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ORIGINAL RESEARCH

Causal Relationships Between Blood Lipid Levels and Chronic Obstructive Pulmonary Disease: A Mendelian Randomization Analysis

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Background: In preliminary research and literature review, we identified a potential link between chronic obstructive pulmonary disease (COPD) and lipid metabolism. Therefore, this study employed Mendelian randomization (MR) analysis to investigate the potential causal connection between blood lipids and COPD.

Materials and Methods: A genome-wide association study (GWAS) on COPD was conducted, encompassing a total of 112,583 European participants from the MRC-IEU. Additionally, extensive UK Biobank data pertaining to blood lipid profiles within European cohorts included measurements for low-density lipoprotein cholesterol (LDL-C) with 440,546 individuals, high-density lipoprotein cholesterol (HDL-C) with 403,943 individuals, triglycerides (TG) with 441,016 individuals, total cholesterol (TC) with 187,365 individuals, apolipoprotein A-I (apoA-I) with 393,193 individuals, and apolipoprotein B (apoB) with 439,214 individuals. Then, MR analyses were performed for lipids and COPD, respectively. The primary analytical technique employed was the inverse-variance weighted (IVW) approach, which included a 95% confidence interval (CI) to calculate the odds ratio (OR). Additionally, a sensitivity analysis was conducted to assess the dependability of the MR analysis outcomes.

Results: MR analysis was primarily based on IVW, unveiled a causal link between COPD and LDL-C (OR=0.994, 95% CI (0.989, 0.999), P=0.019), TG (OR=1.005, 95% CI (1.002, 1.009), P=0.006), and apoA-I (OR=0.995, 95% CI (0.992, 0.999), P=0.008), in addition, no causal link was found with HDL-C, TC, apoB. Sensitivity analysis demonstrated the robustness of these causal relationships. However, through multivariate MR(MVMR) and multiple testing correction, LDL-C and TG had no causal effect on the outcome. ApoA-I remained a protective factor for the risk of COPD (OR=0.994, 95% CI (0.990–0.999), P=0.008).

Conclusion: Through MR analysis, this study offers evidence of a causal link between apoA-I with COPD. This further substantiates the potential role of lipid metabolism in COPD, and has significant clinical implications for the prevention and management of COPD.

Keywords: lipid metabolism, COPD, Mendelian randomization analysis, apolipoprotein A-I

Introduction

Chronic obstructive pulmonary disease (COPD), the fifth leading cause of mortality globally, is characterized by persistent respiratory symptoms and airflow limitation. It has a high incidence and fatality rate.[1] As the world population continues to expand and experiences overall demographic aging, coupled with the significant demographic impact of Asia, including high smoking rates and other factors such as air pollution, it is certain that COPD will remain an increasingly serious issue in the 21st century.[2] COPD is part of the WHO Global Action Plan for the Prevention and Control of Noncommunicable Diseases and the United Nations 2030 Agenda for Sustainable Development.[3]

Active smoking is considered a primary risk factor for COPD, as are occupational factors, infections, and other contributors such as air pollution.[4] Cigarette smoke extract can disrupt lipid metabolism in human bronchial epithelial cells, particularly

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leading to the accumulation of lipids through the sphingolipid pathway.[5] The accumulation of phospholipid peroxide in human lung epithelial cells leads to ferroptosis, and the disruption of iron homeostasis results in an increase in oxidative stress levels in COPD, exacerbating lung tissue damage.[6] This indicates that the risk factors of COPD are also factors that affect lipid metabolism in the body. Many studies have pointed out that abnormal blood lipid levels are related to inflammation, oxidative stress, and lung function.[7] The development of dyslipidemia is associated with plasma C-reactive protein, and a variety of inflammatory cells, as mediators, participate in the prevention and progression of hyperlipidemia by regulating inflammatory processes.[8,9] In research on pharmacological treatment of hyperlipidemia (specifically statins and fibrates), elevated cumulative exposure to lipid-lowering agents has been found to significantly and dose-dependently reduce the risk of chronic lung disease among patients with hyperlipidemia.[10] A meta-analysis found that, after excluding the influence of lipid-lowering treatments on lipid levels, COPD patients had higher TG levels than healthy individuals.[11] Patients with COPD exhibit elevated lipid ratios and oxidative stress levels, accompanied by decreased antioxidant capacity.[12] It is acknowledged that COPD is a multisystemic illness with systemic and pulmonary inflammation. Alterations in major lipid metabolism pathways force lung tissues to initiate synthetic pathways to meet energy demands, thereby promoting the synthesis of inflammatory factors.[13] There existed a strong association between blood lipid levels and inflammation. IL-6 and TC have a positive correlation in individuals with severe COPD, but IL-10 and HDL-C have a negative correlation. In individuals with mild COPD, a significant inverse relationship was observed between TNF-α and HDL-C levels.[14] During periods of stability in individuals with COPD, there was a notable increase in TG levels and a concurrent decrease in HDL-C levels compared to those observed in the control group.[15] Nevertheless, other data indicate a negative relationship between lung function and HDL-C levels, and they attribute this variation to the variability of COPD itself.[16] Furthermore, lipid metabolism disturbances in COPD patients may influence changes in lung function. Research has indicated that elevated levels of serum triglycerides might exacerbate respiratory resistance, whereas elevated cholesterol levels can heighten both centraland total respiratory resistance.[17] The serum apoM concentration gradually increases with the severity of COPD.[18] Additionally, the prognosis for survival and quality of life are strongly correlated with lipid metabolic disorders in patients with COPD.[19] It is crucial to acknowledge the constraints of these studies, notably the limited sample sizes and the possibility of confounding variables.

MR is a statistical methodology designed to deduce possible causal linkages from correlations that are found. The determination of causality linking an exposure to its corresponding outcome utilizes single nucleotide polymorphisms (SNPs) as instrumental variables, which act as proxies for the exposure factor. Given that the variant forms of alleles for particular SNPs are distributed randomly at the time of birth, genetic variations are not influenced by potential confounding factors. Furthermore, genetic variations are determined before the onset of the disease, reducing the likelihood of reverse causation associations.[20,21] This investigation applies the MR methodology to explore the potential causal links between circulating lipid concentrations and the progression and treatment of COPD, thereby laying a groundwork for subsequent studies into the lipid metabolism mechanisms implicated in COPD.

Materials and Methods

Data Sources

Summary data for genome-wide association studies (GWAS) were obtained for lipid-related indicators from the study by Willer et al[22] and the UK Biobank:[23] Total cholesterol (Dataset: ieu-a-301, Sample size: 187,365, Number of SNPs: 2,446,982), triglycerides (Dataset: ieu-b-111, Sample size: 441,016, Number of SNPs: 12,321,875), LDL cholesterol (Dataset: ieu-b-110, Sample size: 440,546, Number of SNPs: 12,321,875), HDL cholesterol (Dataset: ieu-b-109, Sample size: 403,943, Number of SNPs: 12,321,875), apoA-I (Dataset: ieu-b-107, Sample size: 393,193, Number of SNPs: 12,321,875), and apoB (Dataset: ieu-b-108, Sample size: 439,214, Number of SNPs: 12,321,875).

Genetic data for COPD were sourced from the GWAS data on COPD by Ben Elsworth et al and MRC-IEU, with the data ID: ukb-b-20464, comprising a total sample size of 112,583 (1,658 COPD patients and 110,925 control subjects) and 9,851,867 SNPs.

Selection of Genetic Instrumental Variables

SNPs serving as instrumental factors must adhere to three assumptions (Figure 1): (1) all genetic variations exhibit a statistically significant correlation with TC, TG, LDL-C, HDL-C, apoA-I, and apoB levels ($p<5\times10^{-8}$); (2) instrumental

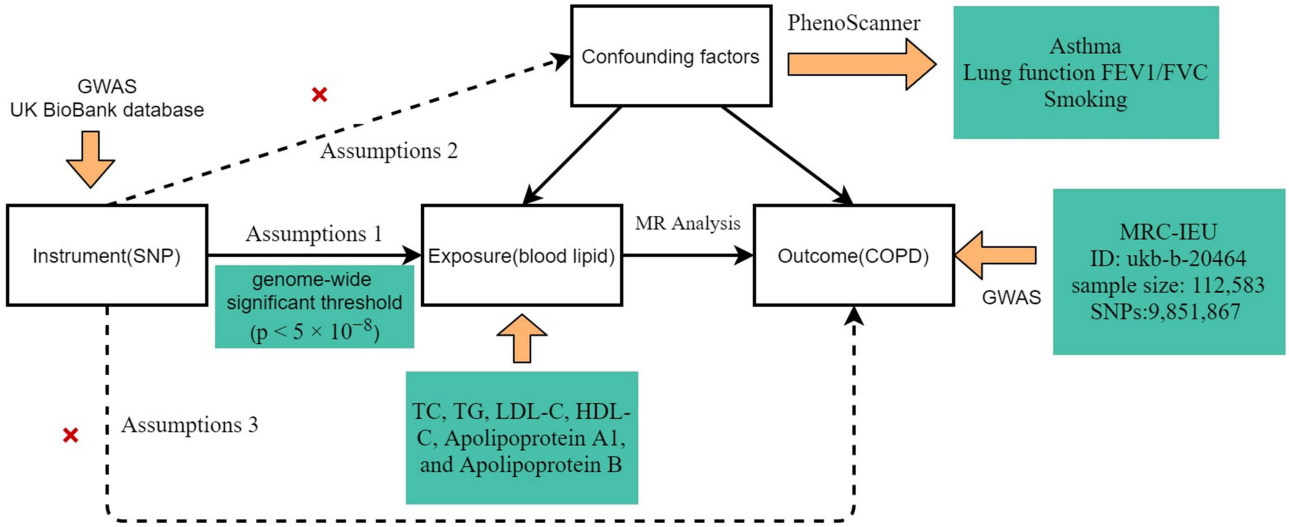

Figure 1 Overview of the research design.

variables have no pleiotropic associations with any known confounding factors; and (3) instrumental variables are not directly related to the outcome unless they are associated with the exposure factor. One of the principles of MR is the absence of linkage disequilibrium between selected SNPs, with a threshold set at 10,000 kb and a r^2<0.001 to minimize bias caused by residual linkage disequilibrium. PhenoScanner[24] (http://www.phenoscanner.medschl.cam.ac.uk/) was used to search for all eligible SNPs, excluding those related to confounding factors (such as smoking, chronic lung diseases, lung function) and those associated with COPD. All instrumental variables were filtered based on the calculation of F-statistics to avoid bias from weak instrumental variables, ensuring that the F-statistic for each instrument exceeded the threshold of 10.[25]

MR Analysis

The causal links between blood lipid profiles, including LDL-C, HDL-C, TG, TC, apoA-I, apoB, and COPD were investigated. The primary methodology employed was the inverse-variance weighted (IVW) method, complemented by the weighted median method and MR-Egger regression analysis as secondary approaches. In the absence of horizontal pleiotropy, IVW can offer robust and precise causal associations by integrating the estimated causal impacts of individual SNPs through meta-analytic techniques. Therefore, the IVW method is commonly adopted as the principal statistical technique for carrying out MR analysis.[26,27] The Weighted Median method and the MR-Egger regression are utilized as supplementary techniques within MR analysis. The former operates by taking the median of variant-specific estimates, thereby rendering it sensitive to alterations in genetic variants; whereas, the latter performs pleiotropy testing and adjustment.[28]

Sensitivity Analysis

Sensitivity analysis comprised tests for horizontal pleiotropy, heterogeneity, and leave-one-out analysis. The MR-Egger regression analysis was applied to assess the presence of horizontal pleiotropy, and a significant intercept in MR-Egger analysis indicated horizontal pleiotropy. Cochran's Q test assessed SNP heterogeneity; a statistically significant Cochran's Q statistic ($P \leq 0.05$) indicated notable heterogeneity in the analysis outcomes. The MR pleiotropy residual sum and outlier test (MR-PRESSO) identified outliers, and if detected, these outliers were removed, and the remaining instrumental variables were reanalyzed. A leave-one-out approach was implemented to evaluate if the statistical significance of the results was influenced by the inclusion of particular SNPs. The correlation between blood lipid levels and the likelihood of COPD onset was quantified using the odds ratio (OR) alongside its 95% confidence interval (CI). A P-value of 0.05 or lower was interpreted as suggestive of a possible causal link.

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Statistical Software Version and Names

The MR analyses were performed employing R software (version 4.3.1), specifically utilizing the TwoSampleMR and MR-PRESSO packages for comprehensive analysis.

Results

Instrumental Variable Results

SNPs meeting the criteria of the three major assumptions were selected, and variables potentially influencing the outcome were removed using the PhenoScanner database (Table 1). All instrumental variables had an F-value exceeding 10, weak instrumental variables did not introduce bias. In the MR analysis, we included a total of 22 independent SNPs associated with TC, 372 independent SNPs associated with TG, 80 independent SNPs associated with LDL-C, 80 independent SNPs associated with HDL-C, 160 independent SNPs associated with apoA-I, and 91 independent SNPs associated with apoB. All SNPs met the criteria of being in linkage disequilibrium independence and achieving genome-wide significance ($P < 5\times10^{-8}$).

Causal Relationship Between Blood Lipids and COPD

Employing the IVW approach, we detected an inverse relationship between LDL-C and COPD [OR=0.994, 95% CI (0.989, 0.999), P=0.019]. MR-Egger regression analysis showed no evidence of horizontal pleiotropy for LDL-C and COPD (intercept P=0.639). ApoA-I exhibited a negative correlation with COPD [OR=0.995, 95% CI (0.992, 0.999), P=0.008], and MR-Egger regression supported the absence of horizontal pleiotropy (intercept P=0.639). TG was positively correlated with COPD [OR=1.005, 95% CI (1.002, 1.009), P=0.006], and MR-Egger regression confirmed that the absence of horizontal pleiotropy (intercept P=0.639). HDL-C, TC, apolipoprotein B, and COPD were not significantly correlated ($P > 0.05$). The IVW method showed that LDL-C and apoA-I could suppress the risk of COPD, while TG could promote the risk of COPD. HDL-C, TC, and apoB show no significant genetic correlation with the occurrence of COPD (Table 2).

Multiple Testing Correction

Given the range of contacts, the Benjamini-Hochberg program was used to adjust for multiple comparisons, with the FDR utilized to address this issue,[29] The test results showed that the P-values for TG, LDL-C, and ApoA-I were significant (Table S1).

Sensitivity Analysis

The presence and outcome of horizontal pleiotropy among SNPs were evaluated by MR-Egger regression analysis. For apoA-I (intercept P=0.470), TG (intercept P=0.408), and LDL-C (intercept P=0.361), all MR-Egger regression intercepts were greater than 0.05, indicating the lack of horizontal pleiotropy between SNPs and outcomes. Additionally, the funnel plot displayed a symmetrical distribution of points representing individual SNPs, suggesting the absence of pleiotropy in the instrumental variables (Figure 2). Cochran's Q test results for apoA-I, TG, and LDL-C in both IVW and MR-Egger analyses showed Q_pval>0.05, confirming the absence of heterogeneity in the selected SNPs. The results indicate the robustness of the MR analysis, as shown in Table 3. Visual representation through scatter plots illustrated the individual

Table 1 Information on SNPs with Potential Pleiotropy in the Instrumental Variables for Blood Lipids

Exposure	SNPs	Trait	P
apoA-I	rs174566	Asthma	1.02E-09
	rs4795386	Asthma	1.26E-13
LDL-C	rs174564	Asthma	6.24E-10
TG	rs2284746	Lung function FEV1/FVC	1.00E-10
	rs6265	Smoking	2.00E-08

Table 2 Mendelian Analysis of the Causal Relationship Between Blood Lipids and COPD

Exposure	Ways	nsnp	β	pval	OR (95% CI)
TC	MR Egger	22	−0.011	0.129	0.989(0.975,1.003)
	Weighted median		−0.001	0.774	0.999(0.992, 1.006)
	Inverse variance weighted		−0.0004	0.872	0.999(0.994, 1.005)
TG	MR Egger	372	0.010	0.110	1.010(0.998, 1.023)
	Weighted median		0.004	0.121	1.004(0.999, 1.010)
	Inverse variance weighted		0.005	0.006	1.005(1.002, 1.009)
LDL-C	MR Egger	79	−0.002	0.755	0.998(0.988, 1.009)
	Weighted median		−0.001	0.757	0.999(0.991, 1.006
	Inverse variance weighted		−0.006	0.019	0.994(0.989, 0.999)
HDL-C	MR Egger	188	−0.002	0.620	0.998(0.990, 1.006)
	Weighted median		−0.002	0.312	0.997(0.991, 1.003)
	Inverse variance weighted		−0.004	0.051	0.996(0.992, 1.000)
apoA-I	MR Egger	158	−0.007	0.037	0.993(0.987, 1.000)
	Weighted median		−0.005	0.122	0.995(0.989, 1.001)
	Inverse variance weighted		−0.005	0.008	0.995(0.992, 0.999)
apoB	MR Egger	91	0.002	0.674	1.002(0.994, 1.010)
	Weighted median		−0.001	0.701	0.999(0.993, 1.005)
	Inverse variance weighted		−0.003	0.215	0.997(0.993, 1.002)

SNP impacts and aggregated effects for each MR method. Figure 3 is the graphical representation that apoA-I and LDL-C act as protective factors for COPD risk, while TG increases the risk of COPD.

Multivariable Mendelian Randomization (MVMR) Analysis

MVMR analysis, a statistical methodology, facilitates the integration of genetic variant-risk factor associations into its framework. This approach permits both the adjustment for confounding variables and the investigation of potential mediators along the causal pathway linking a targeted risk factor to the outcome of interest. Employing the MR package within the R programming environment, version 4.3.0, MVMR analysis was performed to investigate the associations between TG, LDL-C, apoA-I, and COPD. No significant results were observed between TG and LDL-C with COPD [OR=0.997, 95% CI (0.992–1.002), P=0.233)] [OR=0.997, 95% CI (0.992–1.003), P=0.357]. However, apoA-I remained negatively linked to the risk of COPD [OR=0.994, 95% CI (0.990–0.999), P=0.008] (Table S2).

Discussion

Identifying disease-related exposure factors is crucial in the prevention and treatment of diseases, as it can reduce the incidence rate, delay the onset, alleviate patient suffering, and minimize economic burdens. MR analysis, through statistical methods, can clarify genetically related exposure factors. MR analysis has revealed that high BMI is a risk factor for multiple chronic diseases, therefore, reducing overweight or obesity may be pivotal in the prevention of chronic diseases.[30] MVMR analysis, building upon the foundation of two-sample MR analysis, assesses the impact of each exposure factor on the outcome across multiple exposure-related genetic variations. The application of MVMR can not only mitigate biases in causal inference but also allow for the estimation of various effects necessary for mediation analysis.[31] The MVMR analysis examined the independent causal mediation effects of elevated blood eosinophil and neutrophil counts on COPD risk, decline in FEV1/FVC, and COPD-related hospitalizations. It highlighted that eosinophils, rather than neutrophils, could serve as therapeutic targets for preventing the onset and exacerbation of COPD, as well as the decline in FEV1/FVC.[32]

Our findings indicate a negative correlation between LDL-C, apoA-I, and COPD, while TG exhibits a positive correlation with COPD. No causal relationship was discerned between HDL-C, TC, apoB, and COPD. However, in MVMR analysis, no notable causal links were observed between LDL-C and TG with COPD, suggesting that caution

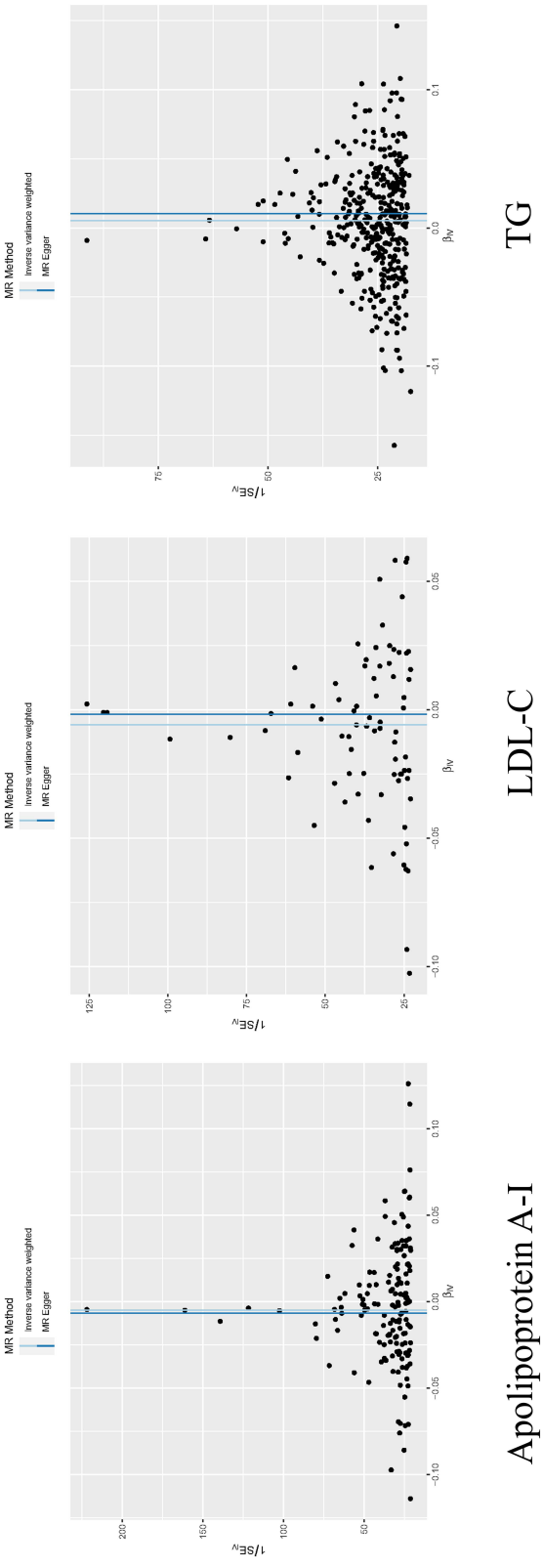

Figure 2 Funnel plots of blood lipids and COPD.

Table 3 Sensitivity Analysis of the Causal Relationship Between Blood Lipids and COPD

Exposure Factor	Heterogeneity			Pleiotropy	
	Method	Q	P	Egger-Intercept	P
ApoA-I	IVW	159.772	0.423	5.534E-05	0.470
TG	IVW	363.489	0.600	−7.904E-05	0.408
LDL-C	IVW	69.577	0.741	−1.163E-04	0.361

should be exercised in interpreting this conclusion. The results indicate a significant causal relationship between apoA-I and COPD at the genetic level, with a negative correlation with the risk of COPD onset.

Apolipoprotein is gaining increased recognition in the pathogenesis and treatment of pulmonary diseases. During diseases or acute phase reactions, the decrease in apoA-I-mediated reverse cholesterol transport from cells and its diminished anti-inflammatory properties can result in lipid metabolism dysfunction in the body.[33] By interacting with the ABCA1 transporter protein, apoA-I releases cholesterol and phospholipids from cells via the apoA-I/ABCA1 pathway. This decreases respiratory inflammation and mucous membrane cell biochemistry, as well as immune cell function.[34] Intrinsic apoA-I has the capacity to attenuate the neutrophilic inflammation in the airways of mice, which is provoked by ovalbumin exposure, via the action of granulocyte colony-stimulating factor.[35] Concentrations of apoA-I are notably decreased in the pulmonary tissues of individuals suffering from COPD and in mice subjected to cigarette smoke (CS). Conversely, the overexpression of apoA-I has been shown to mitigate pulmonary inflammation, oxidative stress, metalloprotease activation, and cellular apoptosis triggered by CS exposure. The potential mechanisms may involve a reduction in the translocation of fatty acid synthase (FASN) to lipid rafts, leading to an impaired formation of the death signal-initiating complex and a subsequent decrease in caspase-8 activation,[36,37] this suggests a protective role of apoA-I in preventing cigarette smoke-induced emphysema. Preliminary investigations have uncovered abnormal expression of FASN, a key enzyme in de novo lipogenesis, in lung tissues of COPD rats.[38] Similarly, research indicates that mice with targeted FASN deficiency in alveolar epithelial type 2 (AEC2) cells exposed to CS exhibit higher neutrophil counts, increased protein levels of neutrophilic bronchoalveolar lavage fluid (BALF), along with more severe enlargement of the airspaces. Crucially, these mice demonstrated lower levels of critical surfactant phospholipids, elevated BALF ether phospholipids, sphingomyelin, and phospholipids containing polyunsaturated fatty acids, accompanied by increased BALF surface tension.[39] During the repair process of small airway epithelial damage, the loss of the gene encoding adipose triglyceride lipase (Pnpla2) resulted in the accumulation of triglycerides, reduced organelle quantity, and impaired mitochondrial respiration within bronchial cells. This was manifested as the thickening of bronchial epithelium and increased airway resistance under baseline conditions.[40] Nineteen lipid species, including plasmenyl phosphatidylcholine (PC O-), phosphatidylcholine (PC), and TG, underwent significant changes in COPD, PC (34:3) and TG (52:3) may serve as potential lipid features associated with COPD, correlating with alterations in lung function and oxidative status.[41]

In adult lungs, alveolar epithelial cells and alveolar macrophages show apoA-I expression, alveolar macrophages may undergo GOLD grade-dependent lipid metabolism changes through their influence on pulmonary surfactant.[42] Dysfunction or low expression of apoA-I may lead to the build-up of cholesterol mass in alveolar macrophages, resulting in the formation of foam cells.[43] In patients with oxidative stress and COPD, increased concentrations of surfactant protein D (SP-D) are commonly observed, along with the presence of lipid-filled (FM) foam macrophages. Through in vitro experiments, we found that the recombination-generated human SP-D fragment could effectively prevent the development of FM induced by oxidized Low-density lipoprotein when used externally. Furthermore, when administered in vivo, these SP-D fragments were able to attenuate airway inflammation and counteract oxidative stress and emphysema alterations induced by exposure to cigarette smoke.[44] Lipid rafts in the cytoplasmic membrane participate in various processes related to pathogen detection, signal transduction, and pathogen entry into cells.[45] Therefore, the specific mechanisms underlying lipid metabolism changes in COPD pathogenesis still hold significant research value. Scholars have proposed the development of inhaled apoA-I mimetic peptides as a novel clinical therapy for patients with severe asthma. In animal experiments, the apoA-I mimetic peptide D-4F facilitates the generation of pre-beta HDL particles, which enhances the cholesterol transport capacity of HDL. It

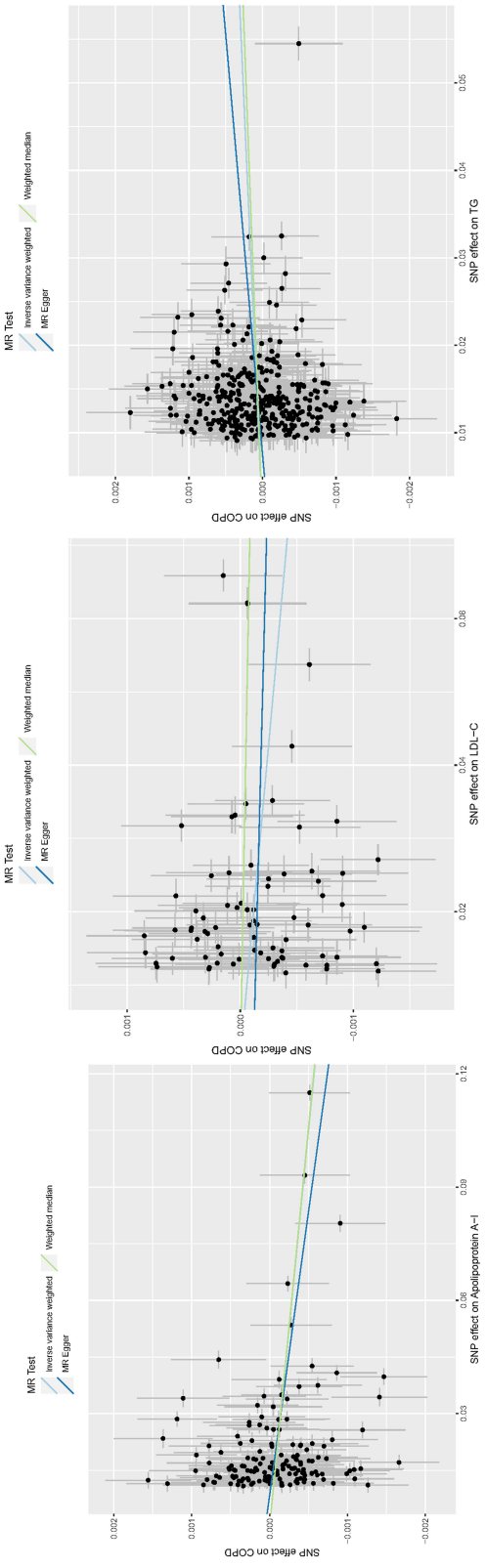

Figure 3 Main effects of blood lipids on COPD.

also lessens the lipid peroxide content of lipoproteins, boosts the enzymatic activity of paraoxonase, and shifts the functional orientation of HDL from pro-inflammatory to anti-inflammatory.[46] Furthermore, apoA-I and its peptide mimetics have demonstrated potent effects on the development of experimental lung injury and fibrosis.[33,47] Alterations in several inflammatory and anti-inflammatory proteins in the lung are closely associated with the pathogenesis of pulmonary fibrosis.

Lipid metabolism disorder typically refers to abnormalities in the quantity and quality of lipids in the plasma. In summary, the relationship between lipid metabolism disorder and COPD is mainly manifested in the increase of inflammatory factors in the body, the biosynthesis of unsaturated fatty acids, and the decline in the function of the antioxidant system. Lipid metabolism disorder affects the occurrence of COPD through multiple pathways. Therefore, in the treatment of COPD, besides focusing on issues such as pulmonary inflammation and airway obstruction, attention should also be paid to correcting lipid metabolism disorder to reduce its impact on COPD. Additionally, for individuals with lipid metabolism disorder and high risk of COPD, early intervention and prevention measures should be taken to lower the incidence and severity of COPD.

Study Strengths and Limitations

Based on MVMR analysis, this study found a negative correlation between apoA-I with COPD. Genetically, this illustrates a connection between lipid metabolism and the development of COPD, potentially providing fresh perspectives on understanding the mechanisms and treatment of COPD in the future. However, our study has several limitations. Firstly, the study primarily focused on Europeans, neglecting the impact of dietary or regional differences on the disease. Secondly, the MR analysis revealed a linear relationship between exposure and outcome in causal analysis, and these causal effects may be weakened by other potential non-linear relationships. Lastly, there are different stages of outcomes, making it challenging to elucidate the causal link relationship between blood lipid levels and different stages of COPD. Nonetheless, the necessity for additional research remains to substantiate these discoveries and bring clarity to the foundational mechanisms involved.

Conclusion

In conclusion, our study findings support to the hypothesis of a causal relationship between COPD and apoA-I levels. Based on this, we recommend that changes in patients' lipid levels should be considered in the prevention, early diagnosis, and treatment of COPD. However, to validate the results of this study, we suggest incorporating a broader range of lipid-related GWAS datasets, along with additional genetic IVs, and continuing in-depth research in this field.

Ethics Approval

The data involved all originate from publicly published GWAS summary databases, which complies with the conditions for exemption from review as stated in the "Ethical Review Measures for Life Sciences and Medical Research Involving Humans".

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Disclosure

The authors declare no competing interests in this work.

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