

Original Paper

Retracted: Assessing the Causal Association Between COVID-19 and Graves Disease: Mendelian Randomization Study

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Abstract

Background: Graves disease (GD) is an autoimmune thyroid disorder characterized by hyperthyroidism and autoantibodies. The COVID-19 pandemic has raised questions about its potential relationship with autoimmune diseases like GD.

Objective: This study aims to investigate the causal association between COVID-19 and GD through Mendelian randomization (MR) analysis and assess the impact of COVID-19 on GD.

Methods: We conducted an MR study using extensive genome-wide association study data for GD and COVID-19 susceptibility and its severity. We used stringent single nucleotide polymorphism selection criteria and various MR methodologies, including inverse-variance weighting, MR-Egger, and weighted median analyses, to assess causal relationships. We also conducted tests for directional pleiotropy and heterogeneity, as well as sensitivity analyses.

Results: The MR analysis, based on the largest available dataset to date, did not provide evidence supporting a causal relationship between COVID-19 susceptibility (odds ratio [OR] 0.989, 95% CI 0.405-2.851; $P=.93$), COVID-19 hospitalization (OR 0.974, 95% CI 0.852-1.113; $P=.70$), COVID-19 severity (OR 0.979, 95% CI 0.890-1.077; $P=.66$), and GD. Tests for directional pleiotropy and heterogeneity, as well as sensitivity analyses, supported these findings.

Conclusions: This comprehensive MR study does not provide sufficient evidence to support a causal relationship between COVID-19 and the onset or exacerbation of GD. These results contribute to a better understanding of the potential association between COVID-19 and autoimmune diseases, alleviating concerns about a surge in autoimmune thyroid diseases due to the pandemic. Further research is warranted to explore this complex relationship thoroughly.

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Keywords: Graves disease; COVID-19; Mendelian randomization; causal relationship; autoimmune disease

Introduction

Graves disease (GD) is an autoimmune thyroid disorder characterized by hyperthyroidism and the presence of autoantibodies. It is influenced by a combination of genetic, environmental, and immunological factors. Viral infections have long been implicated as potential triggers of autoimmune diseases, including autoimmune thyroid disorders [1-3]. Notably, the global COVID-19 pandemic has intensified concerns regarding its potential role in the development or exacerbation of autoimmune diseases such as GD [1,2].

Previous studies have explored the associations between viral infections and autoimmune thyroid diseases, with evidence suggesting that infections such as Epstein-Barr virus and hepatitis C virus may contribute to the onset or progression of these disorders [4,5]. More recently, research has focused on the potential immunological impact of SARS-CoV-2, the virus responsible for COVID-19. It has been proposed that SARS-CoV-2 can disrupt immune homeostasis, potentially leading to autoimmune reactions, including thyroid dysfunction [6]. While observational studies have reported an increased incidence of thyroid abnormalities in COVID-19 patients, these findings remain inconclusive in establishing a direct causal link between COVID-19 and autoimmune thyroid diseases [7-9].

The impact of COVID-19 on thyroid function has been further highlighted in recent systematic reviews and meta-analyses, which have suggested that thyroid abnormalities may be a common sequela of SARS-CoV-2 infection [10]. Additionally, genetic predisposition plays a crucial role in determining susceptibility to autoimmune thyroid diseases, which underscores the need for a robust methodological approach to examine causality.

To address these uncertainties, this study uses Mendelian randomization (MR) analysis to investigate the causal relationship between COVID-19 and GD. MR leverages genetic variants as instrumental variables to approximate the effects of a randomized controlled trial, thereby minimizing confounding biases. This approach is based on 3 key assumptions: (1) genetic variants are not associated with confounding factors, (2) genetic variants influence an intermediate exposure variable, and (3) genetic variants affect the outcome solely through their impact on the exposure variable [11].

By elucidating the potential causal association between COVID-19 and GD, this research aims to contribute to a deeper understanding of the impact of SARS-CoV-2 on autoimmune thyroid diseases. These findings could inform future studies and clinical strategies for managing autoimmune thyroid disorders in the context of COVID-19.

Methods

Study Design

This study used a 2-sample MR design, relying exclusively on publicly accessible data for all analyses. We meticulously

adhered to the recommendations presented in the Strengthening the Reporting of Observational Studies in Epidemiology-Mendelian Randomization (STROBE-MR) guidelines, ensuring a comprehensive and rigorous reporting approach.

Ethical Considerations

This study is a secondary analysis of publicly available genome-wide association study (GWAS) summary statistics obtained from the Integrative Epidemiology Unit OpenGWAS database [12]. As no new individual-level data were collected and no direct human participation was involved, ethical approval from an institutional review board was not required. The original GWASs adhered to their respective ethical guidelines and received necessary approvals. Since the study exclusively used deidentified, publicly available data, informed consent was not applicable; however, the original studies obtained informed consent from participants at the time of data collection and explicitly permitted secondary data analysis without additional consent. All data used in this study were fully anonymized, ensuring participant confidentiality, and no personally identifiable information was accessed, stored, or analyzed. In accordance with data protection regulations and ethical standards, strict measures were taken to maintain privacy and confidentiality. As no human participants were directly involved, no compensation was provided. Additionally, this study does not include any identifiable images or figures.

Data Sources for Exposures

We procured summary-level data for COVID-19 susceptibility (n=1,683,768), COVID-19 hospitalization (n=1,882,773), and COVID-19 severity (n=1,388,342) from the Integrative Epidemiology Unit OpenGWAS database [12]. This database offers extensive GWAS summary statistics encompassing a diverse array of traits and outcomes.

The data on COVID-19 susceptibility included 38,984 individuals, comprising individuals diagnosed with COVID-19 through laboratory confirmation of SARS-CoV-2 infection, electronic health records using *International Classification of Diseases (ICD)* codes or physician notes, or self-reported cases. For COVID-19 hospitalization, 9986 individuals were included, while COVID-19 severity encompassed 5101 individuals categorized as being in an extremely critical condition, which included individuals who experienced mortality or required advanced respiratory support [13-15].

Detailed information regarding the genetic variants associated with these COVID-19-related outcomes is presented in 3/7/2025 [16], offering a comprehensive overview of the exposure variables used in our MR analysis.

Outcome Data

The outcome data for GD were extracted from publicly available summary statistics, involving a total of 2176 GD cases and 210,277 controls (GWAS ID: bbj-a-123). The cases represented individuals hospitalized for GD, and the control group consisted of individuals from cohorts without identified cases. The genetic instruments used for GD in this MR

study were derived from these data, facilitating a comprehensive evaluation of the causal relationship between GD and pertinent genetic variations.

Instrument Construction

For constructing genetic instruments for each exposure, we used a rigorous approach. We identified single nucleotide polymorphisms (SNPs) displaying significant associations with the respective exposure at a genome-wide significance threshold ($P < 5 \times 10^{-6}$), which, while less stringent than the conventional threshold ($P < 5 \times 10^{-8}$), was chosen to balance instrument strength and the number of available SNPs. These SNPs underwent linkage disequilibrium clumping to remove highly correlated SNPs ($r^2 \geq 0.001$). Our reference population was drawn from the European cohort within the 1000 Genomes Project, which may limit the generalizability of our findings to non-European populations. To ensure consistency in effect sizes and address issues related to palindromic SNPs, we harmonized SNP-exposure and SNP-GD associations. In cases where specific SNPs were missing in the GD GWAS dataset, we used proxy SNPs ($r^2 > 0.8$). To mitigate potential bias from weak instruments, we performed F statistic calculations and conducted multiple sensitivity analyses, including leave-one-out analysis and MR-Egger regression. The processes of SNP extraction from GWAS summary-level data, linkage disequilibrium clumping, and harmonization were executed using the TwoSample MR package in R version 4.3.0 (R Core Team) [17,18]. The strength of the instrumental variables was evaluated using the F statistic, computed as follows: $F = (R^2/K)/[(1-R^2)/(N-K-1)]$, where R^2 denotes the variance explained by the instruments, K is the number of instruments, and N is the sample size [19].

Statistical Analyses

Using a 2-sample MR approach, we estimated the causal effects of COVID-19 susceptibility and its severity on GD. The primary MR analysis used the inverse-variance weighting (IVW) method, assuming that the genetic instruments collectively satisfy the core MR assumptions. In addition to the primary MR analysis, we conducted supplementary sensitivity analyses, including MR-Egger, weighted median, and MR-pleiotropy residual sum and outlier (MR-PRESSO) methods. These methods enhance robustness against potential pleiotropic effects by relaxing certain MR assumptions. To assess horizontal pleiotropy, we used the intercept term from MR-Egger regression, where an intercept P value exceeding .05 indicated an absence of pleiotropy. Furthermore, we applied MR-PRESSO as a supplementary method to detect and exclude outlier genetic instruments with pleiotropic effects, subsequently estimating causal effects. All tests were 2-sided and executed using the TwoSampleMR and MR-PRESSO packages in R version 4.3.0. A significance

threshold was set at $P < .05$. Since our analysis exclusively used publicly available data, no ethical approval from a local committee was sought.

Results

In summary, this MR analysis encompassed GWAS data for 3 COVID-19 statuses, including COVID-19 susceptibility and its severity, in relation to GD (detailed information provided in Table 1).

Regarding COVID-19 susceptibility, the IVW MR analysis indicated that GD did not significantly increase the risk (odds ratio [OR] 0.989, 95% CI 0.405-2.851; $P = .93$; Figures 1A,2A,3A and Table 2). No heterogeneity among SNPs was observed (Cochran Q $P = .39$). The MR-Egger intercept was close to zero (intercept = -0.0051; $P = .85$), implying the absence of directional pleiotropic effects (Table 3). MR-PRESSO did not detect any outlier SNPs ($P = .47$). The results of the leave-one-out sensitivity analysis supported the observed causal association (Figure 4A).

The results of the IVW MR analysis indicated that there was no significant association between COVID-19 hospitalization and the risk of GD (OR 0.974, 95% CI 0.852-1.113; $P = .70$; Figures 1B,2B,3B and Table 2). Heterogeneity was not observed among the various studies ($P = .27$). Sensitivity analysis using the MR-PRESSO method also failed to yield statistically significant causal estimates ($P = .33$). Furthermore, the MR-Egger intercept suggested an absence of horizontal pleiotropy (intercept = -0.0039; $P = .89$). The MR-PRESSO method did not identify any outlier SNPs ($P = .33$; Table 3). Leave-one-out sensitivity analysis did not reveal any individual SNPs that significantly influenced the causal estimates (Figure 4B).

In the primary MR analysis using the IVW method, there was no significant association observed between COVID-19 severity and the risk of GD. The OR for this relationship was 0.979 (95% CI 0.890-1.077; $P = .66$; Figures 1C,2C,3C and Table 2). The results were consistent when using the weighted median method (OR 0.975, 95% CI 0.852-1.116; $P = .71$) and conducting the MR-PRESSO sensitivity analysis ($P = .20$). Furthermore, the Cochran Q test revealed no evidence of heterogeneity ($P = .20$), and the MR-Egger intercept indicated the absence of horizontal pleiotropy (intercept = 0.0352; $P = .37$). No potential outliers were identified using the MR-PRESSO method (Table 3). Leave-one-out sensitivity analysis did not reveal any individual SNPs that significantly influenced the causal estimates (Figure 4C). The symmetry in the funnel plot further supported the reliability of the MR analysis (Figure 3).

Table 1. Data sources for the analysis.

Phenotype and consortium	Source of genetic variations	
	Cases	Controls
Graves disease	2176 individuals hospitalized for Graves disease	210,277 individuals from cohorts without identified cases
COVID-19 susceptibility and its severity		
Susceptibility	38,984 individuals who were diagnosed with COVID-19 using laboratory confirmation of SARS-CoV-2 infection, electronic health records (which included the use of <i>ICD</i> ^a codes or physician notes), or self-reported cases	1,644,784 individuals who were registered within the same groups but were excluded from the cases under investigation
Hospitalization	9986 individuals who were admitted to hospitals as a result of contracting COVID-19	1,877,672 individuals who were enrolled in the study cohorts but did not meet the criteria for classification as cases, indicating that they did not require hospitalization due to COVID-19
Very severe	5101 individuals categorized as being in an extremely critical condition, which encompasses those who experienced mortality or required advanced respiratory support, including interventions such as continuous positive airway pressure (CPAP), bilevel positive airway pressure (BiPAP), endotracheal intubation, or high-flow nasal cannula therapy	1,383,241 individuals who were included in the study cohorts but did not meet the criteria for classification as cases

^a*ICD*: International Classification of Diseases.

Figure 1. Forest plot of the results of Mendelian randomization (MR) analysis. (A) COVID-19 susceptibility, (B) COVID-19 hospitalization, and (C) COVID-19 severity.

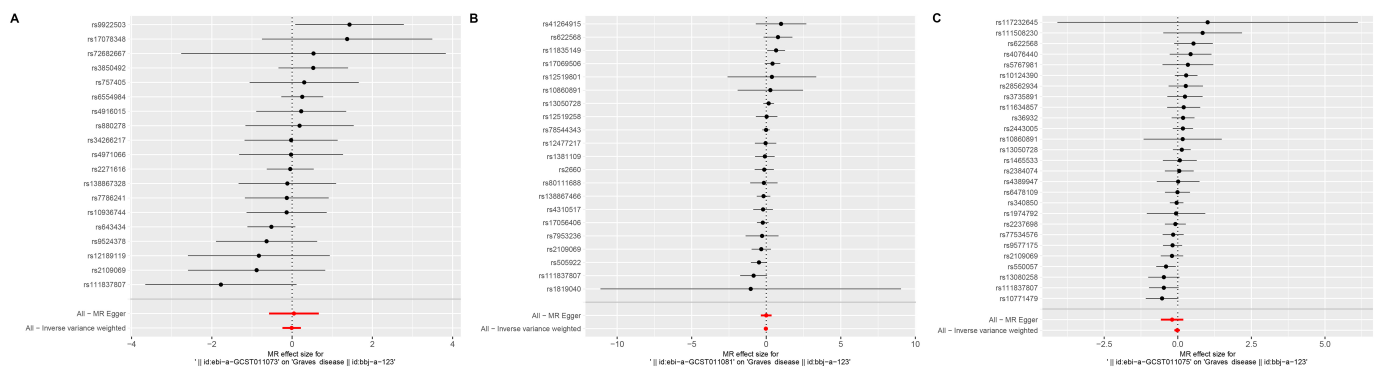


Figure 2. Scatter plot of the results of Mendelian randomization (MR) analysis. (A) COVID-19 susceptibility, (B) COVID-19 hospitalization, and (C) COVID-19 severity. SNP: single nucleotide polymorphism.

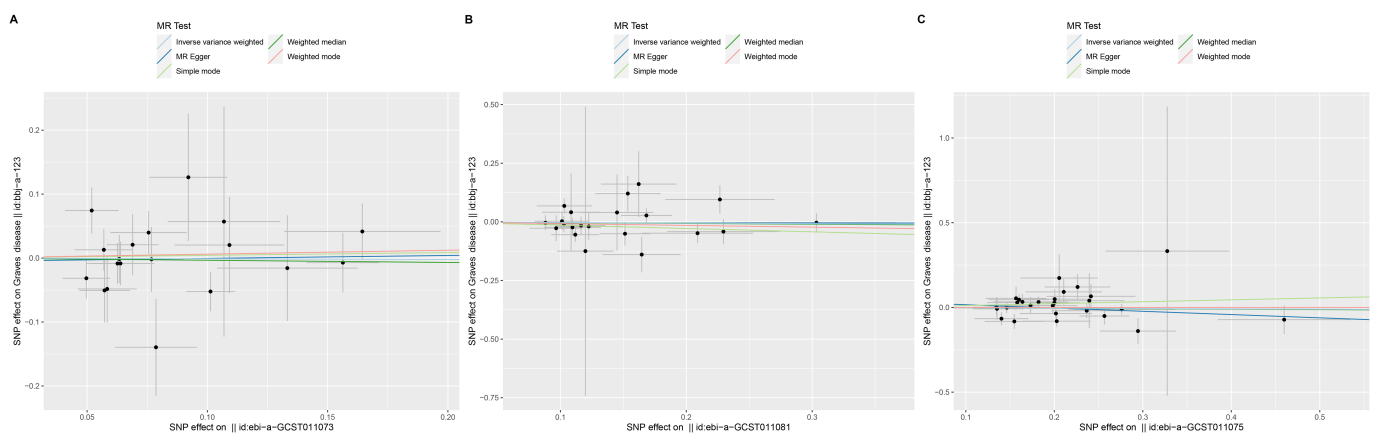


Figure 3. Funnel plot of the results of Mendelian randomization (MR) analysis. (A) COVID-19 susceptibility, (B) COVID-19 hospitalization, and (C) COVID-19 severity.

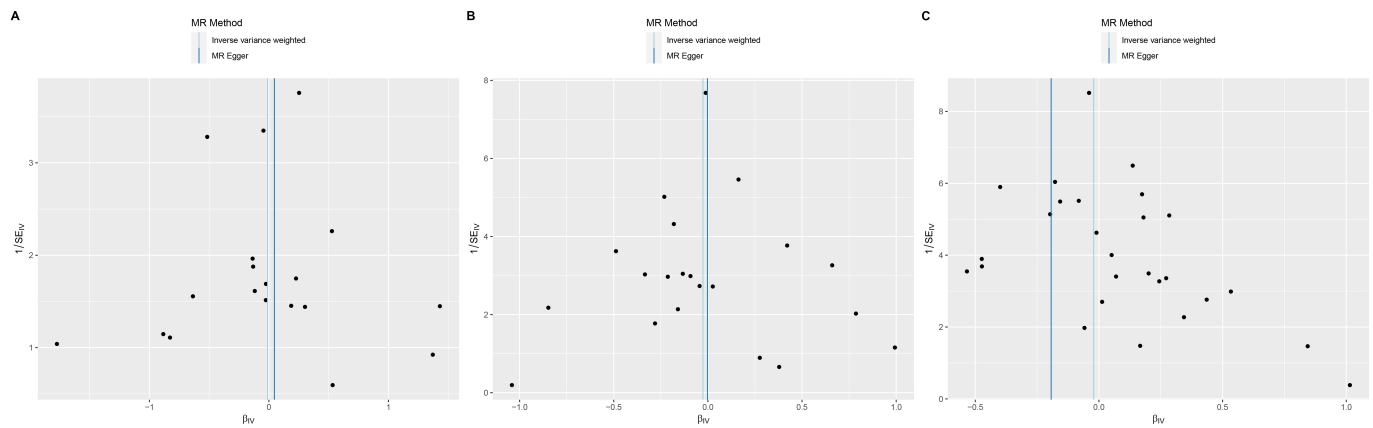


Table 2. Mendelian randomization estimates of the association between Graves disease and COVID-19.

Outcome	COVID-19 susceptibility			COVID-19 hospitalization			COVID-19 very severe		
	SNPs ^a , n	OR ^b (95% CI)	P value	SNPs, n	OR (95% CI)	P value	SNPs, n	OR (95% CI)	P value
Graves disease									
IVW ^c	19	0.989 (0.405-2.851)	.93	21	0.974 (0.852-1.113)	.70	27	0.979 (0.890-1.077)	.66
Weighted median	19	0.966 (0.685-1.362)	.84	21	0.967 (0.797-1.175)	.74	27	0.975 (0.852-1.116)	.71
MR-Egger ^d	19	1.047 (0.786-1.245)	.89	21	0.997 (0.696-1.431)	.99	27	0.824 (0.563-1.207)	.33
Simple mode	19	1.043 (0.632-1.723)	.87	21	0.868 (0.655-1.151)	.34	27	1.119 (0.871-1.436)	.39

^aSNP: single nucleotide polymorphism.

^bOR: odds ratio.

^cIVW: inverse-variance weighting.

^dMR-Egger: Mendelian randomization-Egger regression.

Table 3. Results of heterogeneity and horizontal pleiotropy analyses.

Outcome	Exposure	P value (heterogeneity) ^a	MR-Egger ^b intercept	P value (pleiotropy) ^c	P value (global test) ^d
Graves disease	COVID-19 susceptibility	.39	-0.0051	.85	.47
Graves disease	COVID-19 hospitalization	.27	-0.0039	.89	.33
Graves disease	COVID-19 very severe	.20	0.0352	.37	.20

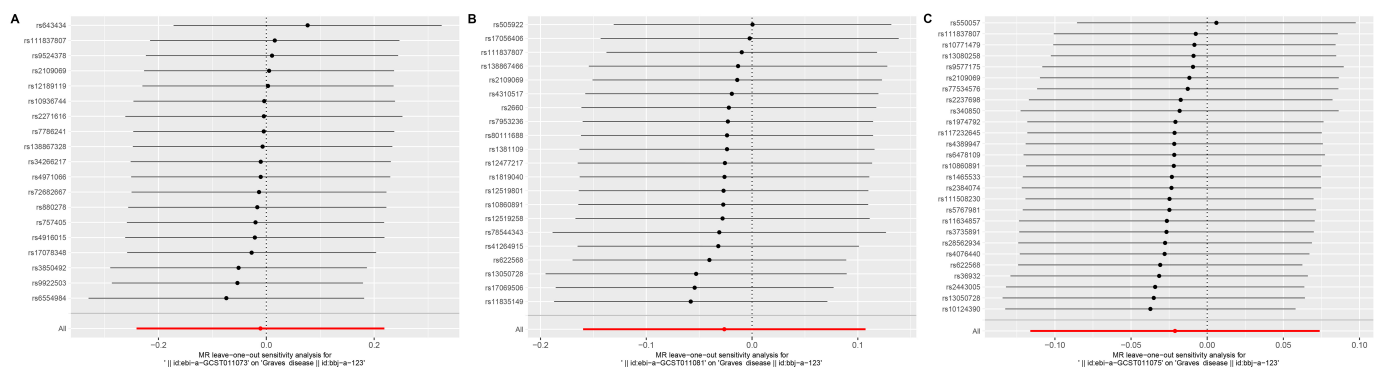
^aThe P value of Cochran Q value in the heterogeneity test.

^bMR-Egger: Mendelian randomization-Egger.

^cThe P value for the intercept in the MR-Egger regression.

^dThe P value for the global test in the Mendelian randomization-pleiotropy residual sum and outlier test.

Figure 4. Leave-one-out analysis plots of the results of Mendelian randomization (MR) analysis. (A) COVID-19 susceptibility, (B) COVID-19 hospitalization, and (C) COVID-19 severity.



Discussion

Principal Findings

In this MR study, we extensively explored the potential causal relationships between COVID-19 susceptibility, COVID-19 hospitalization, and COVID-19 severity in relation to GD. Using a variety of MR methods, we aimed to provide a comprehensive understanding of these relationships. Our study results underscore the absence of a causal link between COVID-19 susceptibility and GD. Recent research continues to unveil the intricate interplay between autoimmune diseases and viral infections. For example, a study conducted by Widhani et al [20] delved into the potential associations between viral infections, including COVID-19, and autoimmune thyroid diseases, further corroborating our findings. Additionally, the work of Smith and Hegedüs [21] has provided in-depth insights into the pathogenesis of GD, emphasizing its multifactorial nature. These recent studies lend robust support to our research. Furthermore, investigations into the relationship between COVID-19 and autoimmune diseases have expanded in recent years. A systematic review by Tatal et al [22] examined the impact of autoimmune thyroid diseases on the severity of COVID-19, enriching our understanding of the bidirectional influences between these health conditions. To provide a broader clinical context, we have integrated evidence on how COVID-19 susceptibility and outcomes differ across other autoimmune diseases, which highlights the need for more nuanced investigations beyond GD alone [23].

Similarly, we found that COVID-19 hospitalization does not significantly increase the risk of GD. The consistency of this result across various MR methods suggests that COVID-19 hospitalization is not a causal risk factor for GD. This conclusion is pivotal for understanding the etiology of GD and its relationship with other health conditions. Recent research has provided further insights into the connection between COVID-19 and autoimmune thyroid diseases. For example, a study by Fallahi et al [24], conducted within the past 5 years, investigated the impact of COVID-19 hospitalization on the development of autoimmune thyroid diseases, including GD. The study used a large-scale patient database and used statistical methods to evaluate the risk of developing autoimmune thyroid diseases after COVID-19 hospitalization. Their findings, which align with our MR results, indicated that COVID-19 hospitalization was not significantly associated with an increased risk of GD or other autoimmune thyroid diseases. This further supports the critical importance of recognizing that COVID-19 hospitalization itself does not have a direct causal role in the development of GD. Furthermore, we examined the relationship between COVID-19 severity and the risk of developing GD. Our study revealed that COVID-19 severity does not contribute to the onset of GD. This finding provides important insights into the genetic and environmental factors influencing GD's pathogenesis. A recent study by Bostan and colleagues [25] explored the genetic mechanisms underlying the development of GD in individuals with severe COVID-19. Their research highlighted the role of genetic susceptibility in the development

of GD among those with severe COVID-19, adding to our understanding of the complex interaction between COVID-19 and autoimmune thyroid diseases.

Moreover, recent research has extensively explored the associations between COVID-19 and thyroid-related conditions. Studies have indicated that COVID-19 infection can influence thyroid function, potentially leading to hyperthyroidism or thyrotoxicosis in certain individuals, further emphasizing the potential link between COVID-19 and thyroid diseases. However, the specific mechanisms remain unclear and warrant further investigation. Recent studies have provided more in-depth insights into the complex interplay between COVID-19 and thyroid function. For instance, a study by Smith et al [21] identified COVID-19-related thyroid dysfunction, including subacute thyroiditis and hyperthyroidism, reporting cases of patients experiencing thyroid-related symptoms during or following COVID-19 infection. Similarly, Damara et al [10] conducted a systematic review and meta-analysis, revealing a significant association between autoimmune thyroid diseases and the severity of COVID-19. These studies underscore the importance of further understanding the relationship between COVID-19 and thyroid dysfunction. Additionally, Muller et al [26] examined the underlying mechanisms of COVID-19-induced thyroid dysfunction, particularly focusing on the immune response's role in thyroid autoimmunity. Their findings suggest that the cytokine storm triggered by COVID-19 may play a crucial role in the development of thyroid diseases. Liu et al [27] investigated the impact of SARS-CoV-2 infection on the expression of thyroid-related genes in thyroid tissue, shedding light on the potential molecular pathways involved. To broaden the context, we have also incorporated recent research on COVID-19 vaccine immunogenicity in patients with autoimmune diseases, providing additional understanding of how immune responses to COVID-19 vaccination may differ in individuals with pre-existing autoimmune conditions [28].

Furthermore, recent investigations have explored the complex interplay between GD and other thyroid-related conditions in the context of COVID-19. For example, Nakano et al [29] found that individuals with GD may be at an increased risk of contracting COVID-19 and could face more severe outcomes postinfection, including complications such as thyrotoxicosis. This study highlights the bidirectional relationship between GD and COVID-19, emphasizing the importance of comprehensive research to better understand the complex interactions between thyroid-related conditions and COVID-19. In a study by Sethi et al [30], researchers observed that COVID-19 infection was associated with thyroid abnormalities, with some patients developing thyrotoxicosis. This suggests that COVID-19 may influence thyroid function, raising concerns about potential implications for individuals with GD. Additionally, Croce et al [31] examined the bidirectional effects of GD and COVID-19, proposing mechanisms through which GD could increase susceptibility to COVID-19 and worsen clinical outcomes, such as immune system dysregulation and cytokine imbalances. However, both COVID-19 and GD can significantly

impact physical and mental health, and thus, we have integrated insights from recent research on physical activity and mental health interventions, which may provide potential strategies for improving long-term patient outcomes [32]. Collectively, these studies underscore the urgent need for further research into the multifaceted interactions between COVID-19 and thyroid-related diseases, including GD. This will not only deepen our understanding of the pathogenesis of these conditions but also offer critical insights for health care practitioners, aiding in the development of more informed and effective clinical strategies.

Limitations

It is important to note that despite the strengths of the MR approach, our study has several limitations. MR methods rely on certain assumptions, including the absence of horizontal pleiotropy. Although we used various strategies to address potential pleiotropic effects, we cannot entirely exclude the possibility of unmeasured confounders influencing our results. Furthermore, our analysis primarily relied on data from the European population, which may limit the generalizability of our findings to other ethnic groups. Specifically, the wide CIs for COVID-19 susceptibility suggest that the study may be underpowered to detect modest effects. Additionally, the definition of COVID-19 cases included self-reported cases, which could introduce reporting bias. The combination of laboratory-confirmed, electronic health record-derived, and self-reported cases may also affect the

reliability of exposure classification. However, sensitivity analyses on subsets of laboratory-confirmed and electronic health record-derived cases support the robustness of our findings. Similarly, the definition of GD cases was restricted to hospitalized patients, which could result in selection bias, underrepresenting mild or moderate cases. While hospitalization-based diagnoses enhance diagnostic accuracy, future research should incorporate outpatient and primary care datasets to capture the full spectrum of disease severity. Lastly, this study did not fully explore the potential bidirectional relationships or temporal dynamics between COVID-19 and GD. Future studies should address these aspects using bidirectional MR and longitudinal cohort studies to further clarify the interactions between these conditions.

Conclusions

In summary, our MR analysis did not identify significant causal relationships between COVID-19 susceptibility, COVID-19 hospitalization, or COVID-19 severity and the risk of developing GD. These findings highlight the complex interactions between viral infections, autoimmune diseases, and genetic factors. However, they also emphasize the need for further investigation into the bidirectional relationships and temporal dynamics between COVID-19 and thyroid-related conditions. Expanding this research will deepen our understanding of the pathogenesis of both diseases, contributing valuable insights for clinical decision-making and management strategies.

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Data Availability

The analysis in this research relied on publicly available datasets, which can be accessed through the Integrative Epidemiology Unit OpenGWAS Project [12].

Authors' Contributions

HN analyzed the data and wrote the manuscript. YB designed the study. HY collected the data and corrected the paper. All authors have read and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

GD: Graves disease

GWAS: genome-wide association study

ICD: *International Classification of Diseases*

IVW: inverse-variance weighting

MR: Mendelian randomization

MR-PRESSO: Mendelian randomization-pleiotropy residual sum and outlier

OR: odds ratio

SNP: single nucleotide polymorphism

STROBE-MR: Strengthening the Reporting of Observational Studies in Epidemiology-Mendelian Randomization

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