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ARTICLE

A Causal Relationship Between Hypothyroidism and Gestational Hypertension: Results From a Two-Sample Mendelian Randomization Analysis

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Abstract

Aims/Background Although hypothyroidism induced thyroid hormone disorders affect cardiovascular system homeostasis, whether hypothyroidism has a causal effect on gestational hypertension remains unknown. Therefore, our research aims to explore the causal relationship between hypothyroidism and gestational hypertension using Mendelian randomization (MR) analysis.

Methods Summary data genome-wide association study of hypothyroidism (30,155 cases and 379,986 controls in the discovery dataset; 26,342 cases and 59,827 controls in the replicated dataset) and gestational hypertension (14,727 cases and 196,143 controls) were used for analysis. Inverse-variance weighted (IVW), weighted median, weighted mode and MR-Egger methods were used to estimate the causality between hypothyroidism and gestational hypertension.

Results Hypothyroidism significantly increased the risk of gestational hypertension, as indicated by IVW (odds ratio (OR) = 1.0433, 95% confidence interval (CI) = 1.0081–1.0798, $p = 0.0155$), MR Egger (OR = 1.1445, 95% CI = 1.0620–1.2334, $p = 0.0008$), weighted median (OR = 1.0802, 95% CI = 1.0204–1.1435, $p = 0.0079$) and weighted mode (OR = 1.0999, 95% CI = 1.0286–1.1761, $p = 0.0071$) in the discovery analysis, which was consistent with the results of the replicated analysis. There was no bidirectional causality for hypothyroidism or gestational hypertension in the reverse MR analysis.

Conclusion Our findings highlight the importance of hypothyroidism induced thyroid hormone disorder in increasing the risk of gestational hypertension by affecting cardiovascular system homeostasis. Early intervention in patients with hypothyroidism might reduce the risk of gestational hypertension and maternal and neonatal morbidity and mortality. Further studies are needed to determine the relationship between these factors and the underlying mechanism in detail.

Key words: gestational hypertension; hypothyroidism; Mendelian randomization

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Introduction

Hypertension is the most common medical disorder encountered during pregnancy, and gestational hypertension is associated with increased risks of maternal and neonatal morbidity and mortality worldwide (Barry et al, 2023). Hypertensive disorders of pregnancy were responsible for 6.8% of pregnancy-related deaths in America (Barry et al, 2023). Although hypertension, obesity, black race, diabetes

mellitus, insulin resistance, collagen vascular disease, obesity, increased serum testosterone concentrations and thrombophilia are considered risk factors for gestational hypertension (Chou, 2022), the potential causal risk factors for gestational hypertension remain unknown.

Hypothyroidism is characterized by increased serum levels of thyroid-stimulating hormone (TSH) with or without serum free T4 and/or free T3 levels below the normal reference ranges. The lifetime risk of hypothyroidism is approximately 5–9%, which is associated with atherosclerosis, hypertension, cardiac dysfunction, and coagulopathy (Danzi and Klein, 2022), suggesting that hypothyroidism might have an impact on the cardiovascular system. Since the heart and vascular system are the major target organs of thyroid hormone action, hypothyroidism is related to hypertension through the regulation of metabolic and haemodynamics characteristics and diminished myocardial oxygen demand (Eagan et al, 2020; Song et al, 2023). Furthermore, although studies have reported that hypothyroidism is a risk factor for gestational hypertension (Toloza et al, 2022; Turunen et al, 2020), the results are still controversial (Casey et al, 2006; Cleary-Goldman et al, 2008; Männistö et al, 2010). Therefore, whether exposure to hypothyroidism has a causal effect on gestational hypertension is still unknown.

In this study, a two-sample Mendelian randomization analysis was conducted to evaluate the causal effect of hypothyroidism on gestational hypertension using the summary data of genome-wide association studies (GWASs) in the European population. Single-nucleotide polymorphisms (SNPs) were selected as instrumental variables (IVs) to estimate the potential causal effects of hypothyroidism on gestational hypertension.

Methods

Samples and Study Designs

We used Two-sample Mendelian randomization (MR) analysis of genetic summary data to investigate whether exposure to hypothyroidism has a causal effect on gestational hypertension. In addition, we estimated genetic correlations and heritability between hypothyroidism and gestational hypertension using linkage disequilibrium (LD) score regression analysis (Bulik-Sullivan et al, 2015) with GenomicSEM R packages (Grotzinger et al, 2019). The genetic associations with gestational hypertension were acquired from the FinnGen study (Kurki et al, 2023), which collected the deep traits and genetic data of 210,870 participants (14,727 cases and 196,143 controls) with gestational hypertension. The GWAS datasets of hypothyroidism were obtained from published studies (Sakaue et al, 2021) and public databases (Kurki et al, 2023) (Table 1). This study selected SNPs, obtained from the European population, as IVs to investigate whether exposure to hypothyroidism increased the risk of gestational hypertension (Fig. 1).

Table 1. The GWAS data source details in our study.

Phenotype	Data source	PMID	Case	Control	Sample size	Ancestry
Hypothyroidism						
	Sakaue et al (2021) [discovery]	34594039	30,155	379,986	410,141	European
	Kurki et al (2023) [replicated]	36653562	26,342	59,827	86,169	European
Gestational hypertension						
	Kurki et al (2023)	36653562	14,727	196,143	210,870	European

GWAS, genome-wide association studies.

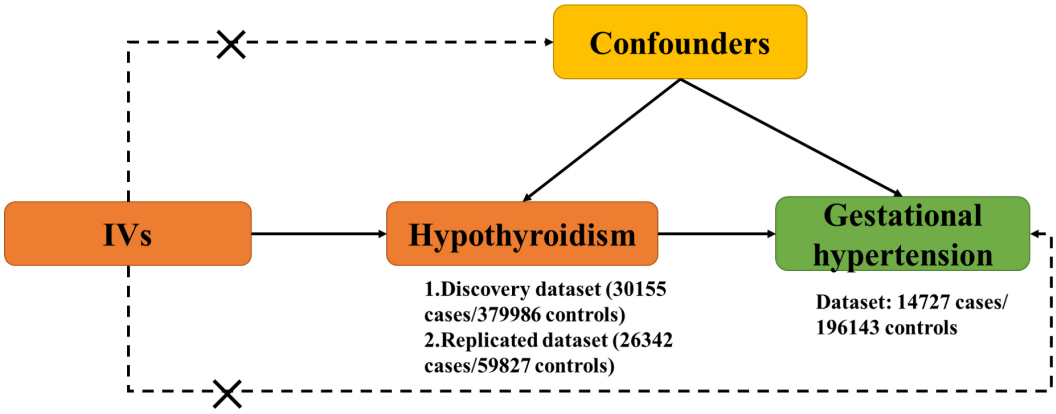

Fig. 1. The schematic of study design. IVs, instrumental variables.

IV Selection

The IVs were selected based on three important assumptions: (I) the selected IVs were directly associated with exposure; (II) each IV was independent of confounding factors; (III) each IV affected outcomes only through exposure.

To ensure that each SNP had an independent effect and avoid potential bias due to LD, we conducted a clumping procedure (clumping distance = 10,000 kb, $R^2 < 0.001$). Furthermore, SNPs with incompatible alleles or located in palindromic sequences were excluded from this study via a harmonized analysis. Finally, the outlier SNPs were identified by conducting Mendelian randomization pleiotropy residual sum and outlier (MR-PRESSO) analysis and were excluded from this study.

MR and Sensitivity Analyses

All MR analyses were performed in R 4.3.0 (R Development Core Team, Vienna, Austria). The MR analyses were conducted using the TwoSampleMR R package (Hemani et al, 2018). The inverse variance weighted (IVW) method, which is the most reliable method when there is no horizontal pleiotropy of the IVs, was selected to calculate the primary results. Mendelian randomization-egger (MR-Egger), weighted mode, simple mode and weighted median methods were used to test the robustness of our primary results. Moreover, MR-PRESSO was used to exclude outlier SNPs with potential pleiotropy (Verbanck et al, 2018). Cochran's Q test and leave-one-out analysis were used to determine the heterogeneity of the MR analysis. Additionally, MR-Egger regression analysis was performed to in-

Table 2. MR estimates of hypothyroidism associated with the risk of gestational hypertension.

Data source	Method	IVs (n)	Beta	SE	OR (95% CI)	*p*
Discovery analysis	Inverse variance weighted	61	0.0424	0.0175	1.0433 (1.0081–1.0798)	0.0155
	MR Egger	61	0.1349	0.0382	1.1445 (1.0620–1.2334)	0.0008
	Weighted median	61	0.0771	0.0290	1.0802 (1.0204–1.1435)	0.0079
	Weighted mode	61	0.0952	0.0342	1.0999 (1.0286–1.1761)	0.0071
Replicated analysis	Inverse variance weighted	23	0.0688	0.0247	1.0712 (1.0205–1.1244)	0.0054
	MR Egger	23	0.1320	0.0614	1.1411 (1.0118–1.2870)	0.0433
	Weighted median	23	0.0943	0.0346	1.0989 (1.0269–1.1759)	0.0064
	Weighted mode	23	0.1076	0.0444	1.1136 (1.0208–1.2149)	0.0240

MR, Mendelian randomization; IVs, instrumental variables; SE, standard error; OR, odds ratio; CI, confidence interval.

vestigate the potential pleiotropy. Finally, we performed reverse MR analysis to investigate potential bidirectional causality for the hypothyroidism and gestational hypertension traits, and the procedures of IV selection in the reverse MR analysis were similar to those in the forward MR analysis.

Results

IVs for Hypothyroidism

For the discovery MR analysis, 75 SNPs were significantly associated with hypothyroidism in the GWAS ($p < 5 \times 10^{-8}$), of which 65 SNPs were identified in the datasets of gestational hypertension. After harmonies and outlier analysis, rs2412976, rs2921053, rs2988277 and rs3184504 were excluded from the discovery MR analysis, and 61 SNPs were selected as IVs (**Supplementary Table 1**). Consistent with the identification of IVs in the discovery MR analysis, 23 SNPs were chosen as IVs in the replicated MR analysis (**Supplementary Table 1**).

Forward MR and Sensitivity Analyses

The discovery MR analysis revealed a positive causal correlation between hypothyroidism and gestational hypertension, as indicated by the IVW (odds ratio (OR) = 1.0433, 95% confidence interval (CI) = 1.0081–1.0798, $p = 0.0155$), weighted median (OR = 1.0802, 95% CI = 1.0204–1.1435, $p = 0.0079$), MR Egger (OR = 1.1445, 95% CI = 1.0620–1.2334, $p = 0.0008$), and weighted mode (OR = 1.0999, 95% CI = 1.0286–1.1761, $p = 0.0071$) methods (Table 2, Fig. 2). Consistently, gestational hypertension was associated with an increased risk of gestational hypertension in the replicated MR analysis, as indicated by the IVW (OR = 1.0712, 95% CI = 1.0205–1.1244, $p = 0.0054$), weighted median (OR = 1.0989, 95% CI = 1.0269–1.1759, $p = 0.0064$), MR Egger (OR = 1.1411, 95% CI = 1.0118–1.2870, $p = 0.0433$) and weighted mode (OR = 1.1136, 95% CI = 1.0208–1.2149, $p = 0.0240$) methods (Table 2, Fig. 2).

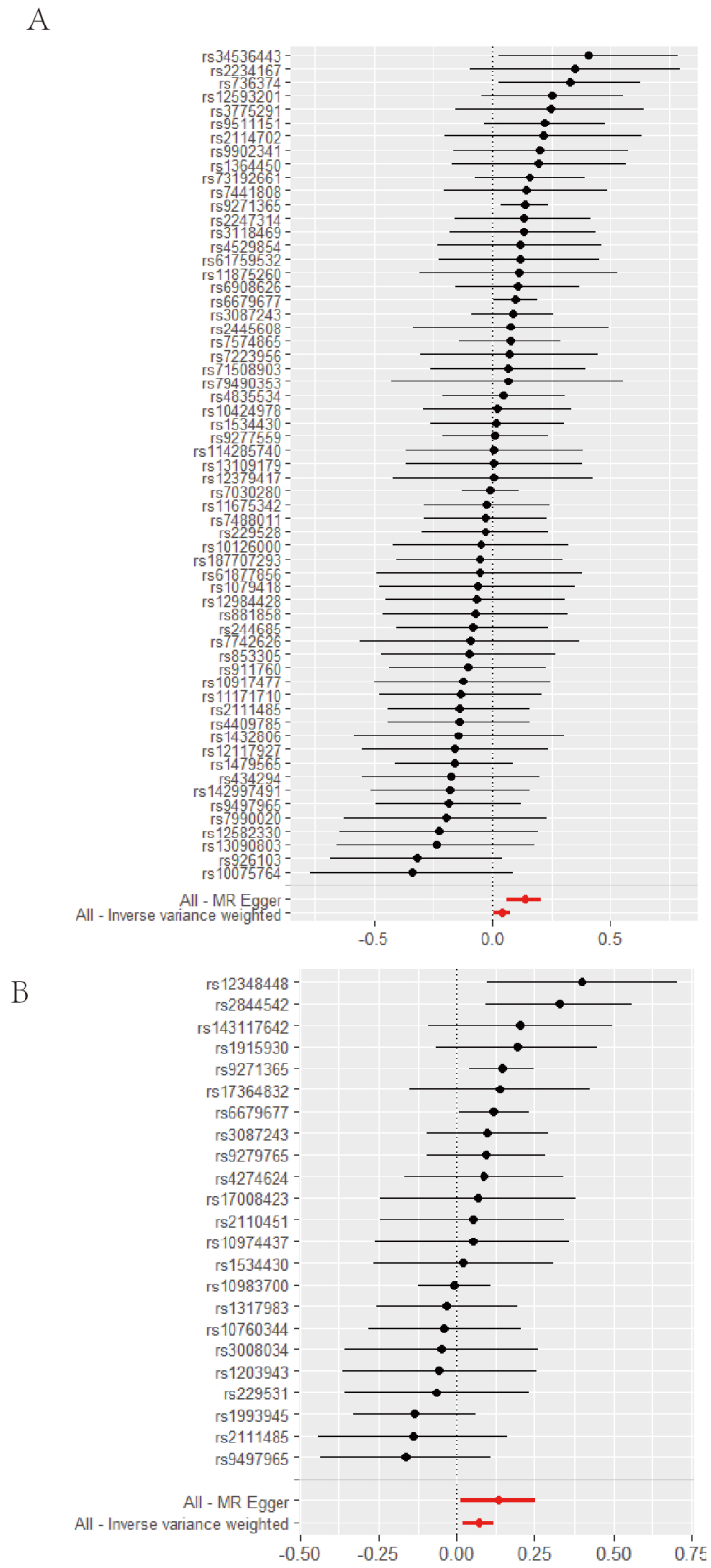

Fig. 2. Forest plot estimates the causal relationship between hypothyroidism and gestational hypertension. (A) Discovery MR analysis. (B) Replicated MR analysis. MR-Egger, Mendelian randomization-egger.

No obvious heterogeneity was observed when the Cochran's Q test was performed (**Supplementary Table 2**). The MR-PRESSO global tests were insignificant ($p > 0.05$) in both the discovery and replicated MR analyses, but the MR Egger intercept tests were significant ($p < 0.05$) in the discovery MR analysis, indicating some potential evidence of pleiotropy (**Supplementary Table 2**). Moreover, no obvious or potential outlier IVs were observed in this study by scatter plot (Fig. 3), leave-one-out (Fig. 4) and funnel plot (Fig. 5). Collectively, these sensitivity analyses confirmed the primary result.

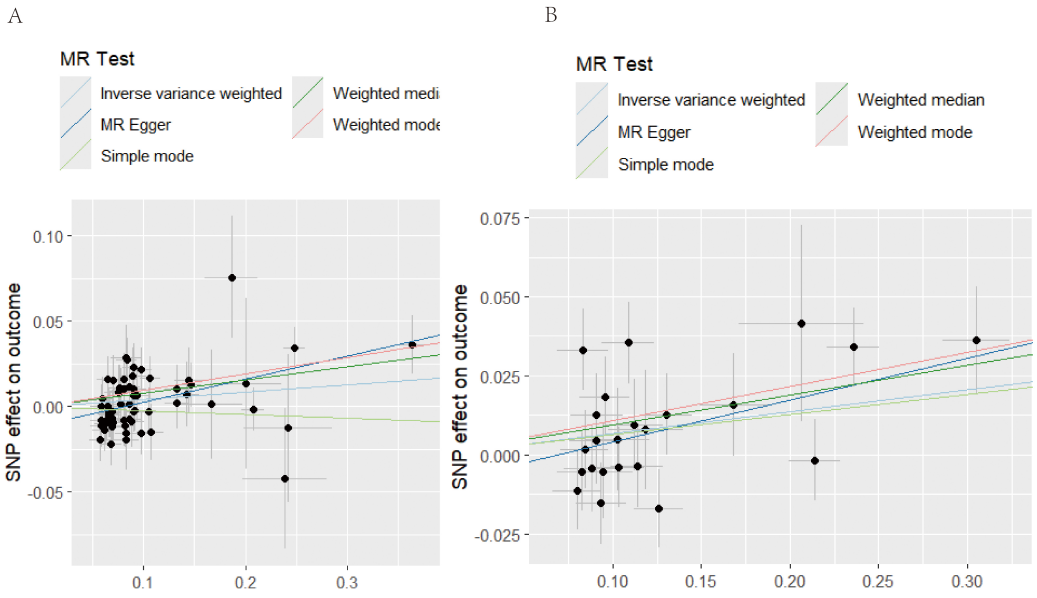

Fig. 3. The scatterplot depicts the causal relationship between hypothyroidism and gestational hypertension. (A) Discovery MR analysis. (B) Replicated MR analysis. SNP, single-nucleotide polymorphisms; MR, Mendelian randomization.

Reverse MR Analysis

We found that 677 SNPs were significantly associated with gestational hypertension ($p < 5 \times 10^{-8}$). After clumping analysis, 15 SNPs were found to be independently associated with gestational hypertension. However, rs9855086 was removed for being palindromic with intermediate allele frequencies in the discovery and replicated MR analyses after harmonizing the data. Moreover, rs10882398 was identified as a palindromic SNP with intermediate allele frequencies, which was removed for MR in the replicated dataset. Therefore, 14 SNPs were selected as IVs in the discovery MR analysis, and 13 SNPs were selected as IVs in the replicated MR analysis (**Supplementary Table 3**).

We found no significant causal relationship between gestational hypertension and hypothyroidism according to the *p* values of the IVW ($p = 0.4322$), MR Egger ($p = 0.8366$), weighted median ($p = 0.0587$) and weighted mode ($p = 0.1278$) methods in the discovery dataset (Table 3), which was similar to the findings in the replicated dataset.

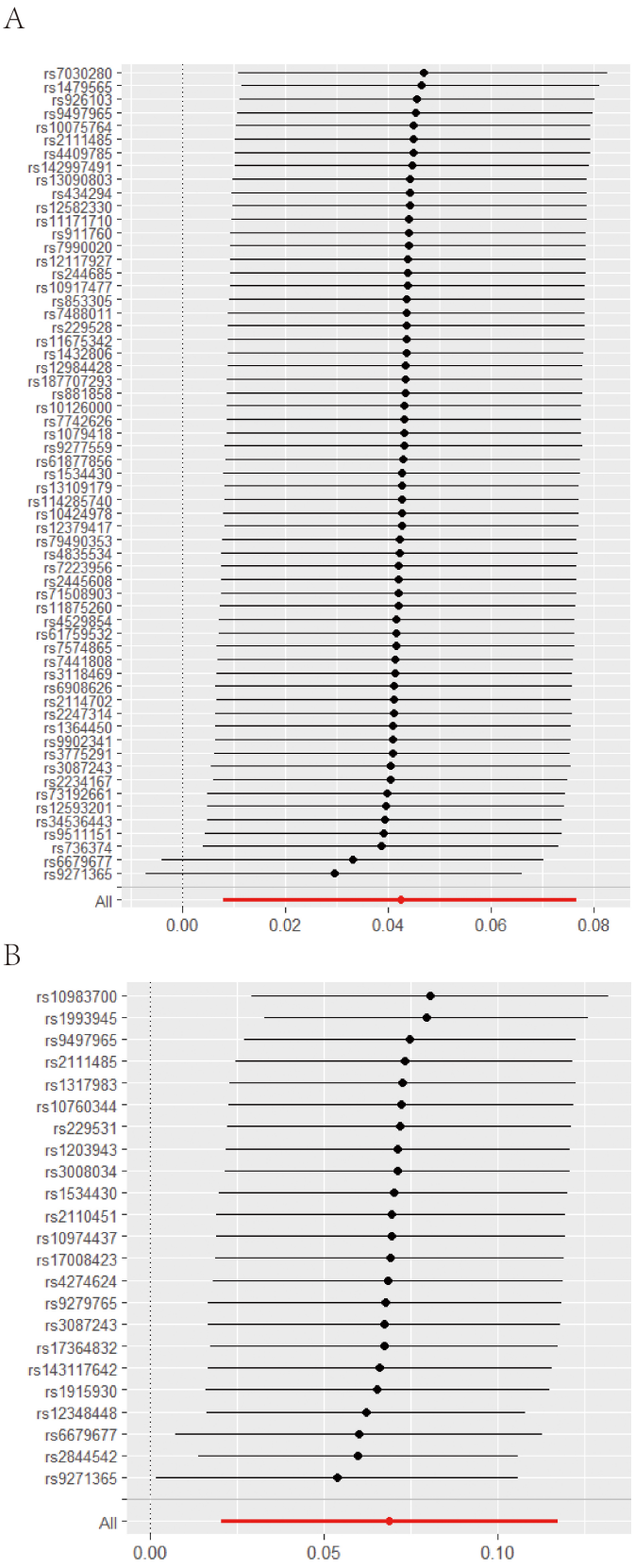

Fig. 4. Leave one out analysis. (A) Discovery MR analysis. (B) Replicated MR analysis. MR, Mendelian randomization.

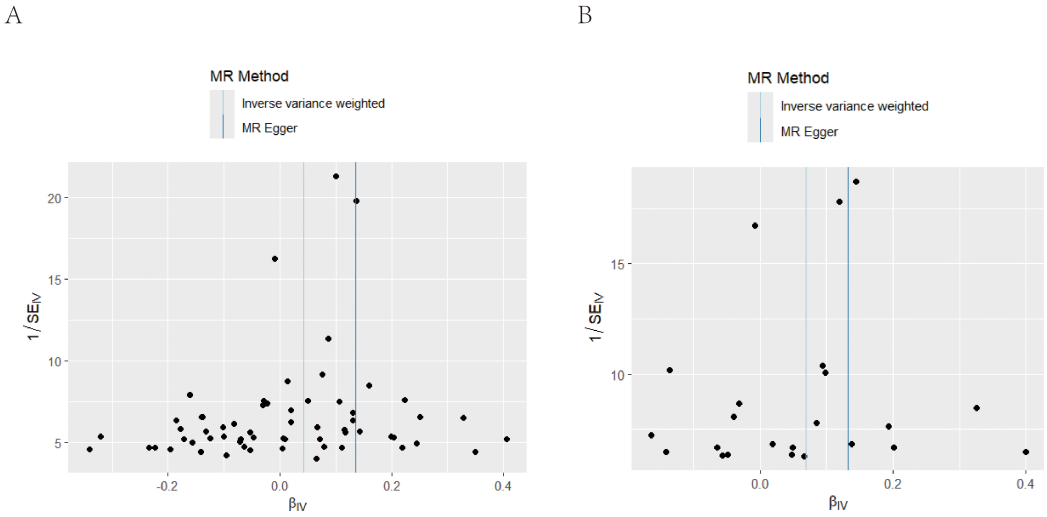

Fig. 5. Funnel plots of individual variant effects for the instrumental variables. (A) Discovery MR analysis. (B) Replicated MR analysis. MR, Mendelian randomization; MR-Egger, Mendelian randomization-egger.

Table 3. MR estimates of gestational hypertension disassociated with the risk of hypothyroidism.

Data	Method	IVs (n)	Beta	SE	OR (95% CI)	*p*
Discovery dataset	Inverse variance weighted	14	–0.1234	0.1571	0.8839 (0.6497–1.2026)	0.4322
	MR Egger	14	0.1289	0.6114	1.1376 (0.3432–3.7708)	0.8366
	Weighted median	14	–0.1369	0.0724	0.8720 (0.7566–1.0050)	0.0587
	Weighted mode	14	–0.2213	0.1360	0.8015 (0.6139–1.0464)	0.1278
Replicated dataset	Inverse variance weighted	13	–0.0989	0.1667	0.9058 (0.6533–1.2560)	0.5531
	MR Egger	13	0.3757	0.6554	1.4560 (0.4030–5.2609)	0.5780
	Weighted median	13	0.0335	0.0519	1.0341 (0.9341–1.1448)	0.5183
	Weighted mode	13	0.0496	0.0653	1.0509 (0.9247–1.1943)	0.4617

MR, Mendelian randomization; IVs, instrumental variables; SE, standard error; OR, odds ratio; CI, confidence interval; MR-Egger, Mendelian randomization-egger.

Discussion

We conducted MR analyses to explore the causal effect of hypothyroidism and gestational hypertension in individuals of European ancestry, and reported that exposure to hypothyroidism increased the risk of gestational hypertension (IVW, OR = 1.0433, 95% CI = 1.0081–1.0798; weighted median, OR = 1.0802, 95% CI = 1.0204–1.1435; MR Egger, OR = 1.1445, 95% CI = 1.0620–1.2334; weighted mode, OR = 1.0999, 95% CI = 1.0286–1.1761) in the discovery MR analysis, which was consistent with the results of the replicated MR analysis. Furthermore, the MR results were robust and reliable in the sensitivity analysis. In addition, no bidirectional causal relationship was found between hypothyroidism and gestational hypertension.

Indeed, several studies have explored the relationship between hypothyroidism and gestational hypertension. Thyroid-stimulating hormone (TSH) levels, free thyroxine levels, thyroid peroxidase (TPO)-Ab-positivity and thyroglobulin (TG)-Ab-positivity are disassociated with the risk of gestational hypertension (Casey et al, 2006; Cleary-Goldman et al, 2008; Männistö et al, 2010). However, Turunen et al (2020) reported that maternal hyperthyroidism was associated with a greater risk of gestational hypertension (OR = 1.39) in a population-based study, suggesting that pregnant women with active hyperthyroidism/histories of hyperthyroidism should be considered risk factors for gestational hypertension (Turunen et al, 2020). Moreover, hypothyroidism was found to increase the risk of severe preeclampsia and low birth weight in infants (Hajifoghaha et al, 2022). In addition, subclinical hyperthyroidism during weeks 4–8 of pregnancy might be a risk factor for preeclampsia (Zhang et al, 2019). Furthermore, although subclinical hyperthyroidism, TPO antibody positivity or isolated hypothyroxinaemia were not associated with gestational hypertension or preeclampsia, abnormal concentrations of TSH and subclinical hypothyroidism during pregnancy were associated with a greater risk of preeclampsia in an individual-participant data meta-analysis (Toloza et al, 2022). Collectively, these data are consistent with our conclusion that hypothyroidism is a risk factor for gestational hypertension.

Indeed, thyroid hormone affects the function of the vascular system, and abnormal thyroid function alters cardiovascular haemodynamics. Subclinical hypothyroidism is associated with a 20–80% increase in vascular morbidity (Inoue et al, 2020), indicating that thyroid hormone status plays a vital role in vascular risk in the general population. More importantly, thyroid hormone activity regulates systolic function and myocardial contractility in cardiomyocytes through the activation of sodium/potassium-transporting ATPases, myosin heavy chain-α and sarcoplasmic/endoplasmic reticulum calcium ATPase 2 (Chattergoon, 2019; Yamakawa et al, 2021), which are the risk factors for hypertension and atherosclerosis (Ng et al, 2022; Yang et al, 2020). Therefore, hypothyroidism-induced thyroid hormone disorders increase the risk of gestational hypertension by regulating systolic function and myocardial contractility in the cardiovascular system.

This study had several limitations. First, we detected potential horizontal pleiotropy in the discovery MR analysis, indicating that IVs may affect gestational hypertension indirectly via currently unknown pathways. Second, only 23 SNPs were IVs with limited associations with hypothyroidism (R^2 [%]: 0.29%–2.59%). Therefore, other important factors which affect gestational hypertension risk should be investigated in future studies. Third, the causal effect of hypothyroidism and gestational hypertension was only investigated in the European population; this causal relationship needs to be explored and validated in non-European populations. Finally, inconsistency of the diagnostic criteria for hypothyroidism and gestational hypertension in GWASs may lead to variations in the results.

Conclusion

In conclusion, our study demonstrated that hypothyroidism was associated with a greater risk of gestational hypertension. Our findings highlight the importance of hypothyroidism induced thyroid hormone disorders in increasing the risk of gestational hypertension. Early intervention might reduce the risk of gestational hypertension and maternal and neonatal morbidity and mortality. Further studies are needed to determine their relationship and the underlying mechanism in more detail.

Key Points

- The association between hypothyroidism and gestational hypertension remains controversial in observational studies.
- Hypothyroidism significantly increased the risks of gestational hypertension in genetic levels.
- No bidirectional causality links between hypothyroidism and gestational hypertension.
- Highlighting the importance of hypothyroidism induced thyroid hormone disorder on increasing the risk of gestational hypertension.

Availability of Data and Materials

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

Author Contributions

YC and WZ designed the study. YC and SG acquired the data. WZ interpreted the data. YC drafted the manuscript and all authors contributed to the critical revision of the manuscript for important intellectual content. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgement

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://www.magonlinelibrary.com/doi/suppl/10.12968/hmed.2024.0492.

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