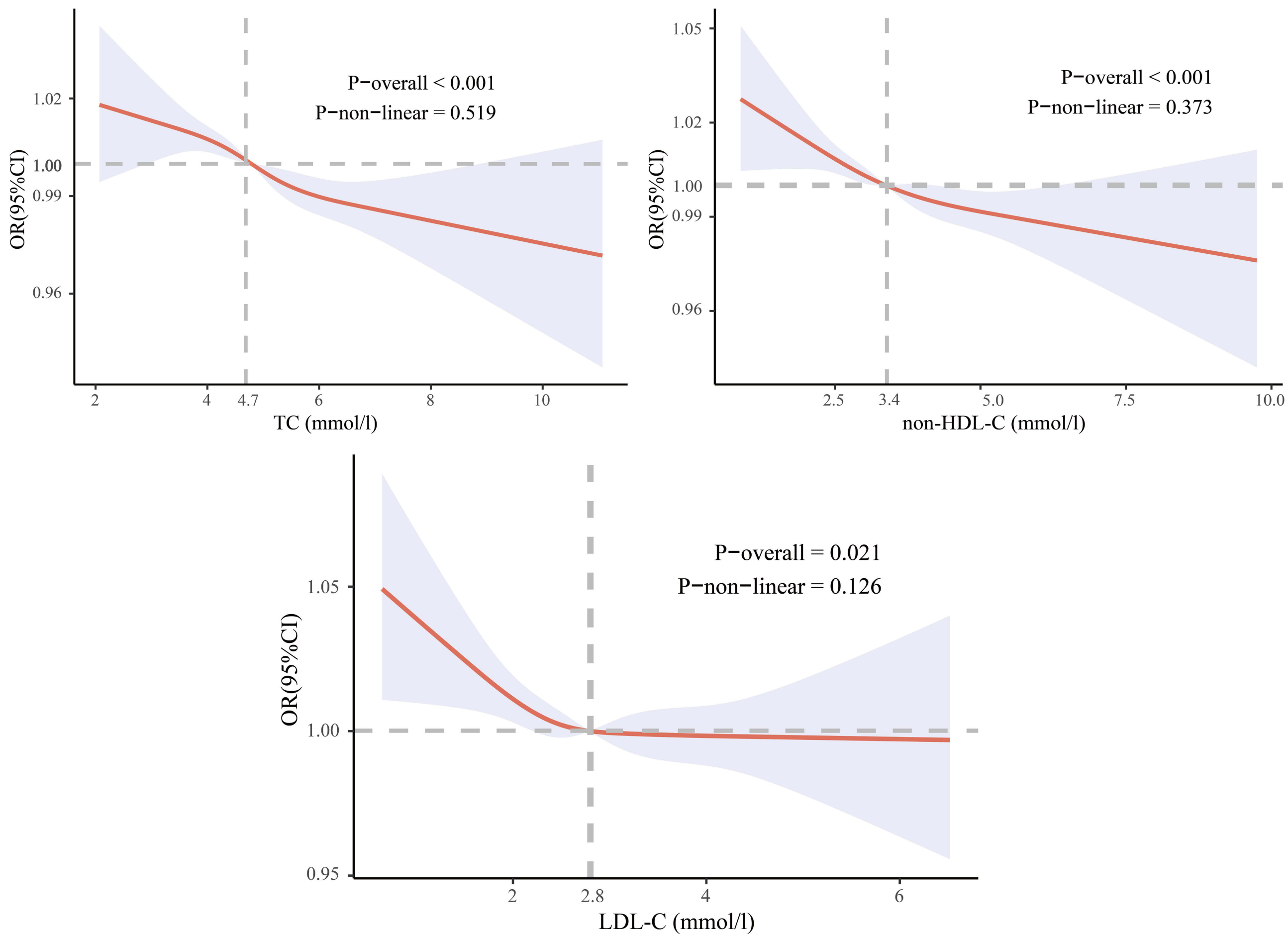

Figure 2 RCS curves of TC, non-HDL-C, and LDL-C with COPD risk in US population.

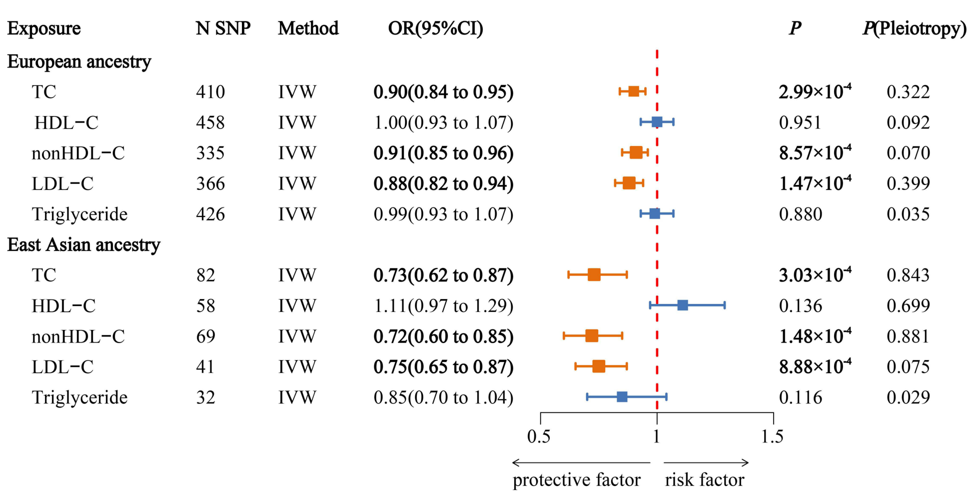

Figure 3 Two-sample MR analyses of serum lipid levels and COPD risk in European and East Asian populations.

of the IVW. The MR-Egger intercept did not suggest pleiotropy (all *P*>0.05), whereas Cochran's Q test indicated the presence of heterogeneity. Additionally, no single SNP was identified as driving the causal effect in the leave-one-out analysis (Figure S9). No association was found between HDL-C or triglycerides and COPD risk (Table S9). After adjusting for three smoking characteristics and BMI using multivariable MR analysis, the causal associations between TC, non-HDL-C, LDL-C, and reduced

COPD risk remained significant, further supporting the robustness of these findings (Table S10). Moreover, similar conclusions were observed in repeated MR analyses of East Asian population, suggesting that these results are applicable to this group as well (Figure 3, Figure S10, Tables S9 and S11).

Discussion

In this study, we analyzed the associations between five lipid traits and COPD risk in populations from the US, Europe, and East Asia, using data from NHANES and GWAS. Our results indicate that higher levels of TC, LDL-C, and non-HDL-C are associated with a reduced risk of COPD. The NHANES analysis revealed a linear relationship between increased levels of TC, non-HDL-C, LDL-C and a reduced risk of COPD. MR analysis confirmed a direct causal association between TC, non-HDL-C, LDL-C and the reduced risk of COPD. These findings suggest that TC, non-HDL-C, and LDL-C may serve as protective factors against COPD.

Several large studies have reached conclusions similar to ours. A cross-sectional study of 107,301 adults from the Copenhagen General Population Study found that lower LDL-C was associated with an increased risk of severe COPD exacerbations and COPD-specific mortality, suggesting a protective role of LDL-C against COPD.[30] Similarly, a study using data from the German COSYCONET (COPD and SYstemic consequences-COmorbidities NETwork) COPD cohort, which included 1,746 COPD patients, showed that hyperlipidemia was linked to reduced hyperinflation, lower airway obstruction, and higher forced expiratory volume in 1 second (FEV1), indicating a potential protective effect of lipids in COPD patients.[31] Furthermore, a genetic analysis of over 100,000 participants from the China Kadoorie Biobank by Michael V. Holmes et al found that PCSK9 gene variants, associated with lower cholesterol levels and a reduced incidence of cardiovascular disease, were also linked to an increased risk of COPD.[32] Although the authors of these studies were skeptical of this conclusion, attributing it to potential drug interference or reverse causation, our study supports this finding by using data from multiple populations. Additionally, the MR methodology used in our study accounts for confounders and eliminates reverse causation, thereby establishing a direct causal relationship and strengthening the plausibility of the results.

The specific mechanism underlying cholesterol's protective effect in COPD remains unclear, though it may be linked to its anti-inflammatory and anti-infective properties. Inflammation is the key pathological factor in the onset and progression of COPD, while infection serves as the primary trigger for acute exacerbations and worsening of lung function.[33,34] Cholesterol exhibits anti-inflammatory effects. In experiments by Nathanael J. Spann et al, the expression of inflammatory genes in peritoneal macrophages from mice fed a high-fat diet and lacking LDL receptors (resulting in elevated circulating LDL-C) was significantly reduced.[35] Cholesterol also contributes to the body's defense against oxidative damage and displays anti-infective properties. An earlier animal study demonstrated that LDL particles can directly neutralize bacterial toxins, reduce pro-inflammatory factor production, and protect mice from the lethal effects of bacterial infections.[36]

Our research presents two significant advantages. First, we integrated NHANES and MR analysis to investigate the relationship between lipids and the risk of COPD. The consistency of conclusions derived from both methodologies enhances the reliability of our findings. Second, we performed a multi-population analysis that yielded consistent results across diverse populations. This not only underscores the generalizability of our conclusions across different racial groups but also further corroborates their robustness.

However, there are certain limitations to our study. One limitation is that COPD is a highly heterogeneous disease, and there is a paucity of data on COPD phenotypes that would enable us to conduct more detailed stratification studies. Additionally, while we made every effort to correct confounding variables in our analysis, it remains challenging to eliminate all potential confounders; thus, our study may still be influenced by unaccounted factors. The diagnosis of COPD in the NHANES dataset was based on participants' medical history, and the potential impact of recall bias on the outcomes should be carefully considered.

Conclusion

Our study identified associations between TC, non-HDL-C, and LDL-C with a reduced risk of COPD. This underscores the importance of monitoring lipid metabolism in patients with COPD and provides supporting evidence for the use of lipid-based therapies in its treatment.

Data Sharing Statement

The data used in this study were obtained from publicly accessible databases. NHANES data can be accessed at https://wwwn.cdc.gov/nchs/nhanes/, and the specific sources of the GWAS data are listed in Table S1.

Ethics Statement

This study is exempt from ethics approval based on item 1 and 2 of Article 32 of the Measures for Ethical Review of Life Science and Medical Research Involving Human Subjects dated February 18, 2023, China. The details are as follows:

Item 1 of Article 32: using legally obtained public data or conducting research through observation without interfering with public behavior. Item 2 of Article 32: using anonymized information data to conduct research.

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Author Contributions

Guobing Jia: Study design, Formal Analysis, Methodology, Writing - original draft. Tao Guo: Data curation, Formal analysis, Visualization. Lei Liu: Data curation, Formal analysis, Visualization, Writing - original draft. Chengshi He: Supervision, Methodology, Writing - review & editing. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that there are no conflicts of interest related to this study.

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