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# Causal associations between thyroid dysfunction and COVID-19 susceptibility and severity: A bidirectional Mendelian randomization study

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**Background:** Observational studies have reported an association between coronavirus disease 2019 (COVID-19) risk and thyroid dysfunction, but without a clear causal relationship. We attempted to evaluate the association between thyroid function and COVID-19 risk using a bidirectional two-sample Mendelian randomization (MR) analysis.

**Methods:** Summary statistics on the characteristics of thyroid dysfunction (hypothyroidism and hyperthyroidism) were obtained from the ThyroidOmics Consortium. Genome-wide association study statistics for COVID-19 susceptibility and its severity were obtained from the COVID-19 Host Genetics Initiative, and severity phenotypes included hospitalization and very severe disease in COVID-19 participants. The inverse variance-weighted (IVW) method was used as the primary analysis method, supplemented by the weighted-median (WM), MR-Egger, and MR-PRESSO methods. Results were adjusted for Bonferroni correction thresholds.

**Results:** The forward MR estimates show no effect of thyroid dysfunction on COVID-19 susceptibility and severity. The reverse MR found that COVID-19 susceptibility was the suggestive risk factor for hypothyroidism (IVW: OR = 1.577, 95% CI = 1.065–2.333,  $P = 0.022$ ; WM: OR = 1.527, 95% CI = 1.042–2.240,  $P = 0.029$ ), and there was lightly association between COVID-19 hospitalized and hypothyroidism (IVW: OR = 1.151, 95% CI = 1.004–1.319,  $P = 0.042$ ; WM: OR = 1.197, 95% CI = 1.023–1.401,  $P = 0.023$ ). There was no evidence supporting the association between any phenotype of COVID-19 and hyperthyroidism.

**Conclusion:** Our results identified that COVID-19 might be the potential risk factor for hypothyroidism. Therefore, patients infected with SARS-CoV-2 should strengthen the monitoring of thyroid function.

## KEYWORDS

COVID-19, hypothyroidism, hyperthyroidism, Mendelian randomization, thyroid dysfunction

## Introduction

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It has rapidly become a global epidemic and a serious health threat (1). Currently, several studies have shown that some susceptible populations include type 2 diabetes, obesity, hypertension, and other metabolic diseases (2–5). However, thyroid disease is not covered in the report.

SARS-CoV-2 virus infection and thyroid-promoted inflammatory responses are related and interact in a complex way. Several small observational case studies now support that thyroid dysfunction is a predisposing factor for COVID-19 (6, 7) and that hospital mortality is higher in patients with COVID-19 hypothyroidism than in patients with COVID-19 normal thyroid function (8). However, some studies have taken the opposite view (9–11), suggesting that the real cause of COVID-19 progression is antithyroid drug-induced neutropenia rather than thyroid disease status. In addition, SARS-CoV-2 may impair the hypothalamic–pituitary–thyroid axis or damage thyroid problems through a viral inflammatory process, which may increase the risk of future partial thyroid dysfunction (12–14). However, these findings remain vulnerable to confounding factors and reverse causality that cannot be fully excluded in observational studies. Further investigation is needed to determine the causal relationship between thyroid dysfunction and COVID-19 infection.

Mendelian randomization (MR) is a new epidemiological approach that uses genetics as a tool to study correlations between exposure and outcome (15). MR is biologically based on the random distribution of gametes in meiosis and has the advantage of overcoming the limitations of confusion and reverse causality often encountered in observational studies (16). In this study, we performed bidirectional MR to explore the causal association between thyroid dysfunction and COVID-19 risk.

## Methods

### Study design

We conducted a bidirectional two-sample MR study to assess the causal relationship between thyroid dysfunction (hypothyroidism and hyperthyroidism) and COVID-19 susceptibility and its severity. The instrumental variables must satisfy three basic principles: (1) Genetic variation is strongly correlated with exposure; (2) genetic variation is not strongly related to potential confounders; and (3) genetic variation does not directly affect the outcome (17). We performed bidirectional MR in this study, and forward MR: thyroid dysfunction genome-

wide association study (GWAS) data were used to explore the effect of thyroid dysfunction on COVID-19. Reverse MR: COVID-19 GWAS was used as an exposure to explore the effect of COVID-19 on thyroid dysfunction (Supplementary Figure 1).

### Data sources

Data from genome-wide association studies of COVID-19 cases were obtained from the COVID19 Host Genetics Initiative GWAS meta-analysis, round 5 (18). In our study, the COVID-19 susceptibility phenotype comprised 38,984 European patients with COVID-19 defined as individuals with laboratory confirmation of SARS-CoV-2 infection or electronic health records [using the International Classification of Diseases (ICD) or physician annotations] or self-reported, with 1,644,784 control individuals. We then used two cohorts to assess the COVID-19 severity phenotype. The first cohort was compared to 9,986 hospitalized patients versus 1,877,672 control individuals. The second cohort compared 5,101 very severe patients, defined as patients who died or required respiratory support (including continuous positive airway pressure (CPAP), bilevel positive airway pressure (BiPAP), intubation, or high-flow nasal cannula). A total of 1,383,241 control individuals were not included as cases (<https://www.COVID19hg.org/blog/2021-03-02-freeze-5-results/>). Details of the phenotypes are shown in Table 1.

Summary statistics of thyroid dysfunctions were from The ThyroidOmics Consortium (<https://transfer.sysepi.medizin.uni-greifswald.de/thyroidomics/datasets/>). The GWAS summary comprised 19 independent cohorts (19). The hypothyroidism cohort included 3,340 cases with thyroid-stimulating hormone (TSH) levels above the reference range, and the hyperthyroidism cohort included 1,840 cases with TSH levels below the cohort-specific reference range. In addition, 49,983 control individuals with TSH levels within the reference range were included in the cohort. Patients receiving medication for thyroiditis were excluded. Genotype data were estimated from the 1,000 genomes, Project Phase 1, Version 3 ALL Population Reference Panel; and all analyses were adjusted for age, age squared, and sex. Details of the 19 cohorts can be found in the original article (19).

The ethical approval and consent information for the above summary statistics were taken from the original publication.

### Selection of genetic instruments

Single nucleotide polymorphisms (SNPs) that met the  $p < 5 \times 10^{-8}$  threshold and minor allele frequency  $>1\%$  were included to avoid potential statistical bias from the original GWAS. We then retained only those SNPs with linkage

TABLE 1 Sources of data for the analysis.

| Phenotype               | Source of Genetic Variants |  |
|-------------------------|----------------------------|--|
|                         | Consortium                 | Participants   |
| Hypothyroidism          | –                          | <b>Cases:</b> 3,340 cases with TSH levels above the reference range.<br><b>Controls:</b> 49,983 individuals with TSH levels in the reference range.  |
| Hyperthyroidism         | –                          | <b>Cases:</b> 1,840 cases with TSH levels below the reference range.<br><b>Controls:</b> 49,983 individuals with TSH levels in the reference range.  |
| COVID-19 susceptibility | Susceptibility             | <b>Cases:</b> 3,8984 individuals with COVID-19 by laboratory confirmation of SARS-CoV-2 infection, or by electrical health records (using ICD or physician notes), or self-reporting.<br><b>Controls:</b> 1,644,784 individuals enrolled in the cohorts and not included as cases. |
| COVID-19 severity       | Hospitalized               | <b>Cases:</b> 9,986 hospitalized individuals with COVID-19.<br><b>Controls:</b> 1,877,672 individuals enrolled in the cohorts and not included as cases  |
|                         | Very severe disease        | <b>Cases:</b> 5,101 very severe patients defined as patients who died or required respiratory support (including CPAP, BiPAP, intubation, or high-flow nasal cannula).<br><b>Controls:</b> 1,383,241 individuals enrolled in the cohorts and not included as cases.                |

disequilibrium ( $R^2 < 0.01$ ) clustered in genomic regions 5,000 kbp apart. We used the PhenoScanner database (<http://www.phenoscanter.medschl.cam.ac.uk/phenoscanter>) to examine the selected instruments variables associated with other phenotypes that may at risk of affecting outcome. rs597808, selected SNP for exposure of hypothyroidism, was correlated significantly with hematological phenotypes (e.g., platelet count, total eosinophil basophil count, percentage of neutrophils in granulocytes, and lymphocyte count). Some studies have shown that changes in blood counts are a marker of SARS-CoV-2 infection and severity, with 25% of patients with COVID19 showing various forms of leucopenia (WBC  $< 4.00E+09$  cells/liter) and the majority (63%) showing lymphocytopenia (20). One other study found that reduced platelet counts can lead to severe COVID-19 (21). Therefore, we conducted MR analysis before and after removed rs597808. We did not detect any SNP association with body mass index, smoking, or drinking, which may be at risk of affecting hyperthyroidism or hypothyroidism when the outcome of MR was thyroid dysfunction (22, 23).

$R^2$  represents the ability of genetic variables to explain the exposures. In our study, the explained variances ranged from 7.1% to 17.6%. In addition, we used F statistics to avoid any weak instrumental variables ( $F > 10$ ). The detailed information for the selected SNP is shown in the [Supplementary File](#).

## Mendelian randomization analysis

We performed a Wald ratio to assess the effect of exposure on an outcome for each genetic instrument. Then, we used the inverse variance-weighted (IVW) method by combining each effect size as the main analysis to estimate the causal effect of exposure on outcome in the fixed-effects model (24). Moreover, the MR-Egger and weighted-median (WM) methods were applied as supplements. The MR-Egger method was based on

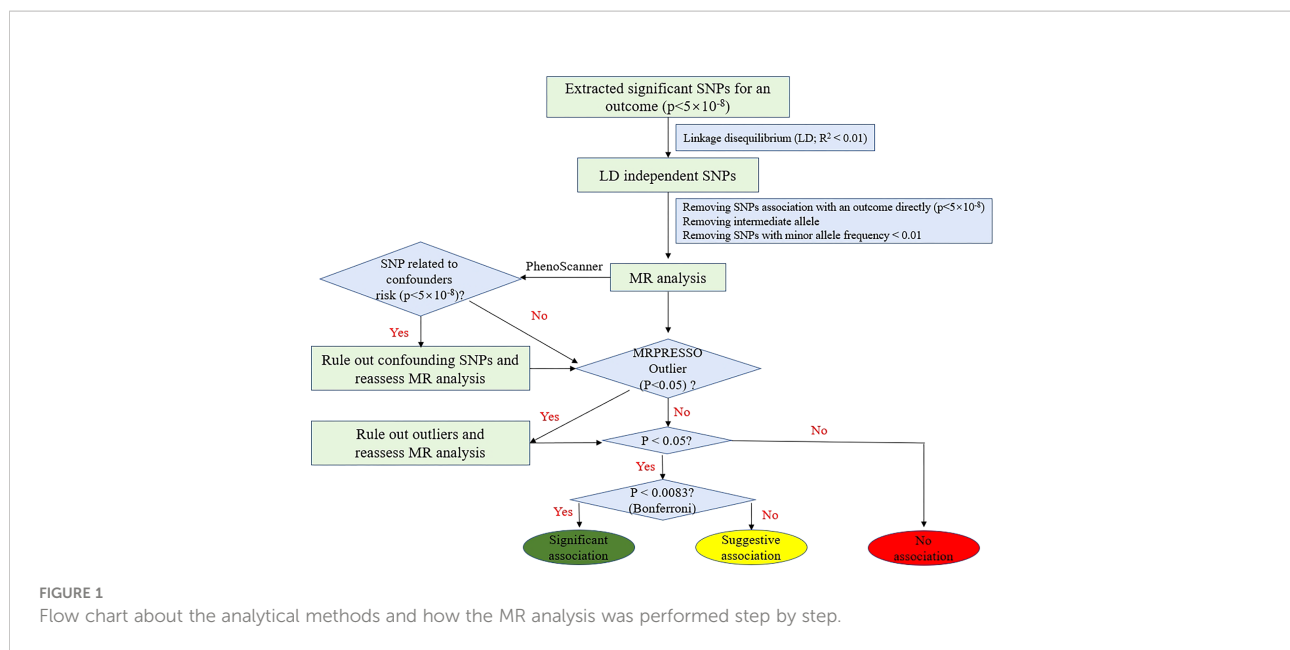
the Instrument Strength Independent of Direct Effect assumption. The MR-Egger method often takes inaccurate and statistically low results, especially in the case of the small size of SNPs (e.g.,  $< 10$ ) (25). In addition, the value of the MR-Egger intercept term is far from zero, indicating horizontal pleiotropy ( $P < 0.05$ ). Therefore, the MR-Egger method was mainly conducted to detect pleiotropy in our MR study. The WM analysis was more reliable if more than one-half of SNPs are invalid genetic instruments (e.g., due to pleiotropy) (26). We applied Cochrane's Q-value to examine the heterogeneity, and we adopted the IVW random-effects method as the main effect size if heterogeneity existed. In addition, MR-PRESSO (27) was performed to detect any outlier which may lead to the heterogeneity. If we detected outliers, then they would be removed, and we reassessed the MR effect. We adjusted the multiple testing by a Bonferroni-corrected threshold of  $p < 0.0083$  ( $p < 0.05/3/2$ ). The  $p$ -values between 0.0083 and 0.05 were considered suggestive associations. A flow chart about how the MR analysis was performed step by step is shown in [Figure 1](#).

We applied the "TwoSampleMR" and "MR-PRESSO" packages to our MR study; all statistical analyses were performed on the basis of the R software 4.1.1, and the data visualization was conducted in R software and STATA 12.0.

## Results

### Causal association of thyroid dysfunction with COVID-19 via forward MR

There was no evidence supporting hypothyroidism as a risk or protective factor for COVID-19 susceptibility, hospitalization, and very severe disease phenotype (IVW: OR = 0.971, 95% CI = 0.826–1.083,  $P = 0.193$ ; OR = 0.983, 95% CI = 0.862–1.121,  $P = 0.798$ ; and OR = 0.911, 95% CI = 0.746–1.112,  $P = 0.359$ ; respectively). In addition, the association between



hyperthyroidism and COVID-19 susceptibility, hospitalization, and very severe disease phenotype risk was not observed (IVW: OR = 0.983, 95% CI = 0.948–1.019,  $P = 0.705$ ; OR = 0.938, 95% CI = 0.873–1.007,  $p = 0.077$ ; and OR = 0.921, 95% CI = 0.826–1.026,  $P = 0.136$ ; respectively).

We detected a significant correlation between the genetic instrument rs597808 and hematological features of hyperthyroidism, which may be a confounding factor for the COVID-19 phenotype. We then removed rs597808 and reassessed the MR analysis but reached the same conclusions as the former. On the basis of Q-tests, MR-Egger intercepts, and MR-PRESSO to detect associations between thyroid dysfunction and COVID-19 risk, there was no significant heterogeneity, horizontal pleiotropy, or outliers. Detailed results of the different MR analyses are shown in [Table 2](#).

## Causal association of COVID-19 with thyroid dysfunction *via* reverse MR

The IVW estimate suggested that the susceptibility of COVID-19 and its severity may increase the risk of hypothyroidism. In addition, we deem that the association was suggestive because the p-values were between 0.0083 and 0.05 (Bonferroni-corrected threshold  $P = 0.0083$ ). The MR results are shown in [Table 3](#) and [Figures 2, 3](#).

COVID-19 susceptibility (IVW: OR = 1.577, 95% CI = 1.065–2.333,  $P = 0.022$ ; WM: OR = 1.527, 95% CI = 1.042–2.240,  $P = 0.029$ ) and hospitalization (IVW: OR = 1.151, 95% CI = 1.004–1.319,  $P = 0.042$ ; WM: OR = 1.197, 95% CI = 1.023–1.401,  $P = 0.023$ ) have a suggestive association with hypothyroidism. There was no association between the severe

disease phenotype of COVID-19 and hypothyroidism. The light heterogeneity was excited when the susceptibility and the severe disease phenotype of COVID-19 were used as the exposure, so we performed the IVW random-effects method as the main analysis. The directional pleiotropy was not detected by the MR-Egger intercept. An outlier was detected by the MR-PRESSO test when the severe disease phenotype was used as the exposure, and we reassessed the MR after removing the outlier ([Table 3](#)).

Any type of COVID-19 phenotypes was not the risk or protective factor for hyperthyroidism ( $P > 0.05$ ) in our study. The light heterogeneity was excited when the susceptibility phenotype of COVID-19 was used as the exposure, so we used the IVW random-effects method for our MR analysis. The directional pleiotropy and outliers were not detected by the MR-Egger intercept and MR-PRESSO, respectively.

The detailed MR results and sensitivity analysis for the previous results are presented in [Table 3](#).

## Discussions

Our bidirectional two-sample MR study included two independent consortiums, and only European ancestry was retained. All genetic instruments were rigorously screened by conducting the PhenoScanner. Finally, our MR studies inferred suggestive causal effects of COVID-19 susceptibility and its severity on a higher risk of hypothyroidism.

Some previous observational studies have provided evidence of COVID-19-related primary hypothyroidism (8, 28, 29). Several studies have suggested that hypothyroidism may be caused by direct damage caused by SARS-CoV-2. Angiotensin-converting enzyme 2 (ACE2) and transmembrane protease

TABLE 2 MR estimates for the causal effect of thyroid dysfunction on COVID-19.

|                | Outcome                  | NSNP | IVW                  |       | Weighted Median      |       | MR-Egger             |       | P(I <sup>2</sup> ) | P(pleiotropy) | P(Global) |
|----------------|--------------------------|------|----------------------|-------|----------------------|-------|----------------------|-------|--------------------|---------------|-----------|
|                |                          |      | OR (95% CI)          | P     | OR (95% CI)          | P     | OR (95% CI)          | P     |                    |               |           |
| Hyper          | COVID-19 susceptibility  | 8    | 0.983 (0.948, 1.019) | 0.705 | 0.972 (0.930, 1.016) | 0.202 | 0.970 (0.835, 1.127) | 0.705 | 0.847              | 0.864         | 0.835     |
|                | COVID-19 hospitalization | 8    | 0.938 (0.873, 1.007) | 0.077 | 0.936 (0.853, 1.028) | 0.165 | 0.918 (0.684, 1.231) | 0.752 | 0.619              | 0.587         | 0.619     |
|                | COVID-19 very severe     | 8    | 0.921 (0.826, 1.026) | 0.136 | 0.947 (0.820, 1.094) | 0.458 | 0.935 (0.587, 1.488) | 0.786 | 0.448              | 0.950         | 0.473     |
| Hypo           | COVID-19 susceptibility  | 7    | 0.971 (0.826, 1.083) | 0.193 | 0.959 (0.907, 1.015) | 0.153 | 0.946 (0.826, 1.083) | 0.458 | 0.711              | 0.701         | 0.730     |
|                | COVID-19 hospitalization | 7    | 0.983 (0.862, 1.121) | 0.798 | 0.903 (0.792, 1.028) | 0.141 | 1.195 (0.791, 1.807) | 0.436 | 0.037              | 0.373         | 0.053     |
|                | COVID-19 very severe     | 7    | 0.911 (0.746, 1.112) | 0.359 | 0.852 (0.689, 1.053) | 0.138 | 0.943 (0.466, 1.908) | 0.877 | 0.057              | 0.923         | 0.060     |
| Hypo-excluded* | COVID-19 susceptibility  | 6    | 0.973 (0.928, 1.021) | 0.267 | 0.956 (0.899, 1.016) | 0.149 | 0.944 (0.825, 1.082) | 0.456 | 0.593              | 0.667         | 0.646     |
|                | COVID-19 hospitalization | 6    | 1.001 (0.871, 1.167) | 0.914 | 0.995 (0.866, 1.143) | 0.939 | 1.181 (0.759, 1.837) | 0.503 | 0.043              | 0.497         | 0.063     |
|                | COVID-19 very severe     | 6    | 0.948 (0.765, 1.174) | 0.627 | 0.971 (0.796, 1.185) | 0.776 | 0.918 (0.446, 1.887) | 0.827 | 0.061              | 0.930         | 0.116     |

Hypo-excluded\*: MR analysis (exposure: hypothyroidism; outcome: COVID-19) after excluded rs597808 (PMID: 27863252), which significantly associated with hematological traits by performing PhenoScanner datasets; hematological parameters are markers of COVID-19 infection and severity; NSNP, number of single-nucleotide polymorphism; MR, Mendelian randomization; IVW, inverse variance weighting; OR, odds ratio. The I<sup>2</sup> statistic was used to present the heterogeneity among estimates for each SNP in one analysis. P(Global): The p-value for the global test in the MR-PRESSO. P(pleiotropy): The p-value for the intercept in the MR-Egger regression was used present the pleiotropy (p < 0.05). Hyper, hyperthyroidism; Hypo, hypothyroidism.

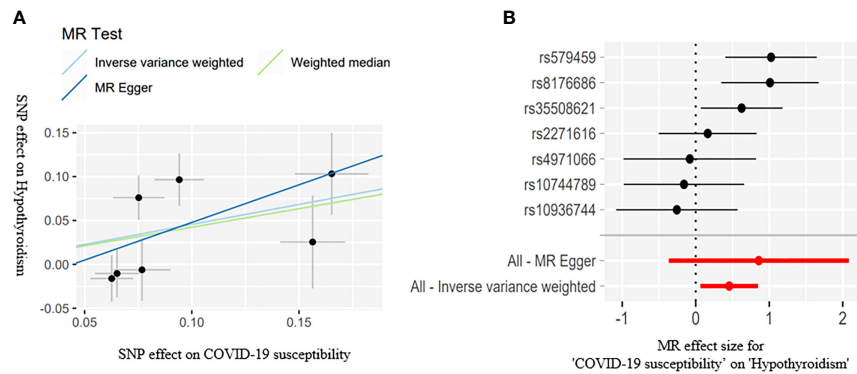
serine 2 (TMPRSS2) binding is a key complex in SARS-CoV-2-infected hosts (30, 31). Notably, ACE2 and TMPRSS2 are expressed at high levels in the thyroid gland, even higher than in the lung tissue (32). Tee et al. (29) reported a case of overt

primary hypothyroidism induced by autoimmune thyroiditis a week after mild COVID-19 symptoms were resolved. A case of hypothyroidism due to Hashimoto's thyroiditis in a 45-year-old man was described (29). A study described that about 7% of

TABLE 3 MR estimates for the causal effect of COVID-19 on thyroid dysfunction.

|   | Outcome | NSNP | IVW                  |              | Weighted Median      |              | MR-Egger             |              | P(I <sup>2</sup> ) | P(pleiotropy) | P(Global) |
|---|---------|------|----------------------|--------------|----------------------|--------------|----------------------|--------------|--------------------|---------------|-----------|
|   |         |      | OR (95% CI)          | P            | OR (95% CI)          | P            | OR (95% CI)          | P            |                    |               |           |
| COVID-19 susceptibility                   | Hyper   | 7    | 0.963 (0.589, 1.575) | 0.881        | 1.072 (0.667, 1.725) | 0.773        | 2.745 (0.825, 9.132) | 0.161        | 0.027              | 0.128         | NA        |
|   | Hypo    | 7    | 1.577 (1.065, 2.333) | <b>0.022</b> | 1.527 (1.042, 2.240) | <b>0.029</b> | 2.358 (0.682, 8.032) | 0.228        | 0.037              | 0.525         | 0.062     |
| COVID-19 hospitalization                  | Hyper   | 5    | 1.131 (0.936, 1.367) | 0.203        | 1.200 (0.980, 1.469) | 0.077        | 1.221 (0.889, 1.670) | 0.214        | 0.284              | 0.185         | 0.324     |
|   | Hypo    | 5    | 1.151 (1.004, 1.319) | <b>0.042</b> | 1.197 (1.023, 1.401) | <b>0.023</b> | 1.342 (1.017, 1.771) | <b>0.038</b> | 0.599              | 0.302         | 0.574     |
| COVID-19 very severe                      | Hyper   | 8    | 1.069 (0.959, 1.193) | 0.228        | 1.094 (0.948, 1.263) | 0.220        | 1.238 (0.955, 1.607) | 0.158        | 0.612              | 0.269         | 0.532     |
|   | Hypo    | 8    | 1.103 (0.963, 1.263) | 0.158        | 1.133 (1.006, 1.277) | <b>0.039</b> | 1.334 (0.979, 1.818) | 0.118        | 0.019              | 0.234         | 0.049     |
| COVID-19 very severe outlier <sup>#</sup> | Hypo    | 7    | 1.060 (0.954, 1.177) | 0.276        | 1.126 (1.002, 1.262) | <b>0.043</b> | 1.182 (0.920, 1.528) | 0.191        | 0.245              | 0.106         | 0.251     |

Severity outlier<sup>#</sup>: MR analysis was reassessed (exposure: very severe COVID-19; outcome: hypothyroidism) after removed the MRPRESSO outlier (rs111837807; outlier test, p = 0.008); NSNP, number of single-nucleotide polymorphism; MR, Mendelian randomization; IVW, inverse variance weighting; OR, odds ratio. The I<sup>2</sup> statistic was used to present the heterogeneity among estimates for each SNP in one analysis. P(Global): The p-value for the global test in the MR-PRESSO. P(pleiotropy): The p-value for the intercept in the MR-Egger regression was used present the pleiotropy (p < 0.05). Hyper, hyperthyroidism; Hypo, hypothyroidism. Bold values indicate p < 0.05.

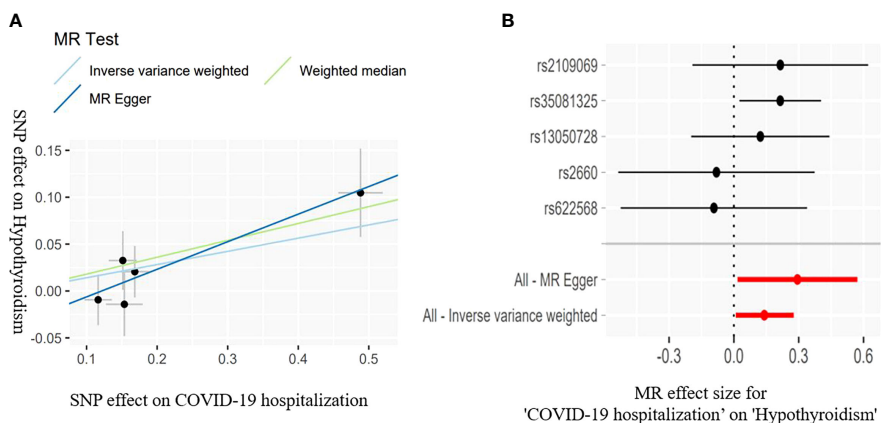


**FIGURE 2** Scatter plots (A) for estimating causal effects of genetically predicted susceptibility on risk of hypothyroidism. Each black point representing the effect sizes of each SNP on the exposure (horizontal axis) and on the outcome (vertical axis) is plotted with error bars corresponding to each standard error (SE). The slope of each line corresponds to the combined estimate using each method of the IVW (light blue line), the MR-Egger regression (blue line), and the weighted median (light green line). Forest plots (B) of susceptibility on the risk of hypothyroidism; the red points showed the combined causal estimate using all SNPs together in a single instrument, using two different methods (MR-Egger and IVW).

patients who survived from severe COVID-19 might have a risk of persistent hypothyroidism, mostly due to Hashimoto’s thyroiditis (33). Another study reported that an 18-year-old woman who was hospitalized with severe viral thyroiditis had a positive oropharyngeal swab for SARS-CoV-2 15 days earlier and had mild symptoms of COVID-19 (34). In addition, some other studies reported that subacute viral thyroiditis appears 16–36 days after symptoms of COVID-19 disappear (35, 36). It is worth noting that the original GWAS defined hyperthyroidism and hypothyroidism based on TSH levels, and some patients with subclinical hypothyroidism might be included in the

GWAS. There are some observational studies regarding subclinical hypothyroidism after COVID-19 infection. A clinical study by Burekovic et al. (37) showed that, at an average of 2 months after COVID-19 infection, some patients developed subclinical hypothyroidism, and another study (38) showed that seven of the 71 patients infected with COVID-19 included developed subclinical hypothyroidism.

Hypothyroidism is a broad spectrum of disorders that may be related to autoimmune disease or other processes such as viral thyroiditis. COVID-19 is associated with some autoimmune diseases other than thyroid disorder, which have been



**FIGURE 3** Scatter plots (A) for estimating causal effects of genetically predicted susceptibility on risk of hypothyroidism. Each black point representing the effect sizes of each SNP on the exposure (horizontal axis) and on the outcome (vertical axis) is plotted with error bars corresponding to each standard error (SE). The slope of each line corresponds to the combined estimate using each method of the IVW (light blue line), the MR-Egger regression (blue line), and the weighted median (light green line). Forest plots (B) of susceptibility on the risk of hypothyroidism; the red points showed the combined causal estimate using all SNPs together in a single instrument, using two different methods (MR-Egger and IVW).

described in many studies, such as Guillain–Barre syndrome, autoimmune hemolytic anemia, and systemic lupus erythematosus (39). Antibodies against SARS-CoV-2 can react with various organs, including the thyroid gland, which can cause damage (40). ACE-2, the receptor through which SARS-CoV-2 infects the host cells, is expressed by various tissues, including the thyroid. Therefore, the SARS-CoV-2 virus will be present not only in the lung tissue but also in the thyroid cells. Hence, the patients may develop subacute thyroiditis following SARS-CoV-2 infection (41). Our MR study was limited by the original GWAS datasets, which were unable to distinguish between these different types of thyroid dysfunction, which may be the main source of heterogeneity. However, combining the results of this study with previous observational studies, we deem that COVID-19 susceptibility and its severity on the higher risk of any type of hypothyroidism.

At present, WHO has already made elderly, pregnant women, and people with heart failure, uncontrolled diabetes, and cancer-related complications as susceptible people of COVID-19. However, such general guidelines do not provide information about the COVID-19 risk of patients with thyroid problems. Most (42–46) epidemiological studies deem that thyroid dysfunction did not have higher rates of COVID-19 susceptibility and its severity, which is consistent with our conclusion. In an epidemiological study in Europe, patients with hyperthyroidism and hypothyroidism did not have an increased risk of COVID-19 infection (45). Two retrospective studies in the US (10) and Iran (46) show that patients with COVID-19 with hypothyroidism will not increase the rates of hospitalization or mortality. There may be multiple impacts of thyroid dysfunction on the risk of COVID-19 susceptibility and its severity due to mixed confounding factors such as an antithyroid drug. Boelaert et al. (47) reported that antithyroid drug-induced neutropenia, but not thyroid disorder status, may promote the progression of COVID-19 and its symptoms (47). We think that whether thyroid dysfunction increases the risk of COVID-19 requires further study, which can provide guidance on the management of thyroid disorder during the COVID-19 pandemic. We note that a recent MR study on COVID-19 and thyroid function showed that patients with COVID-19 susceptibility but not severe were more likely to develop hypothyroidism (48). We point out that the reason our study also found a potential correlation between patients with severe COVID-19 and hypothyroidism is that we included a larger number of patients with COVID-19 GWAS compared to study by Li et al. In addition, our inclusion criteria for genetic instruments were more stringent, as we excluded any genetic instruments that could be associated with confounding factors, whereas the study by Li et al. did not, thus giving our study more credibility.

Our study used the MR method by performing genetic instruments to examine the causal relationship between the characteristics of thyroid dysfunction and COVID-19 risk, and MR analysis can eliminate confounding factors as much as possible. In addition, a large size of independent datasets was

used to obtain genetic instruments, which can mitigate the risk of bias in our results due to a few cases. However, there are some limitations to our study. This study included heterogenous in datasets, and the original GWAS datasets are unable to distinguish between these different types of thyroid dysfunction. However, combined with previous epidemiological studies, we point out that COVID-19 is associated with various types of hypothyroidism; thus, further research is required. As a two-sample MR analysis requires that both samples come from the same population, our study includes only participants of European ancestry; therefore, the generalization of these results to other populations requires further study.

## Conclusion

Our results identified that COVID-19 susceptibility and its severity might increase the risk of hypothyroidism. Therefore, patients infected with SARS-CoV-2 should strengthen the monitoring of thyroid function. However, the effect of thyroid dysfunction on COVID-19 susceptibility and its severity was not found in this MR study.

## Data availability statement

The original contributions presented in the study are included in the article/[Supplementary Material](#). Further inquiries can be directed to the corresponding author.

## Ethics statement

This study only used published or publicly available data. Ethical approval for each study included in the investigation can be found in the original publications (including informed consent from each participant).

## Author contributions

ZZ and TF designed the study. ZZ and TF conducted data analysis. ZZ conceived the project and wrote the manuscript. YL revised and approved the paper. All authors contributed to the article and approved the submitted version.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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## Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fendo.2022.961717/full#supplementary-material>

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