Causal Associations Between Blood Lipids and COVID-19 Risk: A Two-Sample Mendelian Randomization Study

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OBJECTIVE: Coronavirus disease 2019 (COVID-19) is a global pandemic caused by the severe acute respiratory syndrome coronavirus 2. It has been reported that dyslipidemia is correlated with COVID-19, and blood lipids levels, including total cholesterol, HDL-C (high-density lipoprotein cholesterol), and LDL-C (low-density lipoprotein cholesterol) levels, were significantly associated with disease severity. However, the causalities of blood lipids on COVID-19 are not clear.

APPROACH AND RESULTS: We performed 2-sample Mendelian randomization (MR) analyses to explore the causal effects of blood lipids on COVID-19 susceptibility and severity. Using the outcome data from the UK Biobank (1221 cases and 4117 controls), we observed potential positive causal effects of dyslipidemia (odds ratio [OR], 1.27 [95% CI, 1.08–1.49], \(P=3.18 \times 10^{-3}\)), total cholesterol (OR, 1.19 [95% CI, 1.07–1.32], \(P=8.54 \times 10^{-4}\)), and ApoB (apolipoprotein B; OR, 1.18 [95% CI, 1.07–1.29], \(P=1.01 \times 10^{-3}\)) on COVID-19 susceptibility after Bonferroni correction. In addition, the effects of total cholesterol (OR, 1.01 [95% CI, 1.00–1.02], \(P=2.29 \times 10^{-2}\)) and ApoB (OR, 1.01 [95% CI, 1.00–1.02], \(P=2.22 \times 10^{-2}\)) on COVID-19 susceptibility were also identified using outcome data from the host genetics initiative (14134 cases and 1284876 controls).

CONCLUSIONS: In conclusion, we found that higher total cholesterol and ApoB levels might increase the risk of COVID-19 infection.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: blood cholesterol coronavirus dyslipidemias lipids

Coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) is a global pandemic. This disease progresses from asymptomatic to acute respiratory distress syndrome and multiple organ dysfunction and has become a major threat to public health in >160 countries. As of June 21, 2021, there were >179 million confirmed cases, with total deaths increasing over 3.87 million worldwide. Considering the severity of COVID-19, it is urgent to explore the susceptibility factors of COVID-19, which is helpful to develop effective policies and personalized treatments to control the spread of the disease to susceptible groups.

Dyslipidemia is associated with metabolic syndrome, type 2 diabetes, obesity and so on. It is characterized with the maladjustment of blood lipids pattern which can be evaluated through the levels of LDL-C (low-density lipoprotein cholesterol), HDL-C (high-density lipoprotein cholesterol), triglyceride, total cholesterol (TC), ApoA1 (apolipoprotein A1), ApoB (apolipoprotein B), and others. Recent studies reported that HDL-C, LDL-C, and TC levels were significantly lower in patients with COVID-19 as compared with normal subjects. Another study also showed that levels of TC and LDL-C at admission were negatively correlated with the length of hospital stay of hospitalized patients with COVID-19 pneumonia.
Nonstandard Abbreviations and Acronyms

| Acronym | Description |
|---------|-------------|
| ApoA1   | apolipoprotein A1 |
| ApoB   | apolipoprotein B |
| COVID-19 | coronavirus disease 2019 |
| GWAS   | genome-wide association study |
| HDL-C  | high-density lipoprotein cholesterol |
| HGI    | COVID-19 host genetics initiative |
| IVs    | instrumental variables |
| IVW    | inverse-variance weighted |
| LDL-C  | low-density lipoprotein cholesterol |
| MR     | Mendelian randomization |
| OR     | odds ratio |
| SARS-Cov-2 | severe acute respiratory syndrome coronavirus 2 |
| SNP    | single-nucleotide polymorphism |
| TC     | total cholesterol |
| UKB    | UK Biobank |

Contrast, Peng et al.11 observed significantly increased level of LDL-C in patients with COVID-19 compared with age- and sex-matched controls where the levels of HDL-C and TC were inversely correlated with the severity of COVID-19.11 Although above evidences demonstrated the associations between blood lipids and COVID-19, these findings were from observational studies which could be misguided by potential confounders,12 whether these associations are causal is still unclear.

Mendelian randomization (MR) is an epidemiological method in which environmental exposure-related genetic variations are used as instrumental variables (IVs) to evaluate the association between exposures and outcomes.13,14 It can avoid the issues of confusion and has been demonstrated as an effective strategy to identify the causal effect.14,15 Two-sample MR uses genetic associations with the exposure and outcome from the summary statistics of nonoverlapping genome-wide association studies (GWAS) and has facilitated the application of the MR methodology.14,17,18

In this study, we conducted a 2-sample MR study to explore the possible causal effects of 7 blood lipids on COVID-19 susceptibility and severity using data from the UK Biobank (UKB) and the host genetics initiative (HGI).

Materials and Methods

The authors declare that all supporting data are available within the article and its Data Supplement. The data sets used in this study are listed in Major Resources Table in the Data Supplement. A step-by-step workflow in this study is presented in Figure 1.

Data Sources

Details of the contributing GWAS summary data are listed in Table 1. The studies were selected for investigating blood lipids or COVID-19 having the largest sample sizes and consisting of similar populations (>70% White population/Europeans).

Single-Nucleotide Polymorphisms Filter and Data Standardization

For each exposure, we filtered single-nucleotide polymorphisms (SNPs) using the following criteria:

1. Remove the SNPs located in the major histocompatibility complex region.
2. Remove the SNPs with minor allele frequency <0.01 in the 1000 genome European data.
3. The estimated standardize the effect size (β) and SE for each GWAS data was obtained with the function of minor allele frequency and sample size as follows:

\[ \beta = \frac{z}{\sqrt{2p(1-p)(n+z^2)}} \]

\[ SE = \frac{1}{\sqrt{2p(1-p)(n+z^2)}} \]

where \( z = \beta/SE \) from the original summary data, \( p \) is the minor allele frequency, and \( n \) is the total sample size.

IVs Selection

We selected independent and genome-wide significant GWAS SNPs using the clumping algorithm in PLINK (http://pngu.mgh.harvard.edu/purcell/plink/) with \( r^2 \) threshold = 0.001, window size = 1 Mb, \( P \) value threshold = 5×10\(^{-8}\). The 1000 Genomes (http://www.internationalgenome.org/) European data were used as the reference for linkage disequilibrium estimation. For each outcome, we harmonize the data according to the SNPs included in COVID-19 GWAS and their effect allele. After data harmonization, we then removed outlier pleiotropic SNPs using RadialMR26 with the \( P \) value threshold of 0.05. RadialMR26 identified outlier genetic instruments via heterogeneity test (modified Q-statistics). After removal of pleiotropy, the remaining SNPs were used to perform MR analyses.

MR Analyses and Pleiotropy Assessment

We conducted 4 complementary 2-sample MR methods, including inverse-variance weighted (IVW) method, weighted median method, weighted mode method, and MR-Egger method, which make different assumptions about horizontal pleiotropy. The IVW method assumes balanced pleiotropy.27 The pleiotropy is assessed via Cochran \( Q \) statistic and presented as...
excessive heterogeneity which will inflate the estimate of MR analysis.\textsuperscript{26} MR-Egger is based on the assumption which indicates instrument strength independent of the direct effects.\textsuperscript{27} It can be evaluated by the regression dilution $P\ (GX)\textsuperscript{29}$ according to the assumption that no measurement error in the SNP exposure effects. $P\ (GX)$ is an adaptative $P$ statistic which proposes to quantify the strength of no measurement error violation for the MR-Egger method. If $P\ (GX)$ was sufficiently low ($P\ (GX)<0.9$), the correction analysis was conducted to assess the causal effect by simulation extrapolation (SIMEX), which can substantially mitigate adverse effects by simulation extrapolation.\textsuperscript{29} The intercept term of MR-Egger method can be used for evaluating the directional pleiotropic effect.\textsuperscript{30} When the intercept is zero or its $P$ value was not significant ($P>0.05$) were considered as nonpleiotropy. Moreover, we also used the Rucker $Q'$ statistic\textsuperscript{31} to measure the heterogeneity for MR-Egger method. If the difference $Q-O'$ is sufficiently extreme with respect to a $\chi^2$ distribution with 1 degree of freedom, we indicated that directional pleiotropy is an important factor, and MR-Egger model provides a better fit than the IVW method.\textsuperscript{32} All methods of 2-sample MR analyses were measured by TwoSampleMR package in R. For various estimates for different measures, we select the main MR method as following rules:

1. If no directional pleiotropy in MR estimates ($Q$ statistic: $P>0.05$, MR-Egger intercept: intercept$=0$ or $P>0.05$, $Q-O'$: $P>0.05$), IVW method was used.
2. If directional pleiotropy was detected (MR-Egger intercept: intercept$\neq 0$ and $P<0.05$, $Q-O'$: $P<0.05$), and $P>0.05$ for the test of $Q'$, MR-Egger method was used. When MR-Egger was selected as the main method, MR-Egger method adjusted by SIMEX was performed when $P\ (GX)<0.9$.
3. If directional pleiotropy was detected (MR-Egger intercept: intercept$\neq 0$ and $P<0.05$, $Q-O'$: $P<0.05$) and $P<0.05$ for the test of $O'$, weighted median method was used.

Previous observational studies have found that the level of TC was higher in non-O blood group,\textsuperscript{33–35} and the persons with non-O types associated with greater risks of significant coronary artery disease, myocardial infarction, and SARS-CoV-2 infection.\textsuperscript{23,36–39} Considering the associations between ABO blood group and blood lipids levels or COVID-19, we also re-run MR analysis after excluding SNPs in the ABO locus to avoid potential pleiotropy.

### Sensitivity Analysis

Leave-one-out sensitivity analysis was implemented to assess whether the significant results were driven by a specific SNP.
Multiple Testing Correction

We used the Bonferroni approach to address multiple comparisons issue. The significant threshold was set as $P < 7.14 \times 10^{-3}$ (0.05/7 exposures).

RESULTS

IVs Selection

Details of the IVs after linkage disequilibrium clumping are represented in Table I in the Data Supplement. The number of remained IVs after harmonization and radial MR are shown in Table II in the Data Supplement.

MR Estimates for COVID-19 Infection

Pleiotropy Assessment

As shown in Table III in the Data Supplement, the evidence of pleiotropy was observed in TC to COVID-19 infection with the data from the HGI, thus we chose MR-Egger as the main MR method for this exposure-outcome pair and IVW was used in others. In addition, the assumption of no measurement error was not violated ($I^2 [GX] > 0.9$), therefore, we did not perform SIMEX analysis.

MR Results

For the outcome data from the UKB, the MR estimates (Table 2 and Figure 2) showed that 3 blood lipids had potential causality to COVID-19 susceptibility after Bonferroni correction ($P < 7.14 \times 10^{-3}$), including dyslipidemia (odds ratio [OR], 1.27 [95% CI, 1.08–1.49], $P = 3.18 \times 10^{-3}$), TC (OR, 1.19 [95% CI, 1.07–1.32], $P = 8.54 \times 10^{-4}$), and ApoB (OR, 1.18 [95% CI, 1.07–1.29], $P = 1.01 \times 10^{-3}$). The MR result of dyslipidemia indicates that per doubling of prevalence will increase 18% odds (multiply the causal estimate by 0.693) of COVID-19 susceptibility. The performances of the other 3 MR methods were similar. The potential
causality between these 3 traits and COVID-19 susceptibility was supported by at least 2 of the other 3 methods at the nominal significance level of P<0.05. In sensitivity analyses, the results showed that no single SNP was driving the potential causal estimates (Figure I in the Data Supplement).

We detected suggestive causal effects of LDL-C (OR, 1.13 [95% CI, 1.02–1.24], P=1.46×10^{-3}) in the preliminary results. However, the leave-one-out permutation identified 3 IVs with major effects. After excluding the main influential IVs, the marginal significant association of LDL-C was not observed (P>0.05, Table 2). For the other blood lipids (HDL-C, triglyceride, and ApoA1), we did not detect any association (P>0.05, Table 2).

Since TC is mostly LDL-C and the IVs overlap substantially, we further performed MR analysis after excluding the overlapped IVs between TC and LDL-C. The significant causal effect of TC was remained (OR, 1.25 [95% CI, 1.07–1.46], P=5.08×10^{-3}), but no association was detected for LDL-C (P>0.05, Table IV in the Data Supplement).

For the outcome data from the HGI (Table 1), the MR analyses did not detect significant causal associations on COVID-19 susceptibility after Bonferroni correction (P<7.14×10^{-3}; Table 2). However, we successfully observed the possible causal effects of TC (OR, 1.01 [95% CI, 1.00–1.02], P=2.29×10^{-3}) and ApoB (OR, 1.01 [95% CI, 1.00–1.02], P=2.22×10^{-3}; P<0.05), but the association between dyslipidemia and COVID-19 infection was no longer significant.

### Addressing the Potential Pleiotropy Generated by the ABO Locus

If there were IVs located in the ABO locus, we reperformed MR analysis for TC and ApoB after excluding those SNPs. For ApoB, there were no IVs in the ABO locus. As shown in Table V in the Data Supplement, the MR results for TC (OR, 1.18 [95% CI, 1.06–1.31], P=1.68×10^{-3}) were still significant.

We further performed MR analysis after removing IVs on chromosome 9. As shown in Table V in the Data Supplement, the MR results of TC (OR, 1.17 [95% CI, 1.05–1.30], P=3.33×10^{-3}) and ApoB (OR, 1.16 [95% CI, 1.06–1.28] P=2.26×10^{-3}) were still significant. Therefore, we concluded that the potential causality of TC and ApoB on COVID-19 susceptibility were not due to the latent pleiotropy caused by the ABO locus.

### MR Estimates for Severe COVID-19

We also measured the associations between blood lipids and severe COVID-19. According to the evidence of pleiotropy (Table III in the Data Supplement), we chose MR-Egger as main MR method for triglyceride (MR-Egger intercept: P<0.05, Q–Q: P<0.05) while the others used IVW as main method. P (G X) test indicated that there was no need for correcting with SIMEX (all P [G X]>0.9). As shown in Table 3, we did not detect any significant association for all 7 traits (P>0.05).

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**Table 2. Summary of the MR Estimates for Blood Lipids to COVID-19 Susceptibility**

| Blood lipids | IVW method OR (95% CI) | P value | Weighted median method OR (95% CI) | P value | Weighted mode-based method OR (95% CI) | MR-Egger method OR (95% CI) | P value | Main method |
|--------------|------------------------|---------|----------------------------------|---------|--------------------------------------|-----------------------------|---------|-------------|
| Dyslipidemia | 1.00 (0.99–1.02)        |         | 1.01 (0.99–1.02)                 |         | 1.01 (0.99–1.03)                     | 1.02 (0.99–1.05)           | 1.46×10^{-3} | IVW         |
| HDL cholesterol | 1.00 (0.99–1.01)       |         | 1.00 (0.99–1.01)                 |         | 1.00 (0.99–1.01)                     | 1.00 (0.99–1.01)           |         | IVW         |
| LDL cholesterol | 1.00 (0.99–1.01)       |         | 1.00 (0.99–1.01)                 |         | 1.00 (0.99–1.01)                     | 1.00 (0.99–1.01)           |         | IVW         |
| Total cholesterol | 1.00 (0.99–1.01)      |         | 1.00 (0.99–1.01)                 |         | 1.00 (0.99–1.01)                     | 1.00 (0.99–1.01)           |         | IVW         |
| Triglycerides | 0.99 (0.88–1.11)        |         | 1.08 (0.89–1.32)                 |         | 1.09 (0.89–1.33)                     | 3.96×10^{-3}               | 4.07×10^{-3} | IVW         |
| ApoA1 | 1.05 (0.92–1.19)        |         | 1.09 (0.93–1.28)                 |         | 1.10 (0.93–1.30)                     | 3.01×10^{-3}               | 3.24×10^{-3} | IVW         |
| ApoB | 1.18 (1.07–1.29)        |         | 1.22 (1.07–1.40)                 |         | 1.22 (1.03–1.45)                     | 3.61×10^{-3}               | 2.69×10^{-4} | IVW         |

ApoA1 indicates apolipoprotein A1; ApoB, apolipoprotein B; COVID-19, coronavirus disease 2019; HDL, high-density lipoprotein; IVW, inverse-variance weighted; LDL, low-density lipoprotein; MR, Mendelian randomization; and OR, odds ratio.

P<0.05.

†P<0.05.
DISCUSSION

In this study, we implemented 2-sample MR analyses to investigate the possible causal associations of blood lipids profiles on COVID-19 infection or severity. We detected potential causal effects of dyslipidemia, TC, and ApoB on COVID-19 susceptibility. The clinical manifestation of dyslipidemia includes the maladjustment of TC level, LDL-C level, triglyceride level, HDL-C level, and other lipid and lipoprotein levels. We acknowledge that it is hard to summarize the clinical risk factor for dyslipidemia. However, considering over 70% of the dyslipidemia instruments overlapped with the TC instruments in the same effect direction, and 83.22% of dyslipidemia in UKB subjects are hypercholesterolemia, it is likely that dyslipidemia is relatively homogeneous and the clinical causal risk factor of dyslipidemia might be high TC. The specific MR results of TC and ApoB could contribute to interpret the significant MR finding for dyslipidemia.

We also assessed the phenotypic correlations between TC/ApoB and COVID-19 with baseline plasma lipid measures from the UKB. We selected independent white subjects and removed the individuals with confounders of cardiovascular disease, type 2 diabetes, and the treatment of statin. There were no significant correlations between TC/ApoB and COVID-19 (P>0.05). The reason might be that the UKB lipid data were acquired over a decade before COVID-19 pandemic, and the levels of TC/ApoB may be fluctuated with the influence of dietary habits, physical activity, and other variates in the past decade. Although we have excluded the interference of related diseases, medical treatment, and clinical characteristics as far as possible, the retrospective study may still be disturbed by potential confounders and produce bias in phenotypic associations. However, the MR estimation just relies on genetic determination, and therefore, can avoid these issues.

TC is mainly composed of LDL-C, HDL-C, and VLDL (very-low-density lipoprotein) cholesterol. The VLDL particles mainly carry triglycerides. ApoB is the major protein component of VLDL and LDL. It has been found that the amount of cholesterol and ApoB within LDL particles are heterogeneous between persons, and the amount of LDL-C is lower in hypertriglyceridemia. We did not detect significant effects of LDL-C, HDL-C, and triglyceride. It indicates that the potential causality between TC and COVID-19 susceptibility is not attributed to any single component but acted like a combined effect. Although we detected associations with dyslipidemia and COVID-19 more broadly, and with ApoB and TC more specifically, our findings did not clearly prioritize a specific lipoprotein fraction associated with COVID-19 susceptibility or severity.

The positive association between TC and COVID-19 susceptibility might be related to enhanced virus invasion process. Cholesterol is considered to be involved in fusion of the viral membrane to the host cell.
shown in the study by Guo et al.\textsuperscript{51} depleting plasma membrane cholesterol can disrupt the lipid rafts of cellular entry, resulting in suppressed infection of an avian coronavirus (infectious bronchitis virus). Consistently, membrane cholesterol has been found to similarly facilitate virus (infectious bronchitis virus). Consistently, membrane cholesterol can disrupt the lipid rafts of cellular entry, resulting in suppressed infection of an avian coronavirus (infectious bronchitis virus). Although a previous study\textsuperscript{55} detected causal effect of LDL-C on COVID-19 susceptibility, a more recent MR study\textsuperscript{55} covering more subjects only identified a suggestive association with LDL-C ($P = 0.04$) that does not meet Bonferroni standards of significance. In our study, the MR result between LDL-C and COVID-19 was marginal significant ($P = 0.01$) ignoring Bonferroni standards, but this causal link was driven by 3 influential SNPs which need to be cautious. The different MR estimates of LDL-C are likely due to the fact of different exposure and outcome data. In particular, for COVID-19 GWAS data, both of the 2 previous studies used the HGI data sets and individuals with unknown SARS-CoV-2 infection status was used as controls. In our study, we used the GWAS data from the UKB, and the controls were confirmed by polymerase chain reaction tests. For LDL-C GWAS data, we used data sets from the Million Veteran Program which had more subjects.

### STRENGTHS AND LIMITATIONS

This study characterized the potential causality of blood lipids to the susceptibility and severity of COVID-19 using 2-sample MR design. Our findings broaden the understanding of COVID-19 risk and firstly address that higher TC and higher ApoB will increase the odds for COVID-19 susceptibility, which may be helpful to develop effective instructions and policies to control the spread of the disease to susceptible groups. However, the limitations of the current study should be addressed. First, due to the limitation of data resource, our findings are mainly based on the European/White cohort which cannot represent the universal conclusions for other ethnic groups. Second, to minimize the potential bias\textsuperscript{56} of association analyses and strengthen our results, we have added another GWAS data from the HGI, which contains more subjects (14,134 cases and 1,284,876 controls), and the casual effects of TC and ApoB on COVID-19 susceptibility were also detected. Under current conditions, we included all the available data sets and the consistent results support the causal effects of TC and ApoB on COVID-19. Third, although we have been able to evaluate the causal effects on COVID-19 based on the available data and multiple complementary methods, the findings should be verified by additional clinical resource and in-depth exploration on the potential mechanisms underlying these causalities is needed, as well.

In summary, we performed a 2-sample MR design for blood lipids and COVID-19 and found that higher TC and ApoB levels might increase the susceptibility of COVID-19.

### ARTICILE INFORMATION

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### Table 3. Summary of the MR Estimates for Blood Lipids to COVID-19 Severity

| Blood lipids      | IIV method OR (95% CI) | $P$ value | Weighted median method OR (95% CI) | $P$ value | Weighted mode-based method OR (95% CI) | $P$ value | MR-Egger method OR (95% CI) | $P$ value | Main method |
|-------------------|------------------------|-----------|-----------------------------------|-----------|---------------------------------------|-----------|--------------------------------|-----------|-------------|
| Dyslipidemia      | 0.83 (0.67–1.02)       | 0.01      | 0.81 (0.61–1.08)                  | 0.54      | 0.83 (0.58–1.17)                      | 0.29      | 0.69 (0.44–1.06)               | 0.12      | IVW         |
| HDL cholesterol   | 0.91 (0.81–1.03)       | 0.08      | 0.98 (0.81–1.18)                  | 0.09      | 0.99 (0.79–1.24)                      | 0.40      | 1.02 (0.82–1.25)               | 0.78      | IVW         |
| LDL cholesterol   | 0.96 (0.85–1.09)       | 0.07      | 0.93 (0.77–1.13)                  | 0.92      | 0.97 (0.78–1.24)                      | 0.32      | 0.89 (0.75–1.05)               | 0.10      | IVW         |
| Total cholesterol | 1.02 (0.9–1.16)        | 0.05      | 0.95 (0.78–1.17)                  | 0.96      | 0.98 (0.78–1.18)                      | 0.17      | 0.92 (0.75–1.12)               | 0.37      | IVW         |
| Triglycerides     | 1.12 (0.98–1.26)       | 0.04      | 1.04 (0.86–1.25)                  | 1.02      | 0.85 (1.22)                           | 0.65      | 0.94 (0.78–1.15)               | 0.56      | IVW-MR-Egger |
| ApoA1             | 1.00 (0.85–1.17)       | 0.01      | 1.00 (0.82–1.21)                  | 0.98      | 0.78 (1.23)                           | 0.86      | 1.08 (0.64–1.84)               | 0.73      | IVW         |
| ApoB              | 0.95 (0.84–1.07)       | 0.09      | 0.95 (0.84–1.15)                  | 0.95      | 0.84 (1.20)                           | 0.98      | 1.01 (0.80–1.27)               | 0.94      | IVW-MR-Egger |
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**Disclosures**

None.

**Supplemental Materials**

Major Resources Table

Data Supplement Figure I

Data Supplement Tables I–V

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