Blood Lipids and Cardiovascular Disease: A Mendelian Randomization Study

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Abstract
Blood lipids have been considered critical risk factors for cardiovascular disease (CVD). The causal relationship between blood lipids (HDL-C, LDL-C and triglycerides) and cardiovascular disease remains uncertain despite negative and positive associations observed in observational studies, which are susceptible to confounding and reverse causation. This study aimed to investigate the potential causal relationship between the three types of blood lipids and CVD using a two-sample Mendelian randomization (TSMR) approach. Instrumental variables (IVs) representing independent genetic variants associated with HDL-C, LDL-C and triglycerides were derived from the UK Biobank consortium, encompassing genetic data from more than 400,000 individuals. Outcome data for CVD events, including heart disease, stroke, atherosclerosis and so on, were obtained from FinnGen consortium. TSMR analyses were conducted using various methods, such as inverse variance weighted (IVW), MR-Egger regression, and weighted median estimator (WME), to explore the causal relationship between HDL-C, LDL-C and triglycerides levels and CVD events. The results from the Mendelian randomization (MR) analyses suggest a potential causal association between elevated HDL-C, LDL-C and triglycerides levels and CVD events, which indicates that increasing the level of HDL-C and restricting the level of LDL-C and triglycerides are possibly effective methods for the prevention of CVD.
Keywords: Mendelian randomization; HDL-C; LDL-C; triglycerides; causal inference; cardiovascular disease

1. Introduction
Cardiovascular disease (CVD) is the world's leading cause of death and disability, one of the vital public health problems, causing a considerable global burden to the healthcare system [1]. By 2015, it was estimated that one in three deaths worldwide was due to CVD [2]. Obesity, alcohol consumption, and congenital inheritance are considered significant risk factors for CVD [3].

The study shows that the top factors associated with obesity were HDL-C, LDL-C and triglycerides levels in the plasma [4]. Studies have shown that high levels of triglycerides, high levels of low-density lipoprotein cholesterol (LDL-C), and low levels of high-density lipoprotein cholesterol (HDL-C) are commonly present in people at high risk of CVD [5]. Therefore, identifying the relationship between HDL-C, LDL-C, triglycerides and CVD events is of significant importance in disease prevention [6].

Mendelian randomization (MR) is a method that uses genetic variants as instrumental variables to determine whether a risk factor causally affects a health outcome [7]. With the advancements in genome-wide association studies (GWAS) in the past decade, MR has been used to establish causal relationships between various factors and diseases [8]. However, there is limited research focused on the causal relationship between HDL-C, LDL-C, triglycerides and CVD events.

In this study, we utilized a two-sample Mendelian randomization (TSMR) approach to estimate the causal effect of HDL-C, LDL-C and triglycerides levels on CVD events. We retrieved data from the publicly available GWAS on the OpenGWAS project.

2. Materials and Methods

2.1 Study Populations

In the study, we included individuals from two studies of the British and Finnish general population. All participants were of European descent. In our study, a total of 403,943, 440,546, and 441,016 individuals were included in the HDL-C, LDL-C, and triglycerides exposures respectively from the British general population and 111,108 cases and 107,684 control individuals from the Finnish general population.

2.2 Study subjects and genotyping

This study utilized data from two large cohort studies, UK Biobank and FinnGen. UK Biobank is a long-term cohort study comprising approximately 500,000 participants from various regions of the United Kingdom, while FinnGen is a genomic initiative covering the Finnish population with over 300,000 participants. Information on study subjects and genotyping data were obtained from these two data sources. Participants in UK Biobank were recruited between 2006 and 2010 and underwent extensive surveys, and measurements, and provided biological samples for genetic analysis. FinnGen participants, on the other hand, were recruited between 2017 and 2020 and also provided biological samples along with detailed health information.

Strict privacy and ethical regulations were followed to select samples from the UK Biobank and FinnGen databases that aligned with the objectives of our study. These samples underwent genotyping, including analysis of common single nucleotide polymorphisms (SNPs) and other genetic variations.

In total, we included 12,321,875 SNPs from UK Biobank and 16,380,466 SNPs from FinnGen for analysis in this study. These samples encompass individuals of different ages, genders, and geographic distributions, providing a rich data resource for our research objectives.

The summary level data can be retrieved on the MRBase database under the accession ID ieu-b-109, ieu-b-110, ieu-b-111 and finn-b-I9_CVD.

2.3 The Selection of Instrumental Variables

All analyses were performed in RStudio using the R programming language. We utilized the TwoSampleMR, RadialMR and MR-PRESSO packages for the analysis. These packages provide comprehensive tools and functions specifically designed for conducting Mendelian randomization analyses.

After obtaining the data, we first screened out SNPs that have genome-wide

significance ($p < 5 \times 10^{-8}$) [9]. We processed the exposure data by performing linkage disequilibrium (LD) pruning, with a threshold of $r^2 < 0.001$ and a distance within 10 Mb and we retrieved 325, 158 and 286 independent SNPs, respectively. Next, we need to harmonize the exposure and outcome data, the effect estimates are always on the same allele and we preserved 274, 153 and 280 SNPs, respectively. Then we use the RadialMR package to conduct Cochran's Q test on SNPs to exclude heterogeneity and use the MR-PRESSO package to exclude pleiotropy in SNP measurements (Distribution = 1000, SignifThreshold = 0.05, default settings). We detected 42, 27 and 45 SNPs as outliers and removed them from the dataset [10]. Finally, we applied 269, 123 and 226 SNPs for each lipid profile as instrument variables.

To assess the strength of the instrumental variables, we performed F statistics on the selected SNPs. The F statistics were calculated according to the formulation $F = \frac{R^2(n-1-K)}{(1-R^2)K}$ (R^2 stands for the proportion of variance, n represents the sample size and K stands for number of the instrumental variables) [11].

2.4 Mendelian Randomization

To estimate the causal effect of triglycerides levels on heart disease, we mainly employed the inverse variance weighted (IVW) method [12], which provides a consistent and efficient estimation. This method combines the genetic variant-specific causal estimates using inverse-variance weighting, giving more weight to the variants with stronger instrument-exposure associations [13].

Furthermore, an MR-Egger regression was conducted to check for any possible pleiotropic effects. We also used the weighted median, which determines whether there is a pleiotropic effect to estimate the association between exposure and outcome [14]. By comparing the results from these different methods, we aimed to gain a more comprehensive understanding of the causal relationship between the exposure and outcome variables and assess the robustness of our findings. Additionally, we employed the simple mode and weighted mode as alternative approaches to address potential biases and provide additional insights into the causal inference process. These methods allowed us to explore the consistency and stability of our results, further strengthening the validity of our conclusions. Moreover, we include the multiplicative random effects (MRE) model in our study. The MRE model incorporates over-dispersion into the regression model, allowing for heterogeneity between the causal estimates targeted by the genetic variants.

2.5 Sensitivity Analyses

To assess the robustness of our findings, we performed several sensitivity analyses. Wetested for horizontal pleiotropy on the data [15]. Additionally, we conducted a leave-one-out analysis to examine the influence of single genetic variants on the overall causal estimate [16].

3. Results

3.1 Selection and validation of instrumental variables

To perform the two-sample MR, we selected 325, 158 and 286 SNPs associated with HDL-C, LDL-C and triglycerides, respectively, in the European population from the

UK Biobank. GWAS summary statistics of CVD events were derived from the FinnGen. After linkage disequilibrium clumping, 269, 123 and 226 SNPs were retained and served as instrumental variables to estimate the causal relationship between HDL-C, LDL-C and triglycerides and CVD events. To test the robustness of instrumental variables, F values were calculated. F values were 15.2 for HDL-C, 16.3 for LDL-C and 39.9 for triglycerides, respectively (F > 10) in our experiment, indicating the strong instrumental variables were reliable.

3.2 Mendelian Randomization

We observed a negative correlation between HDL-C and CVD events. When the levels of HDL-C increased, the incidence of CVD events decreased. On the other hand, we observed a positive correlation between LDL-C, triglycerides, and CVD events. When the levels of LDL-C and triglycerides increased, the incidence of CVD events also increased.

Using the IVW (Inverse Variance Weighted) method, we found a causal relationship between the three types of blood lipid and CVD events; an increase of one standard deviation (SD) in genetically determined HDL-C is associated with an 8% relative decrease in CVD events (N = 269 SNP; OR = 0.92; 95% CI = 0.89-0.96; P = 9.56e-05), an increase of one SD in genetically determined LDL-C is associated with a 10% relative increase in CVD events (N = 123 SNP; OR = 1.10; 95% CI = 1.05-1.15; P = 5.53e-05), an increase of one standard deviation (SD) in genetically determined triglycerides is associated with a 14% relative increase in CVD events (N = 226 SNP; OR = 1.14; 95% CI = 1.09-1.18; P = 2.68e-10). (Table 1 - 3 and Figure 1)

We also used MR Egger and Weighted median, which determines whether there is a pleiotropic effect to estimate the association between HDL-C, LDL-C, triglycerides and CVD events, and the results were similar to those estimated by MR-IVW, further showing there was no evidence for any pleiotropic effect (Table 1 - 3 and Figure 3).

Other methods, Weighted mode, and Simple mode, demonstrate a consistent negative correlation between HDL-C and CVD events and a positive correlation between LDL-C, triglycerides and CVD events. This finding aligns with the results obtained from the IVW method.

We also attempted to exchange exposure and outcome data, and the results showed that the reverse Mendelian randomization experiments did not show the causality.

Table 1. MR estimates from each method of assessing the causal effect of HDL-C levels on CVD events.

MR Method	No. of SNPs	Beta	SE	P Value	OR (95%CI)
IVW	269	-0.080	0.021	9.56e-05	0.92 (0.89–0.96)
MR Egger	269	-0.004	0.032	9.04e-01	1.00 (0.94-1.06)
Weighted median	269	-0.017	0.036	6.34e-01	0.98 (0.91-1.06)
Weighted mode	269	-0.016	0.034	6.44e-01	0.98 (1.02-1.15)
Simple mode	269	-0.135	0.070	5.69e-02	0.87 (0.96-1.00)

SE, standard error; OR, odds ratio; CI, confidence interval.

Table 2. MR estimates from each method of assessing the causal effect of LDL-C levels on CVD events.

MR Method	No. of SNPs	Beta	SE	P Value	OR (95%CI)
IVW	123	0.097	0.024	5.53e-05	1.10 (1.05–1.15)
MR Egger	123	0.123	0.035	5.18e-04	1.13 (1.06-1.21)
Weighted median	123	0.105	0.038	5.21e-03	1.11 (1.03-1.20)
Weighted mode	123	0.108	0.032	9.06e-04	1.11 (1.05-1.19)
Simple mode	123	0.099	0.067	1.42e-01	1.10 (0.97-1.26)

SE, standard error; OR, odds ratio; CI, confidence interval.

Table 3. MR estimates from each method of assessing the causal effect of triglycerides levels on CVD events.

MR Method	No. of SNPs	Beta	SE	P Value	OR (95%CI)
IVW	226	0.128	0.020	2.68e-10	1.14 (1.09–1.18)
MR Egger	226	0.090	0.029	2.37e-03	1.09 (1.03-1.16)
Weighted median	226	0.108	0.035	1.72e-03	1.11 (1.04-1.19)
Weighted mode	226	0.091	0.027	1.05e-03	1.09 (1.04-1.15)
Simple mode	226	0.098	0.065	1.36e-01	1.10 (0.97-1.25)

SE, standard error; OR, odds ratio; CI, confidence interval.

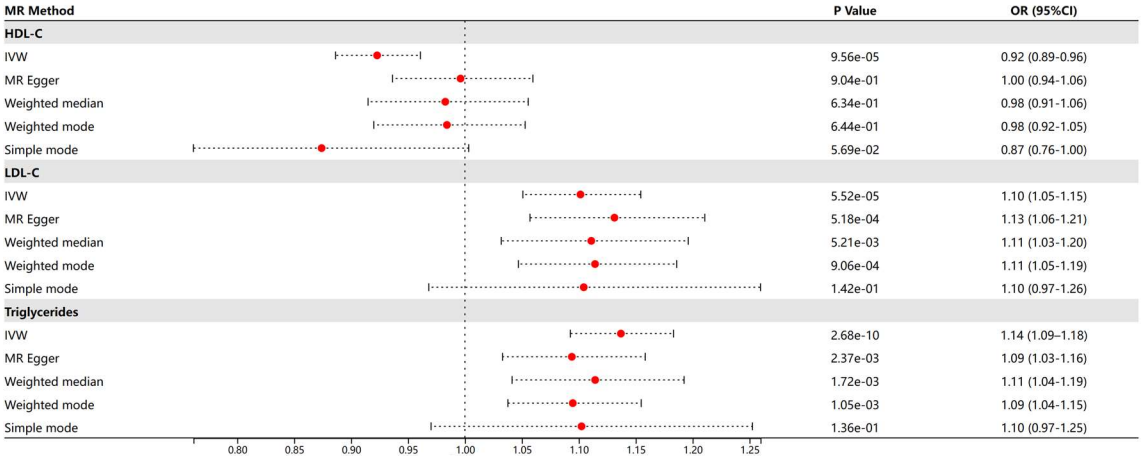

Figure 1. Forest plot of five MR estimators of the effect of HDL-C, LDL-C and triglycerides levels on CVD events [17-18].

OR, odds ratio; CI, confidence interval.

The multiplicative random effects (MRE) model incorporates over-dispersion into the regression model, allowing for heterogeneity between the causal estimates targeted by the genetic variants. We conducted the MRE model, suggesting the negative causal relationship between HDL-C and CVD events and the positive causal relationship between LDL-C, triglycerides and CVD events, in line with the main analysis.

Table 2. MR estimates of multiplicative random effects model assessing the causal effect of blood lipid levels on CVD events.

MR Method (MRE)	No. of SNPs	Beta	SE	P Value	OR (95%CI)
IVW_HDL-C	269	-0.803	0.019	2.78e-05	0.92 (0.89–0.96)
IVW_LDL-C	123	0.097	0.023	2.04e-05	1.10 (1.05–1.15)
IVW_Triglycerides	226	0.128	0.019	6.38e-12	1.14 (1.09~1.18)

MRE, multiplicative random effects; SE, standard error; OR, odds ratio; CI, confidence

interval.

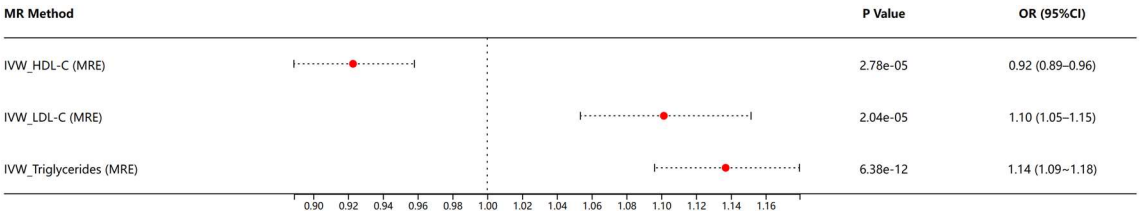

Figure 2. Forest plot of multiplicative random effects of HDL-C, LDL-C and triglycerides levels on CVD events. OR, odds ratio; CI, confidence interval [17-18].

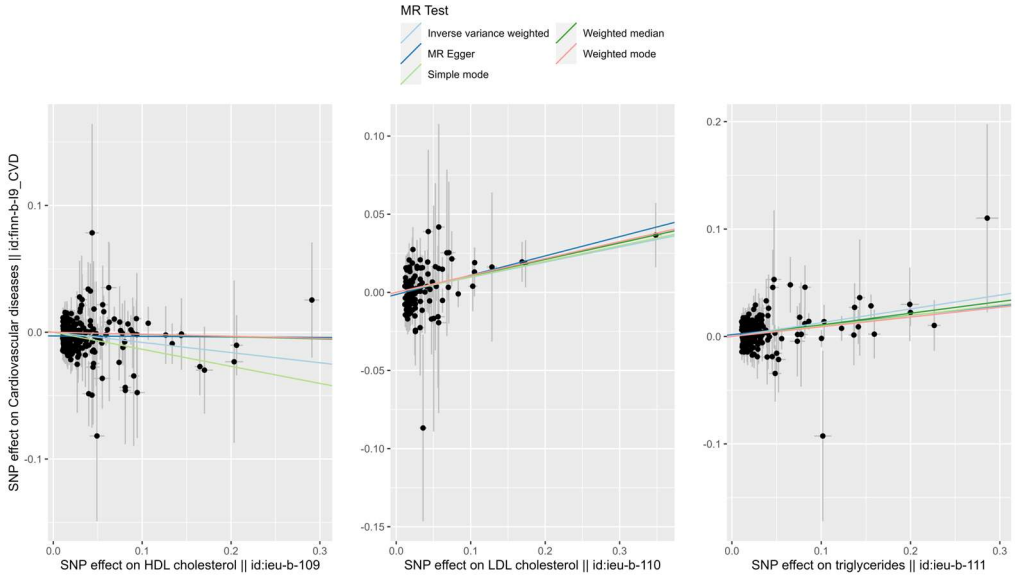

Figure 3. Scatter plots of the association between triglycerides levels and CVD events. The x-axis represents the association between SNPs and three types of blood lipid levels in standard deviation units, while the y-axis represents the association between SNPs and the CVD events using log odds ratios with 95% confidence intervals. The regression slopes of the line correspond to causal estimates using five MR methods (the inverse variance weighted method, MR-Egger regression, weighted median estimator, simple mode and weighted mode.

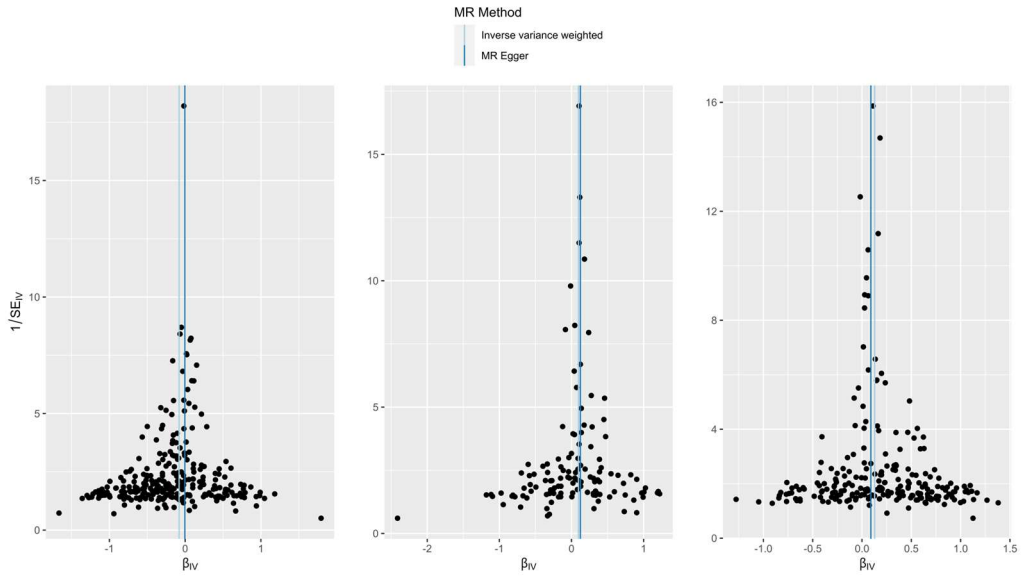

Figure 4. Funnel plots, to evaluate the robustness of MR. The points represented the estimated effect using a single SNP as an instrumental variable. The two lines represent the overall estimates obtained from the inverse variance-weighted method and MR-Egger regression.

All these findings suggested a causal role for high HDL-C levels in restraining an increase in CVD events and high LDL-C and triglycerides levels in promoting CVD events.

3.3 Sensitivity Analyses

We conducted a heterogeneity analysis on the results of Mendelian randomization using Cochran's Q test. The results showed no evidence suggesting heterogeneity in the results of the Mendelian randomization analysis ($p > 0.05$)

Table 3. Heterogeneity test of MR.

Lipid	Method	Q	P
HDL-C	MR Egger	222.09	0.98
HDL-C	IVW	232.30	0.94
LDL-C	MR Egger	108.14	0.79
LDL-C	IVW	109.29	0.79
Triglycerides	MR Egger	186.76	0.97
Triglycerides	IVW	190.15	0.96

We further performed a test to assess the presence of horizontal pleiotropy in the data. We found there is no significant evidence to suggest the existence of horizontal pleiotropy. This finding indicated that the observed associations of HDL-C, LDL-C and triglycerides are unlikely to be confounded by horizontal pleiotropy, further supporting the robustness and validity of the Mendelian randomization analysis.

In addition, we performed a leave-one-out analysis as a sensitivity analysis, and the results showed consistency with the main analysis, indicating that no single SNP had a significant impact on the MR analysis.

To confirm our results, we performed a bidirectional MR analysis. Following the same methods that we had previously used to select SNPs, the results show no evidence indicating a bidirectional causal correlation.

4. Discussion

The present study examined the causal relationship between blood lipid (HDL-C, LDL-C, and triglycerides) levels and CVD events using Mendelian Randomization analysis. Our findings provide evidence supporting a causal effect of elevated HDL-C, LDL-C and triglycerides levels on the risk of heart disease. These results are consistent with previous observational studies that have reported an association between triglycerides levels and cardiovascular outcomes [19].

LDL-C is a type of low-density lipoprotein that can deposit on the walls of blood vessels, leading to narrowing and blockage of blood vessels, increasing the risk of cardiovascular disease. HDL-C, on the other hand, is a type of high-density lipoprotein that can remove cholesterol from the blood and transport it to the liver for metabolism and excretion, thereby reducing the level of cholesterol in the blood, decreasing the occurrence of atherosclerosis, and lowering the risk of cardiovascular disease [20].

The potential mechanisms underlying the association between elevated triglycerides levels and heart disease may include atherosclerosis, inflammation, insulin resistance and other factors [21]. According to recent research, GDF15 regulates triglycerides metabolism to coordinate tolerance to inflammatory damage [22] and triglycerides glucose index can be a biomarker for identification of insulin resistance [23]. The states of insulin resistance contribute significantly to the development of CVD [24].

The use of large-scale cohort studies, namely UK Biobank and FinnGen, provided a robust dataset for our analysis. The inclusion of individuals from both British and Finnish populations enhances the generalizability of our findings to European populations. The extensive surveys, measurements, and provision of biological samples in UK Biobank and FinnGen allowed for comprehensive genetic analysis, including genotyping of millions of SNPs.

The strength of the present study is an exploration of the independent effects of plasma lipid levels on the risk of CVD using MR design, providing a chance to overcome several limitations in conventional epidemiological studies and attenuate confounders. The consistency of our results across different statistical methods strengthens the validity of our findings. The IVW method, as the primary analysis, provided a consistent and efficient estimation of the causal effect. The MR-Egger regression analysis and other analyses did not indicate significant pleiotropic effects, further supporting the causal relationship between HDL-C, LDL-C and triglycerides levels and CVD events.

There are also limitations in our study. First, the genetic variants detected by GWASs could explain a limited variance of blood lipid levels and CVD events, and some SNPs are not available in both cohorts. Although we employed stringent criteria for SNP selection and sensitivity analysis was performed, it is impossible to completely rule out the bias due to selected SNPs and pleiotropism. Secondly, our study focused on European populations, and caution should be exercised when generalizing these findings to other ethnic groups.

5. Conclusion

In conclusion, our findings indicate that LDL-C and triglycerides levels are an important risk factor for heart disease. Reducing LDL-C and triglycerides level in plasma can have a positive effect on preventing heart disease. HDL-C was considered beneficial in preventing the onset of heart disease in this experiment and increasing the level of HDL-C appropriately will be beneficial in preventing heart disease.

Using two-sample MR, our findings provided evidence for a causal association between plasma lipid levels including LDL-C, HDL-C and triglycerides and risk of CVD events. Our findings suggest that the control of plasma lipid levels helps to reduce the risk of CVD.

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