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The risk of common hypoglycemic and antihypertensive medications and COVID-19

A 2-sample Mendelian randomization study

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Abstract

Background: It has been reported that diabetes and hypertension increase the adverse outcomes of coronavirus disease 2019 (COVID-19). Aside from the inherent factors of diabetes and hypertension, it remains unclear whether antidiabetic or antihypertensive medications contribute to the increased adverse outcomes of COVID-19. The effect of commonly used antidiabetic and antihypertensive medications on COVID-19 outcomes has been inconsistently concluded in existing observational studies. Conducting a systematic study on the causal relationship between these medications and COVID-19 would be beneficial in guiding their use during the COVID-19 pandemic.

Methods: We employed the 2-sample Mendelian randomization approach to assess the causal relationship between 5 commonly used antidiabetic medications (SGLT-2 inhibitors, Sulfonylureas, Insulin analogues, Thiazolidinediones, GLP-1 analogues) and 3 commonly used antihypertensive medications (calcium channel blockers [CCB], ACE inhibitors, β-receptor blockers [BB]), and COVID-19 susceptibility, hospitalization, and severe outcomes. The genetic variations in the drug targets of the 5 antidiabetic medications and 3 antihypertensive medications were utilized as instrumental variables. European population-specific genome-wide association analysis (GWAS) data on COVID-19 from the Host Genetics Initiative meta-analyses were obtained, including COVID-19 susceptibility (n = 2597,856), COVID-19 hospitalization (n = 2095,324), and COVID-19 severity (n = 1086,211). The random-effects inverse variance-weighted estimation method was employed as the primary assessment technique, with various sensitivity analyses conducted to evaluate heterogeneity and pleiotropy.

Results: There were no potential associations between the genetic variations in the drug targets of the 5 commonly used antidiabetic medications (SGLT-2 inhibitors, Sulfonylureas, Insulin analogues, Thiazolidinediones, GLP-1 analogues) and the 3 commonly used antihypertensive medications (CCBs, ACE inhibitors, BBs) with COVID-19 susceptibility, hospitalization, and severity (all $P > .016$).

Conclusion: The findings from this comprehensive Mendelian randomization analysis suggest that there may be no causal relationship between the 5 commonly used antidiabetic medications (SGLT-2 inhibitors, Sulfonylureas, Insulin analogues, Thiazolidinediones, GLP-1 analogues) and the 3 commonly used antihypertensive medications (CCBs, ACE inhibitors, BBs) with COVID-19 susceptibility, hospitalization, and severity.

Abbreviations: ARB = angiotensin receptor blockers; BB = β-receptor blockers; CCB = calcium channel blockers; COVID-19 = coronavirus disease 2019; DPP-4i = dipeptidyl peptidase-4 inhibitors; GLP-1RA = GLP-1 receptor agonists, GWAS = genome-wide association analysis, IVW = inverse variance weighted, RAS = renin-angiotensin system, T2DM = type 2 diabetes mellitus.

Keywords: antidiabetic medications, antihypertensive medications, causal effect, COVID-19, mendelian randomization

1. Introduction

Coronavirus disease 2019 (COVID-19) is an illness caused by the infection of SARS-CoV-2,[1] on March 11, 2020, the World Health Organization (WHO) declared COVID-19 a global pandemic, according to the WHO, as of June 20, 2022, over 535 million people worldwide have been infected with COVID-19, resulting in a death toll exceeding 6.3 million.[2] Most existing evidence

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The datasets generated during and/or analyzed during the current study are publicly available.

We use public data for analysis, so no ethical approval is required.

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indicates a substantial increase in the severity and mortality rate among individuals with type 2 diabetes mellitus (T2DM) who are also diagnosed with COVID-19 compared to those without diabetes.[3–6] Similarly, it has been evidenced by several studies that patients with hypertension who also contract COVID-19 experience increased severity of the disease and higher mortality rates. A meta-analysis involving 18 studies and 13,293 patients revealed a significant elevation in the risks of in-hospital mortality, ICU admission, and the need for invasive ventilation among hypertensive individuals with COVID-19.[7] Multiple studies have reported that hypertension is an independent risk factor for the severity and mortality rates of COVID-19 patients.[8,9] Another meta-analysis, encompassing 19 studies and 15,302 participants, revealed a significant increase in adverse outcomes among COVID-19 patients with hypertension.[10] Whether glucose-lowering and antihypertensive medications are involved in exacerbating COVID-19 in addition to the effects of the disease itself has aroused great interest among scholars, numerous observational studies have examined the influence of these medications on COVID-19, yet the conclusions have been inconsistent, leading to ongoing debates regarding the association between these medications and COVID-19 outcomes.

Regarding dipeptidyl peptidase-4 inhibitors(DPP-4i), studies have reported an increased risk of ICU admission among diabetes patients with COVID-19 who use DPP-4i, compared to non-users of DPP-4i,[11] another observational study, involving 2851,465 participants, reported an increased risk of mortality associated with the use of DPP-4i.[12] On the contrary, multiple studies have reported a reduction in the risk of severe illness and mortality among diabetes patients with COVID-19 who use DPP-4i, and this association remains valid even after adjusting for various confounding factors.[13,14] Furthermore, there are studies reporting an increased risk of COVID-19 among type 2 diabetes patients using DPP-4, but without any impact on the severity of COVID-19.[15] Insulin, the most commonly used antidiabetic medication in severe cases of COVID-19 with diabetes complications, has been associated with an increased risk of poor prognosis among diabetes patients with COVID-19, as reported by studies,[16] insulin may potentially augment the severity and mortality risk among diabetes patients with COVID-19 through Na/H exchange.[17] However, there are also studies reporting an increased risk of COVID-19 among type 2 diabetes patients who use insulin without any influence on the severity of the disease.[15] There is considerable controversy surrounding the impact of sulfonylureas, DPP-4 inhibitors, SGLT-2 inhibitors, and GLP-1 receptor agonists (GLP-1RA) on diabetes patients with COVID-19. A meta-analysis encompassing 3061,584 patients suggests that GLP-1RA and SGLT-2 inhibitors reduce the mortality rate among individuals with T2DM and COVID-19. However, no significant effect on mortality is observed with sulfonylureas or thiazolidinediones.[18] DPP-4 inhibitors, sulfonylureas, SGLT-2 inhibitors, and GLP-1 receptor agonists do not exert adverse effects on diabetes patients with COVID-19, Sulfonylureas may reduce mortality risk in patients with T2DM and COVID-19, while DPP-4 inhibitors exhibit a neutral effect.[19] A large-scale observational study reported a significant reduction in the mortality rate among diabetes patients with COVID-19 associated with SGLT-2 inhibitor 12.

Angiotensin-converting enzyme 2 (ACE2) serves as the receptor for SARS-CoV, functioning as a crucial binding site through which SARS-CoV-2 enters the host organism.[20] Studies indicate that angiotensin receptor blockers (ARB) or ACE inhibitors upregulate ACE2 expression, thereby increasing the risk of severe COVID-19 in hypertensive, cardiovascular, or diabetic patients treated with ACE inhibitors.[21] Some scholars suggest temporarily discontinuing angiotensin-converting enzyme inhibitors or ARBs in COVID-19 patients, as these medications carry potential risks for worsening clinical outcomes.[21] Some scholars hold opposing views, suggesting that activating the renin-angiotensin system (RAS) may mediate acute lung injury in COVID-19 patients, they propose that RAS inhibitors could slow the progression of COVID-19 and recommend them as a potential therapeutic approach for COVID-19.[22,23] Subsequent multiple observational studies examining the effects of antihypertensive drugs on COVID-19 have reached divergent conclusions. They found that prior use of a combination of RAS inhibitors with other antihypertensive medications is associated with higher in-hospital mortality rates than using RAS inhibitors alone. Additionally, the mortality rate increases significantly when ACE inhibitors are used alone instead of ARBs in hospitalized COVID-19 patients.[24] ACE inhibitors are associated with an increased risk of mortality in male patients with COVID-19.[25] The utilization of ACE inhibitor, β-receptor blockers(BB), and calcium channel blockers(CCB)does not significantly increase the risk of testing positive for Covid-19 or developing severe Covid-19.[24] The utilization of ACE inhibitors, ARB, BB, and CCB has not been found to increase the likelihood of testing positive for Covid-19 or the risk of developing severe COVID-19.[15] A meta-analysis incorporating ten randomized controlled trials[25] revealed that ACE inhibitors/ARBs have no impact on the hospitalization duration, severity, or mortality rate of COVID-19.[26] Furthermore, studies have demonstrated that the utilization of RAS inhibitors is associated with a reduced risk of mortality in hypertensive patients with COVID-19,[27] the utilization of BB is associated with favorable outcomes in patients with COVID-19, whereas the use of calcium channel blockers is linked to poorer outcomes in COVID-19 patients,[25] using BB is associated with favorable outcomes in patients with COVID-19, whereas using calcium channel blockers is linked to poorer outcomes in COVID-19 patients.[15] using calcium channel blockers can decrease the risk of hospitalization in male patients with COVID-19,[25] ACE inhibitors, β-blockers, and CCB are not associated with increased susceptibility to COVID-19.[25] Additionally, the administration of metoprolol can reduce pulmonary inflammation related to acute respiratory distress syndrome(ARDS) in COVID-19, thereby improving oxygenation.[28]

Existing observational studies on the impact of commonly used antidiabetic and antihypertensive medications on the outcomes of COVID-19 yield inconsistent conclusions. The current scale of randomized controlled trials is insufficient to establish the safety and benefits of these drugs in patients with T2DM and COVID-19. Furthermore, observational studies are often confounded by various factors, such as social and cultural influences, as well as demographic characteristics. Mendelian randomization, using genetic variation as an instrumental variable, can minimize confounding factors and eliminate reverse causality when studying the causal relationship between exposure and outcomes. This approach strengthens the inferential association between exposure and outcomes.[29] In this study, we employed the Mendelian randomization research method to assess the causal relationship between 5 commonly used antidiabetic medications (SGLT-2 inhibitors, sulfonylureas, insulin analogues, thiazolidinediones, GLP-1 analogues) as well as 3 commonly used antihypertensive medications (calcium channel blockers, ACE inhibitors, BB),and COVID-19 outcomes(susceptibility, hospitalization, and severity).We utilized single nucleotide polymorphisms (SNPs) associated with using these medications as instrumental variables. This research aims to provide guidance for the appropriate use of antidiabetic and antihypertensive drugs in patients with diabetes mellitus and hypertension during the COVID-19 pandemic.

2. Methods

2.1. research process

We employed a 2-sample Mendelian randomization approach to systematically evaluate the causal relationship between 5

commonly used antidiabetic medications (SGLT-2 inhibitors, sulfonylureas, insulin analogues, thiazolidinediones, GLP-1 analogues) and 3 widely prescribed antihypertensive medications (calcium channel blockers, ACE inhibitors, beta-blockers) for COVID-19 outcomes (susceptibility, hospitalization, severity). Firstly, representative genetic variations associated with the targets of those above antidiabetic and antihypertensive medications were selected as instrumental variables. Subsequently, we utilized genome-wide association study (GWAS) data on COVID-19 outcomes (susceptibility, hospitalization, severity) for analysis. Please refer to Figure 1 for an illustration of the study flowchart, and the data sources for this study are shown in Table 1.

Statistical analysis was conducted using the "TwoSampleMR" package in R software (version 4.3.0). All instrumental variables exhibited an F-value exceeding 10, minimizing potential bias resulting from weak instrument variables.

2.2. Instrumental variables and data sources for GWAS

2.2.1. Genetic variations in the drug targets of sulfonylureas, insulin analogues, and thiazolidinediones The instrumental variables for the genetic variations in the drug targets of sulfonylureas, insulin analogues, and thiazolidinediones were derived from a study by Bowen Tang et al[30] (Supplementary table 1, http://links.lww.com/MD/L545, 2, http://links.lww.com/MD/L546, 3, http://links.lww.com/MD/L547). In this study, the genetic aggregation of blood glucose utilized data from 326,885 participants (Individuals with a diagnosis of diabetes mellitus on inpatient case data or self-reported diabetes mellitus on questionnaires were excluded.) provided by the UK Biobank,[30] they identified genetic variations encoding protein targets of antidiabetic medications and used them as proxies for the use of antidiabetic drugs. The instrumental variables were validated through positive control analysis of relevant traits. A total of 5 genetic variations (rs757110, rs117287142, rs2074310, rs3758953, rs4148630) were determined to be associated with Sulfonylureas, 2 genetic variations (rs2894553, rs74569625) with Insulin analogues, and 2 genetic variations (rs138779828, rs2067819) with Thiazolidinediones. Given the relatively large number of genetic variations associated with Sulfonylureas, we set a threshold of $P < 5e\text{-}05$, kb = 1000, clump_r2 = 0.01 to refine the instrumental variables. As a result, rs117287142, rs3758953, and rs757110 were excluded, and 2 genetic variations (rs2074310, rs4148630) related to Sulfonylureas were retained as instrumental variables representing the genetic variants of Sulfonylureas' targets. These instrumental variables explained 0.02% of the genetic variability in Sulfonylureas' target genes, with an F-statistic of 34.50, indicating their strong predictive potential.[31,32] Considering the limited number of instrumental variables for Insulin analogues and Thiazolidinediones, we directly utilized the drug target genetic variations selected in the original study as instrumental variables. In cases where the number of SNPs was restricted, we relaxed the association threshold, a practice widely employed in Mendelian randomization studies.[33–35] The instrumental variables for Insulin analogues accounted for 0.006% of its variability, yielding an F-statistic of 10.43. Similarly, the instrumental variables for Thiazolidinediones explained 0.007% of its variability, with an F-statistic of 12.04.

2.2.2. Genetic variations in the drug targets of GLP-1 Two sets of instrumental variables were used for the genetic variations of GLP-1R(see Supplementary table 4, http://links.lww.com/MD/L548). One set was derived from a study by Bowen Tang et al (Instrumental variables were extracted in the same way as described for instrumental variable extraction in Sulfonylureas, Insulin analogues drug target genetic variation). It identified 3 genetic variations (rs39025882, rs39017062, rs39016357) associated with GLP-1R. These instrumental variables explained 0.01% of the genetic variability in GLP-1R target genes, with an F-statistic of 12.44; The other set of instrumental variables was obtained from a study by Deqiang Zheng, Ning Li, and their colleagues.[36] This study integrated genome-wide association studies (GWAS) of quantitative trait loci with strict diagnostic and exclusion criteria from a cohort of 14,119 participants. These instrumental variables pertained specifically to the drug target genetic variations of GLP-1R,[36] genetic variations in cis-expression quantitative trait loci were employed as instrumental variables for the genetic variations of GLP-1R drug targets. In this study, 1 genetic variation (rs2268650) associated with GLP-1 was identified, explaining 0.34% of the genetic variability in GLP-1 target genes, with an F-statistic of 48.99.

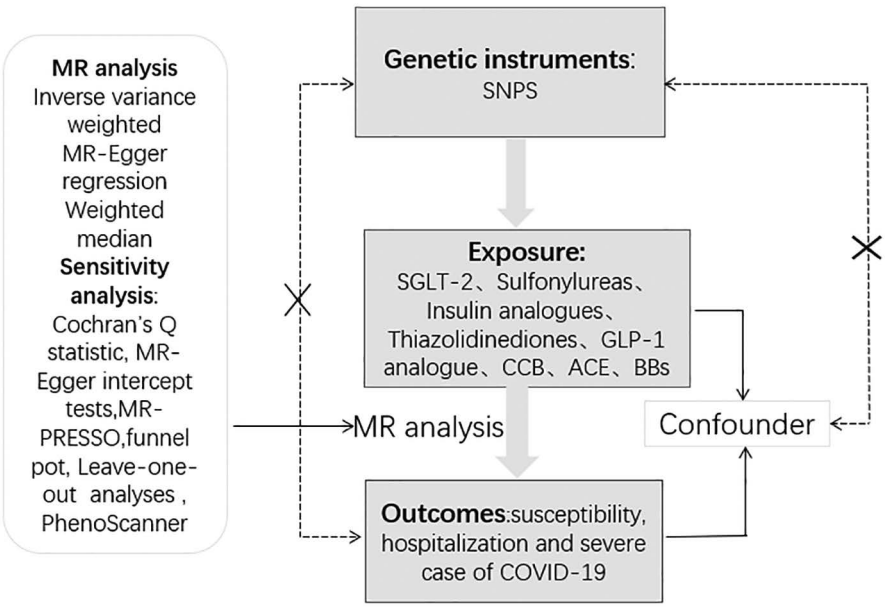

Figure 1. The flow chart of this Mendelian randomization study

Table 1

data sources included in the Mendelian randomization study.

Phenotype	Participants	Web source
Sulfon、Insulin、Thiazo、GLP-1R	326885	PMID: 35654594
GLP-1R	14119	PMID: 36737746
SGLT-2	344182	PMID:36161993
CCBs、BBs	757601	PMID: 35080656
ACE	12537	PMID: 32019855
COVID-19 (susceptibility)	2597856	www.covid19hg.org

ACE = angiotensin-converting enzyme inhibitors, BBs = β-receptor blockers, CCB = calcium channel blockers, COVID-19 = coronavirus disease 2019, GLP-1R = GLP-1 receptor agonists, Insulin = insulinanalogues, SGLT-2 = SGLT-2 inhibitors, Sulfon = sulfonylureas, Thiazo = thiazolidinediones.

2.2.3. Genetic variations in the drug targets of SGLT-2 The genetic variations of SGLT-2 were derived from an article by Min Xu and colleagues published in the journal Diabetes Care in 2022[37] (Supplementary table 5, http://links.lww.com/MD/L549). This study extraction method for genetic variations in SGLT-2 drug target involved utilizing genotype-tissue expression data from the GTEx38[38] and eQTLGen Consortium[39] databases. Significant genetic variations associated with mRNA expression levels of the target gene SLC5A2, which is engaged in SGLT2 inhibition, were selected. Subsequently, significant genetic variations related to glycated hemoglobin were identified among 344,182 non-diabetic (no diagnosis of diabetes mellitus in the case file or self-reported absence of diabetes mellitus) and unrelated European individuals from the UK Biobank. Gene co-localization methods were employed for validation, followed by standard clustering procedures. A total of 6 genetic variations (rs4488457, rs8057326, rs11865835, rs9930811, rs34497199, rs35445454) were determined to be significantly associated with both HbA1c and SGLT-2. To enhance accuracy, a threshold of $P < 5e\text{-}06$, clump_kb = 1000, clump_r2 = 0.01 was set. As a result, rs8057326, rs11865835, rs34497199, and rs35445454 were excluded, leaving 2 SNPs (rs4488457, rs34497199) as instrumental variables for the genetic variability of SGLT-2 drug targets. These SNPs accounted for 0.018% of the genetic variability in SGLT-2 target genes, with an F-statistic of 32.35.

2.2.4. Genetic variations in the drug targets of CCBs an BBs The genetic variations of CCBs and BBs drug targets were obtained from previous studies[40–44] (Supplementary table 6, http://links.lww.com/MD/L550, 7, http://links.lww.com/MD/L551), These studies selected genes encoding the pharmacological targets of these antihypertensive drugs, as identified in DrugBank, or genes present in regulatory regions that were confirmed to be associated with systolic blood pressure in a meta-analysis of UK Biobank GWAS data (involving 757,601 European ancestry participants, mean systolic and diastolic blood pressures were 138.4 mm Hg and 82.8 mm Hg, respectively). Adjustments were made for factors such as age, gender, and body mass index (BMI).[42,43] A total of 8 genetic variations associated with CCBs were identified (rs12258967, rs150857355, rs1888693, rs2488136, rs3821843, rs714277, rs7340705), while 1 variation (rs79253631) was excluded to enhance the accuracy of the instrumental variables. These 7 genetic variations explained 0.13% of the genetic variability in CCBs' target genes, with an F-value of 139.94. Additionally, 2 genetic variations associated with BBs were identified (rs11196549, rs1801253). These variations accounted for 0.04% of the genetic variability in BBs' target genes, with an F-value of 154.77.

2.2.5. Genetic variations in the drug targets of ACE The instrumental variables for genetic variations in the ACE drug target were derived from a study by Marie Pigeyre and her colleagues[45] (Supplementary table 8, http://links.lww.com/MD/L552). This research employed a strategy of selecting genetic variations located within a 300-kilobase range of the ACE gene. Significantly associated SNPs with ACE concentration were identified from the Outcome Reduction with Initial Glargine Intervention (ORIGIN) trial (registered as NCT00069784 on ClinicalTrials.gov), which involved 12,537 participants (diagnosis of T2DM, impaired fasting glucose conditions, or abnormal glucose tolerance). SNPs unobserved in the DIAGRAM database or with a minor allele frequency below 0.05 were excluded. Adjustments were made for age, gender, and baseline use of ACE inhibitors. In total, 17 genetic variations associated with angiotensin-converting enzyme inhibitors were identified (rs4343, rs1074637, rs11650201, rs117808108, rs12452187, rs1260245, rs13342595, rs1443431, rs2137143, rs4313, rs4968780, rs71377703, rs72845888, rs72847305, rs74251225, rs75457471, rs79480822). Specific criteria were set to enhance the accuracy of the instrumental variables further: $P < 5e\text{-}08$, clump_kb = 1000, clump_r2 = 0.05, and population " European," As a result, 6 SNPs (rs4343, rs1074637, rs12452187, rs12602457, rs4968780, rs75457471) were obtained (see supplementary material table). These SNPs accounted for 27% of the genetic variability in the ACE drug target, with an F-statistic of 773.

2.2.6. COVID-19 GWAS data sources The GWAS data for COVID-19 were obtained from the COVID-19 Host Genetics Initiative (HGI) GWAS meta-analyses. COVID-19 was classified into 3 phenotypes: susceptibility, hospitalization, and severe COVID-19. In this study, European population data were selected for all 3 COVID-19 phenotypes. The instrumental variables for susceptibility were derived by comparing COVID-19 cases (122,616 individuals) to non-COVID-19 individuals (control group: 2475,240 individuals). COVID-19 cases were identified based on laboratory confirmation, clinical diagnosis, or self-report through questionnaires. For the hospitalization phenotype, the instrumental variables were obtained by comparing hospitalized COVID-19 patients (32,519 individuals) to non-hospitalized individuals (including both COVID-19 patients who did not require hospitalization and non-COVID-19 individuals) (control group: 2062,805 individuals). Hospitalization was defined as a laboratory-confirmed COVID-19 case that required hospital admission. Regarding the severe COVID-19 phenotype, the instrumental variables were derived by comparing severe COVID-19 patients (13,769 individuals) to non-severe COVID-19 patients or non-COVID-19 individuals (control group: 1072,442 individuals). Severe COVID-19 was defined as cases requiring invasive or noninvasive ventilation or resulting in death due to COVID-19.

2.3. Risk factor analysis

Although sensitivity analysis did not provide evidence of bias in the MR results, we used Phenoscanner to explore further the association between SNPs related to glucose-lowering and blood pressure-lowering drug targets in this study and COVID-19, as well as common risk factors for COVID-19, such as cerebrovascular disease, asthma, interstitial lung disease, COPD, chronic kidney disease, cirrhosis, coronary artery disease, heart failure, HIV, smoking, tuberculosis, lung cancer, breast cancer, and obesity.[46,47]

2.4. Statistical analysis

For instrumental variables consisting of more than 3 SNPs, we employed inverse variance weighted (IVW), weighted median, and MR-Egger analysis methods for MR estimation. IVW served as the primary method, while weighted median and MR-Egger analysis were utilized to improve the MR estimation obtained from IVW. When instrumental variables consisted of 2 SNPs,

we used IVW. For instrumental variables with only a single SNP, Wald-ratio MR estimation was employed. Meta-analysis of MR results for exposures with 2 sets of instrumental variables was conducted using Review Manager to address heterogeneity and multiple effects.

To mitigate heterogeneity and pleiotropy, we utilized MR-PRESSO and the PhenoScanner[48] website to assess the relevance of SNPs in the instrumental variables to COVID-19 or potential confounding factors. Any SNPs found to be relevant were subsequently excluded. In cases where the significant estimates from IVW differed from those of the weighted median and MR-Egger analysis, we adjusted the threshold for instrumental variable *P* values and reanalyzed the data.[49]

Additionally, we employed the MR-Egger intercept test, leave-one-out analysis, Cochran Q test, and funnel plot to assess heterogeneity and pleiotropy. A Cochran Q test with a *P* value <.05 indicated the presence of heterogeneity, while an MR-Egger intercept *P* value <.05 detected pleiotropy. The leave-one-out analysis involved systematically excluding individual SNPs and repeating the IVW analysis to ascertain whether the causal estimates were driven by any single SNP.

Considering the multiple tests conducted in the primary analysis, we applied a Bonferroni correction threshold of $P < .016$ ($\alpha = 0.05/3$).

3. Results

Causal Relationship between Exposure and Outcomes (Fig. 2).

We identified weak evidence suggesting a potential causal effect of SGLT-2 on susceptibility to COVID-19 (IVW: OR = 0.592, 95% CI = 0.368–0.953, *P* = .03). The Cochran Q test yielded a *P* value of .389, indicating no heterogeneity. However, considering the multiple tests conducted in the primary analysis, the *P* value did not reach the Bonferroni correction threshold. Consequently, we were unable to detect a causal effect of SGLT-2 on hospitalization (IVW: OR = 0.814, 95% CI = 0.293–2.255, *P* = .050) or severe illness (IVW: OR = 0.659, 95% CI = 0.057–7.536, *P* = .737), *P* values for Cochran Q test were 0.688 and 0.101, respectively, no heterogeneity was observed based on the Cochran Q test.

Similarly, we could not detect a causal effect of Sulfonylureas on susceptibility to COVID-19 (IVW: OR = 1.486, 95% CI = 0.791–2.791, *P* = .217), hospitalization (IVW: OR = 0.544, 95% CI = 0.143–2.059, *P* = .370), or severe illness (IVW: OR = 0.554, 95% CI = 0.078–3.927, *P* = .554), the *P* values of Cochran Q test were 0.414, 0.882, 0.641, respectively, suggesting that no heterogeneity was detected.

Furthermore, we found no causal effect of Insulin analogues on susceptibility to COVID-19 (IVW: OR = 1.769, 95% CI = 0.196–15.943, *P* = .610), hospitalization (IVW: OR = 0.186, 95% CI = 0.001–24.027, *P* = .498), or severe illness (IVW: OR = 3.415, 95% CI = 0.047–246.406, *P* = .573), the *P* values of Cochran Q test were 0.069, 0.073, 0.635, respectively, suggesting that no heterogeneity was detected.

Lastly, we could not detect a causal effect of Thiazolidinediones on susceptibility to COVID-19 (IVW: OR = 0.380, 95% CI = 0.095–1.511, *P* = .169), hospitalization (IVW: OR = 0.652, 95% CI = 0.018–22.468, *P* = .813), or severe illness (IVW: OR = 0.576, 95% CI = 0.011–29.915, *P* = .784), the *P* values of Cochran Q test were 0.207, 0.151, 0.586, respectively, suggesting that no heterogeneity was detected.

GLP-1 analogues (study conducted by Bowen Tang and colleagues) showed no significant causal effect on susceptibility to COVID-19 (IVW: OR = 1.868, 95% CI = 0.692–5.039, *P* = .216; MR-Egger: OR = 0.694, 95% CI = 0.102–4.722, *P* = .772; Weighted median: OR = 1.341, 95% CI = 0.511–3.517, *P* = .550), hospitalization (IVW: OR = 11.287, 95% CI = 1.934–65.867, *P* = .007; MR-Egger: OR = 8.783, 95% CI = 0.128–600.936, *P* = .497; Weighted median: OR = 9.162, 95% CI = 0.006–12916.125, *P* = .549), or severe illness (IVW: OR = 3.877, 95% CI = 0.195–76.844, *P* = .373; MR-Egger: OR = 12.872, 95% CI = 0.0005–320245.657, *P* = .707; Weighted median: OR = 7.028, 95% CI = 0.293–266.663, *P* = .185), the *P* values of Cochran Q test were 0.198 (susceptibility), 0.536 (hospitalization), 0.324 (severe illness) and the *P* values of MR Egger intercept were 0.454, 0.916, 0.841 respectively, suggesting that heterogeneity and pleiotropy were not detected.

The second set of instrumental variables for GLP-1 (study conducted by Deqiang Zheng, Ning Li, and their colleagues) also showed no significant causal effect on susceptibility to COVID-19 (IVW: OR = 0.991, 95% CI = 0.970–1.013, *P* = .450), hospitalization (IVW: OR = 0.957, 95% CI = 0.914–1.002, *P* = .065), or severe illness (IVW: OR = 0.987, 95% CI = 0.923–1.057, *P* = .724). No heterogeneity was observed based on Cochran Q test. However, when meta-analyzing the results of both instrumental variable sets for GLP-1 and considering heterogeneity detection (*P* = .006) under a Fixed Effects model, we decided to adopt the results from the Random Effects model (OR = 2.79, 95% CI = 0.25–30.64, *P* = .40). This suggests no support for a causal association between GLP-1 and COVID-19 hospitalization (Fig. 3).

Similarly, CCB (calcium channel blockers) showed no significant causal effects on susceptibility to COVID-19 (IVW: OR = 1.021, 95% CI = 0.999–1.043, *P* = .057; MR-Egger: OR = 0.974, 95% CI = 0.896–1.058, *P* = .580; Weighted median: OR = 1.010, 95% CI = 0.992–1.029, *P* = .260), hospitalization (IVW: OR = 1.031, 95% CI = 0.979–1.087, *P* = .241; MR-Egger: OR = 0.872, 95% CI = 0.762–0.997, *P* = .140; Weighted median: OR = 1.017, 95% CI = 0.975–1.061, *P* = .411), or severe illness (IVW: OR = 1.021, 95% CI = 0.999–1.043, *P* = .057; MR-Egger: OR = 0.948, 95% CI = 0.718–1.251, *P* = .733; Weighted median: OR = 1.006, 95% CI = 0.949–1.066, *P* = .823). The IVW test *P* value of .030 in the Cochran Q test for CCB and COVID-19 hospitalization suggests that heterogeneity was detected, and when there is heterogeneity in the IVW in the Cochran Q test, 1 should look at the results of the Weighted median and the MR Egger, neither of which support a Causal association. *P* values for Cochran Q test were 0.030 (hospitalized), 0.118 (severe), MR Egger intercept *P* values were .333 (susceptibility), .085 (hospitalized), .627 (severe), MR-presso.

P value was .143 (susceptibility), .099 (hospitalization), and .201 (severe disease), respectively, indicating that no heterogeneity or pleiotropy was found.

We did not detect any causal effect of ACE inhibitors on susceptibility to COVID-19 (IVW: OR = 1.005, 95% CI = 0.992–1.018, *P* = .415; MR-Egger: OR = 1.015, 95% CI = 0.986–1.045, *P* = .374; Weighted median: OR = 1.006, 95% CI = 0.993–1.020, *P* = .330), hospitalization (IVW: OR = 1.010, 95% CI = 0.981–1.040, *P* = .476; MR-Egger: OR = 1.038, 95% CI = 0.971–1.109, *P* = .346; Weighted median: OR = 1.017, 95% CI = 0.986–1.050, *P* = .270), or severe illness (IVW: OR = 1.000, 95% CI = 0.952–1.051, *P* = .981; MR-Egger: OR = 1.027, 95% CI = 0.922–1.143, *P* = .660; Weighted median: OR = 1.004, 95% CI = 0.954–1.058, *P* = .851). Cochran Q test *P* values were .692 (susceptibility), .396 (hospitalization), .751 (severe disease), MR Egger intercept *P* values were .505 (susceptibility), .436 (hospitalization), .630 (severe disease), MR-presso *P* value was .652 (susceptibility), .484 (hospitalization), and .769 (severe disease), indicating that no heterogeneity or pleiotropy was found.

Similarly, we did not find any causal effects of β-blockers on susceptibility to COVID-19 (Wald ratio: OR = 0.964, 95% CI = 0.933–0.996, *P* = .029), hospitalization (Wald ratio: OR = 0.934, 95% CI = 0.870–1.003, *P* = .062), or severe illness (Wald ratio: OR = 0.972, 95% CI = 0.877–1.078, *P* = .599).

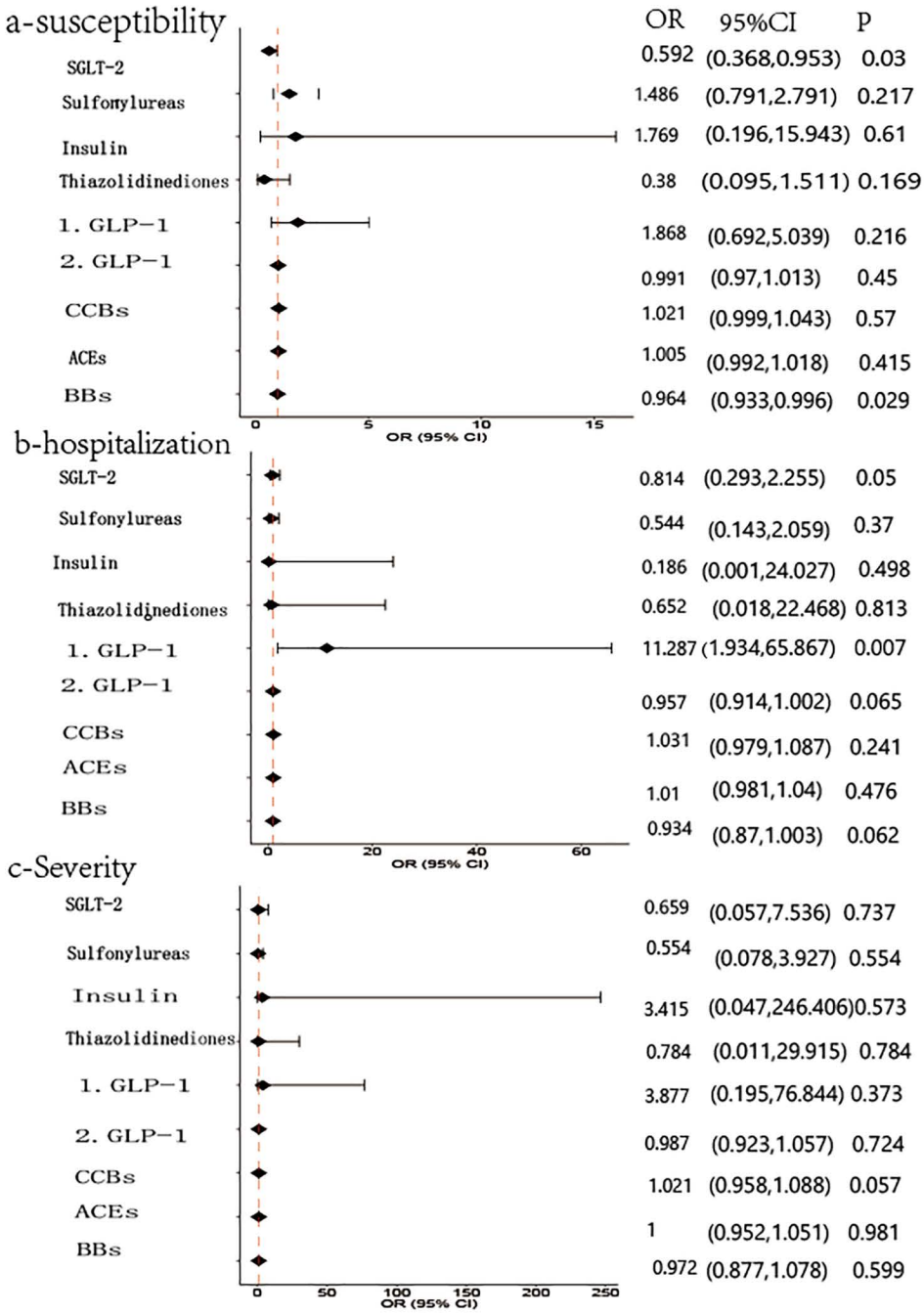

Figure 2. Forest plot for the causal effect of hypoglycemic and antihypertensive drugs on the risk of COVID-19 derived from IVW. ACEs = angiotensin-converting enzyme inhibitors, BBs = β-receptor blockers, CCB = calcium channel blockers, COVID-19 = coronavirus disease 2019, GLP-1 = GLP-1 receptor agonists, OR = odds ratio, SGLT-2 = SGLT-2 inhibitors.

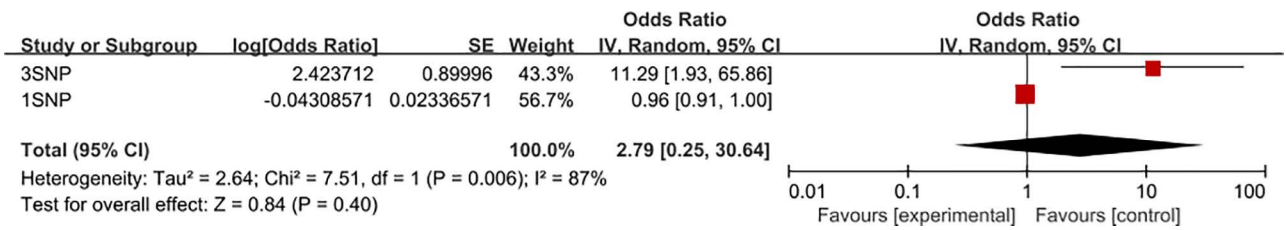

Figure 3. Meta-analysis of the causal associations between GLP-1 and COVID-19. CI = confidence interval, COVID-19 = coronavirus disease 2019.

Please refer to Supplementary table 9, http://links.lww.com/MD/L553 for the sensitivity analysis results of the causal relationship between antidiabetic and antihypertensive medications and susceptibility to COVID-19, hospitalization, and severe illness.

4. Discussion

Currently, there is no consensus regarding the impact of commonly used antidiabetic and antihypertensive medications on the outcomes of COVID-19. Given the substantial population affected by diabetes and hypertension worldwide and the large number of individuals using these medications, various meta-analyses and small-scale observational studies have yielded inconsistent results. Methodological constraints limit these observational studies, as they cannot fully account for confounding factors and reverse causality, where Mendelian randomization (MR) studies offer an advantage. In our study, we designed a Mendelian randomization study to evaluate the effects of commonly used antidiabetic and antihypertensive medications on COVID-19. We employed genetic variants associated with the drug targets of 5 commonly used antidiabetic medications (SGLT-2, Sulfonylureas, Insulin analogues, Thiazolidinediones, GLP-1 analogue) and 3 commonly used antihypertensive medications (CCB, ACE inhibitors, β-blockers) as instrumental variables for exposure. COVID-19 was considered the outcome, with susceptibility, hospitalization, and severe illness analyzed separately.

Our study showed that 1 group of GLP-1 agonist gene proxies exhibited a causal association with COVID-19 (hospitalization) in MR analysis (OR = 11.287, $P = .007$). In contrast, another group of GLP-1 agonists showed no association with COVID-19 hospitalization (OR = 0.957, $P = .065$). Meta-analysis of the MR results did not support a causal relationship ($P = .40$). A meta-analysis involving 31 studies and 66,914 patients indicated that GLP-1RA does not adversely affect individuals with diabetes and COVID-19,[50] which aligns with our research findings.

Furthermore, we observed a weak causal association between SGLT-2 and susceptibility to COVID-19 ($P = .030$, OR = 0.592). SGLT-2 may reduce the susceptibility to COVID-19. However, considering multiple testing, the P value did not reach the Bonferroni corrected threshold. Moreover, we found no literature supporting the reduction of COVID-19 susceptibility by SGLT-2, which further supports our findings.

In the risk factor analysis, using Phenoscanner, we found that SNPs related to BBs, GLP-1 agonists, insulin analogues, SGLT-2 inhibitors, Sulfonylureas, and Thiazolidinediones were unrelated to confounding factors. Among the ACE-related SNPs, rs4343 was associated with asthma. Even after excluding rs4343, the causal relationship remained insignificant (IVW: susceptibility OR = 0.995, 95% CI = 0.967–1.024, $P = .758$; hospitalization OR = 0.983, 95% CI = 0.923–1.046, $P = .598$; severe illness OR = 0.980, 95% CI = 0.892–1.076, $P = .677$). Similarly, among the CCB-related SNPs, rs3821843 was associated with body mass index. Nevertheless, after its exclusion, the causal relationship remained insignificant (IVW: susceptibility OR = 1.025, 95% CI = 0.997–1.054, $P = .078$; hospitalization OR = 1.034, 95% CI = 0.965–1.109, $P = .330$; severe illness OR = 1.025, 95% CI = 0.941–1.115, $P = .567$), which indicates that the MR estimation between the genetic variations of the 5 antidiabetic medications and 3 antihypertensive medications in our study is not influenced by pleiotropic pathways associated with COVID-19.

This study is the first to comprehensively reveal the association between antidiabetic and antihypertensive medications and COVID-19 from a genetic perspective using Mendelian randomization analysis. Compared to observational studies, our study has the advantage of avoiding the influence of reverse causality and confounding factors.

However, our study also has some limitations. Firstly, the study population only consisted of individuals of European descent, limiting its generalizability to other ethnicities. Additionally, there is a relatively limited number of instrumental variables employed as exposure in our study. Secondly, due to the reliance of MR analyses on exploiting the random allocation of genetic variants to extrapolate causal hypotheses, distinguishing between mediation and pleiotropy with MR approaches posed challenges. And finally, due to the reliance of MR analyses on exploiting the random allocation of genetic variants to extrapolate causal hypotheses, distinguishing between mediation and pleiotropy with MR approaches posed challenges.

Conclusion: Our results indicate that there are no potential associations between the 5 commonly used antidiabetic medications (SGLT-2 inhibitors, Sulfonylureas, Insulin analogues, Thiazolidinediones, GLP-1 analogues) and 3 commonly used antihypertensive medications (CCBs, ACE inhibitors, β-blockers) with susceptibility, hospitalization, and severe illness in COVID-19. That is, genetically, SGLT-2 inhibitors, sulfonylureas, insulin analogs, thiazolidinediones, GLP-1 analogs, CCBs, ACE inhibitors, and β-blockers did not increase/decrease the risk of susceptibility, hospitalization, and readmission to COVID-19.

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