Causal associations between COVID-19 and Atrial Fibrillation: A bidirectional Mendelian randomization study

Xiaoyu Zhang\textsuperscript{a,b,1}, PhD; Biyan Wang\textsuperscript{b,1}, MD; Tao Geng\textsuperscript{c}, MD; Di Liu\textsuperscript{b}, PhD; Qiuyue Tian\textsuperscript{b}, PhD; Xiaoni Meng\textsuperscript{b}, MD; Qiaoyun Zhang\textsuperscript{b}, PhD; Mengyang Jiang\textsuperscript{a}, PhD; Yiqiang Zhang\textsuperscript{a}, PhD; Manshu Song\textsuperscript{d}, PhD; Wei Wang\textsuperscript{b,d}, PhD; Youxin Wang\textsuperscript{b,d,*}, PhD; Baoguo Wang\textsuperscript{a,*}, MD

\textsuperscript{a}Department of Anesthesiology, Sanbo Brain Hospital, Capital Medical University, Beijing, China
\textsuperscript{b}Beijing Key Laboratory of Clinical Epidemiology, School of Public Health, Capital Medical University, Beijing, China
\textsuperscript{c}Geriatric Department, Emergency General Hospital, Beijing, China
\textsuperscript{d}School of Medical and Health Sciences, Edith Cowan University, Perth 60127, Australia

Running title: Causal associations between COVID-19 and Atrial Fibrillation

\textsuperscript{1}These authors contributed equally to this work.

*Corresponding author

Youxin Wang, PhD, Professor, School of Public Health, Capital Medical University, No.10 Xitoutiao, Youanmenwai Street, Fengtai District, Beijing, 100069, China. Telephone number and fax number: 00861083911497, E-mail: wangy@ccmu.edu.cn.
Baoguo Wang, MD, Professor, Department of Anesthesiology, Sanbo Brain Hospital, Capital Medical University, No. 50 Xiang Shan Yi-Ke-Song, Haidian District, Beijing, 100095, China. Telephone number and fax number: 00861062856765, E-mail: wangbg@ccmu.edu.cn.
Abstract

Background and aims: Observational studies showed that coronavirus disease 2019 (COVID-19) attacks universally and its most menacing progression uniquely endangers the elderly with cardiovascular disease (CVD). The causal association between COVID-19 infection or its severity and susceptibility of atrial fibrillation (AF) remains unknown.

Methods and results: The bidirectional causal relations of COVID-19 (including COVID-19, hospitalized COVID-19 compared with not hospitalized COVID-19, hospitalized COVID-19 compared with population, and severe COVID-19) and AF are determined by using two-sample Mendelian randomization (MR) analysis. Genetically predicted severe COVID-19 was not significantly associated with risk of AF [odds ratio (OR), 1.037; 95% confidence interval (CI), 1.005-1.071; \( P = 0.023, q = 0.115 \)]. In addition, genetically predicted AF was also not causally associated with severe COVID-19 (OR, 0.993; 95% CI, 0.888-1.111; \( P = 0.905, q = 0.905 \)). There was no evidence to support association between of genetically determined COVID-19 and risk of AF (OR, 1.111; 95% CI, 0.971-1.272; \( P = 0.127, q = 0.318 \)), and vice versa (OR, 1.016; 95% CI, 0.976-1.058; \( P = 0.430, q = 0.851 \)). Besides, no significant association was observed for hospitalized COVID-19 with AF. MR-Egger indicated no evidence of directional pleiotropy.

Conclusion: Overall, this MR study provides no clear support that COVID-19 is
causally associated with the risk of AF.

**KEYWORDS** Coronavirus disease 2019; Atrial Fibrillation; Bidirectional Mendelian Randomization
Introduction

Coronavirus disease (COVID-19), which is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-COV2) and represents the causative agent of a potentially fatal disease, rapidly emerged as a global pandemic and afflicted global finances and healthcare systems severely [1]. The virus attacks universally and is vulnerable to the elderly, especially those with cardiovascular comorbidities such as diabetes mellitus, hypertension, heart failure, and coronary heart disease [2, 3]. Atrial fibrillation (AF) is the most common cardiac arrhythmia worldwide, and its prevalence is higher in patients with other comorbidities [4]. COVID-19 may cause adverse impact on the heart and cardiovascular system. AF is a frequent clinical manifestation in hospitalized COVID-19 patients who require admission to an intensive care unit [5]. In addition, recent studies have found that SARS-COV2 infection may damage cardiomyocytes and increase AF risk [6-8]. However, those findings are still susceptible to unmeasured confounders and reverse causation that cannot be fully ruled out in observational studies. Further investigation is needed to determine the causal association between COVID-19 and AF.

Mendelian randomization (MR) is a burgeoning field that utilizes genetic variants that are robustly associated with such modifiable exposures to generate more reliable evidence [9]. This approach relies on the natural, random assortment of genetic variants during meiosis yielding a random distribution of genetic variants [10]. Genome-wide
association studies (GWAS) data, which typically provide regression coefficients summarizing the associations of many genetic variants with various traits, are potentially a powerful source of data for MR analysis [11]. Therefore, we performed bidirectional MR analyses for causal inference between COVID-19 (including COVID-19, hospitalized COVID-19 compared with not hospitalized COVID-19, hospitalized COVID-19 compared with population and severe COVID-19) and AF using summary statistics results of GWAS. Understanding the bidirectional relations between COVID-19 and AF is of significant public health importance about disease prevention and complications management.

**Methods**

**Data sources**

*Genetic association datasets for COVID-19*

Summary genetic association estimates for risk of COVID-19 were obtained from the most recent version of GWAS analyses of the COVID-19 host genetics initiative in UK Biobank individuals released on January 18, 2021 (https://www.covid19hg.org/results/) [12]. We selected four phenotypes from this GWAS: (1) COVID-19 vs. population including 38,984 patients and 1,644,784 control participants; (2) Hospitalized COVID-19 vs. not hospitalized COVID-19 including 3159 patients and 7206 control participants; (3) Hospitalized COVID-19 vs. population including 9986 patients and 1,877,672 control participants; (4) Very severe respiratory confirmed COVID-19 vs. population
including 5,101 patients and 1,383,241 control participants. All COVID-19 related GWAS summary statistic data were based on European ancestry population.

*Genetic association datasets for AF*

We drew on summary statistics from a recent meta-analysis of GWAS in 31 studies of AF, which were included 18,398 patients and 91,536 control participants [13]. The study majority of the participants were of European ancestry. Details on genotype-quality control and adjudication of AF can be found elsewhere [13].

*Instrumental variables for COVID-19 and AF*

We first performed forward MR analysis to assess the effects of the phenotypes of COVID-19, hospitalized COVID-19 compared with not hospitalized COVID-19, hospitalized COVID-19 compared with population, and severe COVID-19 on AF by using genetic variants associated with exposure as instrumental variables (IVs). Since a few significant single nucleotide polymorphisms (SNPs) of COVID-19 was available at the criteria of $P < 5 \times 10^{-8}$, SNPs were selected as IVs at $P < 1 \times 10^{-5}$ for COVID-19. Then, we conducted reverse MR using genetic variants associated with AF as IVs to investigate its effect on COVID-19. SNPs that achieved significance ($P < 5 \times 10^{-8}$) for the AF were selected as IVs.

We only retained independent variants from each other based on European ancestry reference data from the 1000 Genomes Project (Linkage disequilibrium [LD], $r^2$ threshold = 0.001). The phenotypic variance ($R^2$) explained by the selected SNPs was
about 0.14% for COVID-19, 3.20% for hospitalized COVID-19 compared with not hospitalized COVID-19, 0.49% for hospitalized COVID-19 compared with population, 1.08% for severe COVID-19, and 0.58% for AF, respectively. For each selected instrument variable, $R^2$ was calculated using the formula: $R^2 = 2 \times \beta^2 \times \text{MAF} \times (1-\text{MAF})$ (MAF represented the minor allele frequency and $\beta$ represented the effect estimate of the genetic variant) [14].

**MR analysis**

The inverse variance-weighted (IVW) method was employed as main analysis which estimates the causal effect combines the ratio estimates using each variant in multiplicative random-effects model [11]. Results can be biased if IVs show horizontal pleiotropy, affecting the outcome through other pathways other than the exposure which could violate MR assumptions [15]. Therefore, four sensitivity analyses were performed including the weighted median (WM), penalised weighted median (PWM), Pleiotropy Residual Sum and Outlier (MR-PRESSO) and MR-Egger regression. The WM method which selects the median MR estimate as the causal estimate may provide precise causal estimates against invalid instruments [16]. MR-PRESSO was applied to detect and correct for any outliers reflecting likely pleiotropic effect for all reported results [17]. We conducted MR-Egger analysis which allows the intercept to be freely assessed as an indicator of average pleiotropic effect [15]. In order to assess robustness of significant results, we applied further the Cochran’s Q statistic to detect
heterogeneity among the Wald ratios for each SNP for inferring the presence of horizontal pleiotropy [18]. Leave-one-out analysis was conducted to assess the undue influence of potentially pleiotropic SNPs on the causal estimates [18]. Results are presented as odds ratios (ORs) with 95% confidence intervals (95% CIs). For the multiple corrections, the FDR (false discovery rate) was used based on the Benjamini–Hochberg procedure ($q$) [19].

For bidirectional MR analyses, the causal relationships between COVID-19 and AF were delineated into four potential parts. Figure 1 showed an overview of the bidirectional MR study to investigate these explanations. If the $P$ value was less than 0.05 only in forward MR for Explanation 1, there was significant association of genetically instrumented COVID-19 with higher AF risk. Then we conducted the reverse MR analysis assessing whether AF affected COVID-19. This reverse causal association was existed if $P$ value was less than 0.05 in Explanation 2. The Explanation 3 showed there were bidirectional causality between COVID-19 and AF ($P < 0.05$).

There was no any causal association in forward and reverse MR ($P > 0.05$) as showed in Explanation 4.

All data analyses for MR were conducted by “TwoSampleMR” package (Version 0.5.4) and “MR-PRESSO” package (Version 1.0) in the R environment (R version 4.0.4, R Project for Statistical Computing). This package harmonizes exposure and outcome
data sets including information on SNPs, alleles, effect sizes, standard errors, $P$ values, and effect allele frequencies for selected exposure instruments.

**Results**

**Causal Effect of COVID-19 on AF via forward MR**

The summary genetic association data were reported in the Supplement Table 1. In the forward MR analysis, we used 29 independent SNPs as the IVs for COVID-19. As shown in Table 1, IVW estimate showed there was no association between the genetically instrumented COVID-19 and AF risk (OR, 1.11; 95% CI, 0.971-1.272; $P = 0.127$, $q = 0.318$), with heterogeneity ($P = 0.007$) across instrument SNP effects. The MR Egger intercept test further suggested no directional pleiotropy ($P = 0.702$). In addition, genetic predisposition to hospitalized COVID-19 compared with not hospitalized COVID-19 and population were not observed to be statistically significantly associated with AF by performing IVW method (OR=0.991; 95% CI, 0.941-1.044; OR = 1.055; 95% CI, 0.995-1.119, respectively). The lack of causal association remained in all sensitivity analyses (Table 1). Of note, there was no association of the genetically instrumented severe COVID-19 with AF using 33 SNPs presented in Table 1 (OR, 1.037; 95% CI, 1.005-1.071; $P=0.023$, $q=0.115$), without directional pleiotropy ($P=0.996$) and heterogeneity ($P=0.699$).

The results of leave-one-out sensitivity analyses showed that the causal associations between genetically instrumented COVID-19 phenotypes and AF were not
substantially driven by any individual SNP (Supplementary Figures 1A-D). Figures 2A-
D presented the causal effect of the phenotypes of COVID-19 on AF, in which the
regression slopes of the lines corresponded to causal estimates using each of the four
different methods.

Causal association of AF with COVID-19 via reverse MR

The summary genetic association data of AF were reported in the Supplement Table 1.
As shown in Table 2, the reverse MR analysis showed no statistically significant
evidence of a relationship between AF and COVID-19 (OR, 1.016; 95% CI, 0.976-
1.058; \( P = 0.430, q = 0.851 \)), hospitalized COVID-19 compared with not hospitalized
COVID-19 (OR, 1.060; 95% CI, 0.935-1.201; \( P = 0.363, q = 0.453 \)), hospitalized
COVID-19 compared with population (OR, 1.017; 95% CI, 0.944-1.096; \( P = 0.661, q =
0.935 \)) and severe COVID-19 (OR, 0.993; 95% CI, 0.888-1.111; \( P = 0.905, q = 0.905 \)).
The similar results were found in the sensitivity analyses. There was no heterogeneity
and directional pleiotropy based on the Q test and MR-Egger intercept test for the
associations of AF with COVID-19, hospitalized COVID-19 compared with not
hospitalized COVID-19, hospitalized COVID-19 compared with population, and
severe COVID-19. The results of leave-one-out sensitivity analysis showed that the
association between genetically instrumented AF with COVID-19, hospitalized
COVID-19 compared with not hospitalized COVID-19, and hospitalized COVID-19
compared with population was not substantially driven by any individual SNP except
rs6843082 in phenotypes for hospitalized COVID-19 compared with population as well
as severe COVID-19 (Supplementary Figures 1E-H). The relations between the effect
sizes of the SNP-AF association and the SNP-the phenotypes of COVID-19
associations were presented in Supplementary Figures 2A-D.

Discussion

To our knowledge, this is the first study to investigate the causal relationship between
COVID-19 and AF using a bidirectional two-sample MR in European population. In
the present study using publicly available summary statistics data, no strong evidence
was found to support associations between COVID-19, hospitalized COVID-19
compared with not hospitalized COVID-19, hospitalized COVID-19 compared with
population and severe COVID-19 and the risk of AF. Furthermore, there was no MR
evidence that genetic liability to AF increases risk of critical COVID-19. The findings
were overall robust in sensitivity analyses.

To date, studies investigating the associations between COVID-19 and AF have
reported inconsistent results. Our study showed a suggestive significance of severe
COVID-19 on AF. However, this slight association disappeared after correction for
multiple testing. Consistent with our results, AF are likely the consequence of systemic
illness and not solely the direct effect of COVID-19 infection [20]. However, some
previous conventional studies have reported a direct association between COVID-19
and the enhanced risk of AF [21]. In further population-based studies with cohort design,
even after adjustment for age, hypertension, coronary artery disease, cerebrovascular
disease, and diabetes and so on, the causal relation between the traits is yet difficult to
be assessed according to the affection by unmeasured confounding effects [22]. The
discrepancy between the results of our study and the observational study may be caused
by unmeasured confounders in the observational study.

Since the cause of the ongoing COVID-19 pandemic, SARS-CoV-2 invades host cells
by attaching to the membrane bound angiotensin-converting enzyme 2 (ACE2) [23].
ACE2 shares similarities with its protein homolog angiotensinconverting enzyme (ACE)
and play a role in the renin–angiotensin–aldosterone system (RAAS) [24]. Previous
studies also found that ACE 2 activity may be related to AF [25, 26]. The reason is that
ACE2 might be a functional receptor and cellular entry point for SARS-CoV-2 to
invade target cardiac cells, it is outstanding expression in the heart [27-30]. Our results
are inconsistent with the above mechanism hypothesis. Further research is required to
clarify these results using animal models in the laboratory.

In our analysis, we did not find any associations between AF and COVID-19. However,
it is not clear whether AF would contribute to increasing the risk for worse prognosis,
or even higher mortality of COVID-19.

Our MR study has several strengths. First, MR analysis is a genetic epidemiology
method that uses genetic determinants of the exposure (COVID-19) to understand the
effect of the exposure on the outcome (AF), which can control the potential bias.
Because genetic variation is not associated with confounding factors, such as age, hypertension, cerebrovascular disease and so on, which may affect observational studies [31]. Besides, MR analysis can avoid reverse causation since genetic variation is allocated at conception. Last, the MR analysis design is less susceptible to potential unmeasured confounding and reverse causation and can strengthen the evidence for causal inference [31].

The limitations of the current study should be addressed. First, due to the limitation of data resource, stratified analyses or analyses adjusted for other covariates were impossible. Second, estimates of SNP-AF association were derived from transancestry studies which might cause bias in terms of population admixture. The same genetic variants could show different effects for different populations. However, this might lead slight effect on the estimates because the majority of individuals were of European ancestry. Third, we cannot exclude that our findings might have been affected by weak instrument bias, which depends on the selection of the genetic instrument through the threshold of $P = 1 \times 10^{-5}$ for phenotypes of COVID-19. Finally, this MR study failed to detect causal associations based on very large sample sizes, which is limited by a small fraction of the variation in phenotypes of COVID-19 explained by SNPs (1%).

**Conclusions**

Our MR study suggested that there was no evidence to support the causal relationship between COVID-19 and AF. Further research is required to clarify these findings.
through using larger samples in European ancestry.

Declaration of Competing Interest

The authors report no relationships that could be construed as a conflict of interest.

Acknowledgments

This work was supported by grants from the Application and Evaluation of Active Health Cloud Platform in China, National Key R&D Program of China (2018YFC2000704), the China-Australian Collaborative Grant (NSFC 81561128020-255 NHMRC APP1112767).
References


[25] Feng W Fau - Sun L, Sun L Fau - Qu X-F, Qu XF. Association of AGTR1 and ACE2 gene polymorphisms with structural atrial fibrillation in a Chinese Han population.

[26] Walters TE, Kalman JM, Patel SK, Mearns M, Velkoska E, Burrell LM. Angiotensin converting enzyme 2 activity and human atrial fibrillation: increased plasma angiotensin converting enzyme 2 activity is associated with atrial fibrillation and more advanced left atrial structural remodelling.


### Table 1. Causal association of COVID-19 with AF via forward MR analyses

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Numbers of SNPs</th>
<th>OR (95% CI)</th>
<th>Beta (SE)</th>
<th>( P )</th>
<th>( q )</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>COVID-19 vs. population</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IVW</td>
<td>29</td>
<td>1.111 (0.971-1.272)</td>
<td>0.106 (0.069)</td>
<td>0.127</td>
<td>0.318</td>
</tr>
<tr>
<td>Weighted median</td>
<td>29</td>
<td>1.011 (0.861-1.186)</td>
<td>0.010 (0.082)</td>
<td>0.898</td>
<td>0.924</td>
</tr>
<tr>
<td>Penalised weighted median</td>
<td>29</td>
<td>1.008 (0.857-1.186)</td>
<td>0.008 (0.083)</td>
<td>0.924</td>
<td>0.924</td>
</tr>
<tr>
<td>MR-PRESSO</td>
<td>29</td>
<td></td>
<td>-0.103 (0.061)</td>
<td>0.103</td>
<td>0.318</td>
</tr>
<tr>
<td>MR-Egger</td>
<td>29</td>
<td>1.196 (0.805-1.775)</td>
<td>0.179 (0.202)</td>
<td>0.383</td>
<td>0.638</td>
</tr>
<tr>
<td><strong>Hospitalized COVID-19 vs. not hospitalized COVID-19</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IVW</td>
<td>20</td>
<td>0.991 (0.941-1.044)</td>
<td>-0.009 (0.027)</td>
<td>0.730</td>
<td>0.730</td>
</tr>
<tr>
<td>Weighted median</td>
<td>20</td>
<td>1.014 (0.952-1.081)</td>
<td>0.014 (0.032)</td>
<td>0.665</td>
<td>0.730</td>
</tr>
<tr>
<td>Penalised weighted median</td>
<td>20</td>
<td>1.015 (0.950-1.085)</td>
<td>0.015 (0.034)</td>
<td>0.655</td>
<td>0.730</td>
</tr>
<tr>
<td>MR-PRESSO</td>
<td>20</td>
<td></td>
<td>-0.018 (0.026)</td>
<td>0.514</td>
<td>0.730</td>
</tr>
<tr>
<td>MR-Egger</td>
<td>20</td>
<td>0.952 (0.838-1.082)</td>
<td>-0.049 (0.065)</td>
<td>0.462</td>
<td>0.730</td>
</tr>
<tr>
<td><strong>Hospitalized COVID-19 vs. population</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IVW</td>
<td>32</td>
<td>1.055 (0.995-1.119)</td>
<td>0.054 (0.030)</td>
<td>0.075</td>
<td>0.125</td>
</tr>
<tr>
<td>Method</td>
<td>Weighted median</td>
<td>Penalised weighted median</td>
<td>MR-PRESSO</td>
<td>MR-Egger</td>
<td>egger_intercept</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>------------------</td>
<td>---------------------------</td>
<td>-----------</td>
<td>----------</td>
<td>-----------------</td>
</tr>
<tr>
<td></td>
<td>32</td>
<td>1.076(0.996-1.163)</td>
<td>0.073(0.040)</td>
<td>0.065</td>
<td>0.125</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.080(1.001-1.166)</td>
<td>0.077(0.039)</td>
<td>0.048</td>
<td>0.125</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.035(0.029)</td>
<td>0.246</td>
<td>0.308</td>
<td></td>
</tr>
<tr>
<td></td>
<td>32</td>
<td>0.963(0.808-1.149)</td>
<td>-0.038(0.090)</td>
<td>0.679</td>
<td>0.679</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.012</td>
<td>0.290</td>
<td></td>
</tr>
</tbody>
</table>

**Severe respiratory confirmed COVID-19 vs. population**

<table>
<thead>
<tr>
<th>Method</th>
<th>Weighted median</th>
<th>Penalised weighted median</th>
<th>MR-PRESSO</th>
<th>MR-Egger</th>
<th>egger_intercept</th>
<th>Q statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>33</td>
<td>1.037(1.005-1.071)</td>
<td>0.037(0.016)</td>
<td>0.023</td>
<td>0.115</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.039(0.994-1.086)</td>
<td>0.038(0.022)</td>
<td>0.092</td>
<td>0.153</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.039(0.995-1.085)</td>
<td>0.038(0.022)</td>
<td>0.081</td>
<td>0.153</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.038(0.920-1.171)</td>
<td>0.037(0.062)</td>
<td>0.551</td>
<td>0.551</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-6.66e-05</td>
<td>0.996</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>33</td>
<td></td>
<td>0.023(0.016)</td>
<td>0.151</td>
<td>0.189</td>
<td></td>
</tr>
</tbody>
</table>

Beta is the estimated effect size. *P* <0.05 were considered statistically significant.

AF: Atrial Fibrillation; CI: confidence intervals; IVs: instrumental variables; IVW, inverse-variance weighted; MR mendelian randomization; MR-PRESSO: Pleiotropy Residual Sum and Outlier; OR: odds ratio; SE, standard error; SNP, single-nucleotide polymorphism.
Table 2. Causal association of AF with COVID-19 via reverse MR analyses

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Numbers of SNPs</th>
<th>OR (95% CI)</th>
<th>Beta (SE)</th>
<th>(P)</th>
<th>(q)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>COVID-19 vs. population</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IVW</td>
<td>20</td>
<td>1.016 (0.976-1.058)</td>
<td>0.016 (0.021)</td>
<td>0.430</td>
<td>0.851</td>
</tr>
<tr>
<td>Weighted median</td>
<td>20</td>
<td>1.011 (0.960-1.066)</td>
<td>0.011 (0.027)</td>
<td>0.675</td>
<td>0.851</td>
</tr>
<tr>
<td>Penalised weighted median</td>
<td>20</td>
<td>1.011 (0.957-1.068)</td>
<td>0.011 (0.028)</td>
<td>0.689</td>
<td>0.851</td>
</tr>
<tr>
<td>MR-PRESSO</td>
<td>20</td>
<td>1.020 (0.962-1.082)</td>
<td>0.020 (0.020)</td>
<td>0.346</td>
<td>0.851</td>
</tr>
<tr>
<td>MR-Egger</td>
<td>20</td>
<td>1.008 (0.927-1.097)</td>
<td>0.008 (0.043)</td>
<td>0.851</td>
<td>0.851</td>
</tr>
<tr>
<td>Q statistic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalized COVID-19 vs. not hospitalized COVID-19</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IVW</td>
<td>20</td>
<td>1.060 (0.935-1.201)</td>
<td>0.058 (0.064)</td>
<td>0.363</td>
<td>0.453</td>
</tr>
<tr>
<td>Weighted median</td>
<td>20</td>
<td>1.112 (0.937-1.319)</td>
<td>0.106 (0.087)</td>
<td>0.224</td>
<td>0.453</td>
</tr>
<tr>
<td>Penalised weighted median</td>
<td>20</td>
<td>1.112 (0.933-1.325)</td>
<td>0.106 (0.089)</td>
<td>0.236</td>
<td>0.453</td>
</tr>
<tr>
<td>MR-PRESSO</td>
<td>20</td>
<td>1.041 (0.963-1.125)</td>
<td>0.041 (0.063)</td>
<td>0.521</td>
<td>0.521</td>
</tr>
<tr>
<td>MR-Egger</td>
<td>20</td>
<td>1.133 (0.878-1.463)</td>
<td>0.125 (0.130)</td>
<td>0.350</td>
<td>0.453</td>
</tr>
<tr>
<td>Q statistic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalized COVID-19 vs. population</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IVW</td>
<td>20</td>
<td>1.017 (0.944-1.096)</td>
<td>0.017 (0.038)</td>
<td>0.661</td>
<td>0.935</td>
</tr>
<tr>
<td>Weighted median</td>
<td>20</td>
<td>1.004 (0.906-1.113)</td>
<td>0.004 (0.053)</td>
<td>0.935</td>
<td>0.935</td>
</tr>
</tbody>
</table>
### Penalised weighted median

<table>
<thead>
<tr>
<th>Method</th>
<th>Beta</th>
<th>SE</th>
<th>P</th>
<th>Q statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penalised weighted median</td>
<td>1.004 (0.907-1.112)</td>
<td>0.004 (0.052)</td>
<td>0.934</td>
<td>0.935</td>
</tr>
<tr>
<td>MR-PRESSO</td>
<td>-0.030 (0.038)</td>
<td>0.429</td>
<td>0.935</td>
<td></td>
</tr>
<tr>
<td>MR-Egger</td>
<td>0.984 (0.845-1.145)</td>
<td>-0.016 (0.077)</td>
<td>0.836</td>
<td>0.935</td>
</tr>
<tr>
<td>Q statistic</td>
<td>0.005</td>
<td>0.628</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Severe respiratory confirmed COVID-19 vs. population

<table>
<thead>
<tr>
<th>Method</th>
<th>Beta</th>
<th>SE</th>
<th>P</th>
<th>Q statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVW</td>
<td>0.993 (0.888-1.111)</td>
<td>-0.007 (0.057)</td>
<td>0.905</td>
<td>0.905</td>
</tr>
<tr>
<td>Weighted median</td>
<td>0.900 (0.775-1.045)</td>
<td>-0.105 (0.076)</td>
<td>0.167</td>
<td>0.465</td>
</tr>
<tr>
<td>Penalised weighted median</td>
<td>0.898 (0.767-1.053)</td>
<td>-0.107 (0.081)</td>
<td>0.186</td>
<td>0.465</td>
</tr>
<tr>
<td>MR-PRESSO</td>
<td>-0.029 (0.054)</td>
<td>0.605</td>
<td>0.756</td>
<td></td>
</tr>
<tr>
<td>MR-Egger</td>
<td>0.938 (0.754-1.167)</td>
<td>-0.064 (0.111)</td>
<td>0.571</td>
<td>0.756</td>
</tr>
<tr>
<td>Q statistic</td>
<td>0.009</td>
<td>0.556</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Beta is the estimated effect size. $P < 0.05$ were considered statistically significant.

AF: Atrial Fibrillation; CI: confidence intervals; IVs: instrumental variables; IVW, inverse-variance weighted; MR mendelian randomization; MR-PRESSO: Pleiotropy Residual Sum and Outlier; OR: odds ratio; SE, standard error; SNP, single-nucleotide polymorphism.
Figure legends

**Figure. 1** Analyses pipeline to evaluate the explanations for the observed associations between COVID-19 and AF

COVID-19: Coronavirus disease 2019; AF: Atrial fibrillation; MR: mendelian randomization; SNP, single nucleotide polymorphism

**Figure. 2A** Scatter plot showing the associations of the SNP effects on the COVID-19 against the SNP effects on the AF.

Circles indicate marginal genetic associations with COVID-19 and risk of AF for each variant. Error bars indicate 95% CIs. COVID-19: Coronavirus disease 2019; AF: Atrial fibrillation; MR: mendelian randomization; SNP, single nucleotide polymorphism

**Figure. 2B** Scatter plot showing the associations of the SNP effects on the hospitalized COVID-19 compared with not hospitalized COVID-19 against the SNP effects on the AF.

Circles indicate marginal genetic associations with hospitalized COVID-19 and risk of AF for each variant. Error bars indicate 95% CIs. COVID-19: Coronavirus disease 2019; AF: Atrial fibrillation; MR: mendelian randomization; SNP, single nucleotide polymorphism

**Figure. 2C** Scatter plot showing the associations of the SNP effects on the hospitalized COVID-19 compared with population against the SNP effects on the AF.
Circles indicate marginal genetic associations with hospitalized COVID-19 and risk of AF for each variant. Error bars indicate 95% CIs. COVID-19: Coronavirus disease 2019; AF: Atrial fibrillation; MR: mendelian randomization; SNP, single nucleotide polymorphism

**Figure. 2D** Scatter plot showing the associations of the SNP effects on the severe COVID-19 against the SNP effects on the AF.

Circles indicate marginal genetic associations with severe COVID-19 and risk of AF for each variant. Error bars indicate 95% CIs. COVID-19: Coronavirus disease 2019; AF: Atrial fibrillation; MR: mendelian randomization; SNP, single nucleotide polymorphism
The causal association between COVID-19 and AF

Instrumental variables for COVID-19 ($P < 1E-05$)

**Explanation 1**
- SNP s a) COVID-19  AF
- Confounders

**Explanation 2**
- SNP s b) AF  COVID-19
- Confounders

**Explanation 3**
- SNP s a) COVID-19  AF
- SNP s b) AF
- Confounders

**Explanation 4**
- SNP s a) COVID-19
- SNP s b) AF
- Confounders

COVID-19 for AF MR: $P < 0.05$
AF for COVID-19 MR: $P > 0.05$

COVID-19 for AF MR: $P > 0.05$
AF for COVID-19 MR: $P < 0.05$

COVID-19 for AF MR: $P < 0.05$
AF for COVID-19 MR: $P > 0.05$

COVID-19 for AF MR: $P > 0.05$
AF for COVID-19 MR: $P < 0.05$
MR Test
- Inverse variance weighted
- Penalised weighted median
- MR Egger
- Weighted median

SNP effect on AF

SNP effect on hospitalized COVID-19 compared with not hospitalized COVID-19
Highlights

• The bidirectional MR analyses were conducted for causal inference between COVID-19 (including COVID-19, hospitalized COVID-19 compared with not hospitalized COVID-19, hospitalized COVID-19 compared with population and severe COVID-19) and AF using summary statistics data of GWAS.

• The inverse variance-weighted (IVW) method was used as main analysis; In addition, four sensitivity analyses were performed including the weighted median (WM), penalised weighted median (PWM), Pleiotropy Residual Sum and Outlier (MR-PRESSO) and MR-Egger regression.

• There was no clear evidence to support association of genetically proxied COVID-19 with risk of AF, and vice versa.