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Genetic Causality of Hypothyroidism and Adverse Pregnancy Outcomes: A Combined Mendelian Randomisation Study and Bioinformatics Analysis

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Background: Observational studies have shown that hypothyroidism is strongly associated with adverse pregnancy outcomes, and that thyroxine during pregnancy comes mainly from the mother; therefore, thyroid defects in women may lead to problems such as miscarriage due to hormonal instability in early pregnancy, and foetal neurological deficits in mid- to late gestation, but whether there is a genetic causality between the two is still a matter of some controversy.

Objective: Goal to investigate the possible causal association between hypothyroidism and unfavorable pregnancy outcomes through the use of bioinformatics and Mendelian randomization (MR).

Methods: We used Mendelian randomization (MR) analyses using single nucleotide polymorphism (SNP) sites as instrumental variables to infer causal associations between exposures and outcomes. The inverse variance weighting method was primarily used in the analysis. Heterogeneity and horizontal multiplicity tests were also conducted to evaluate the results' robustness and the degree of causality. Lastly, preliminary bioinformatics analyses were conducted to investigate the underlying biological mechanisms.

Results: The resultant variance inverse weighting method found that hypothyroidism increased the risk of developing gestational hypertension (OR=1.054, 95% CI: 1.002–1.110 P=0.042) and poor foetal growth (OR=1.081, 95% CI:1.005–1.162 P=0.035). Heterogeneity tests, multiplicity tests and leave-one-out sensitivity analyses did not reveal any heterogeneity or multiplicity effects in the estimated effects of these three exposure factors on the risk of ovarian dysfunction.

Conclusion: Our research establishes genetically the causal relationship between pregnancy-related hypertension, hypothyroidism, and poor fetal growth—a relationship that could be linked to endosomal and cellular transport.

Keywords: hypothyroidism, adverse pregnancy outcomes, Mendelian randomization, integrated bioinformatics

Introduction

The thyroid gland, which consists of two connected lobes of the lungs, is one of the largest endocrine glands in the body, weighing 20 to 30 grams in an adult. Thyroid lesions are commonly found in the gland,[1] and hypothyroidism (SCH), an endocrine disease, is often caused by the autoimmune disease Hashimoto's disease, which is more common in women of childbearing age due to reduced resistance or levels of thyroid hormones in the blood.[2,3] Epidemiological data indicate that the prevalence of SCH during pregnancy ranges from 0.3% to 2.5%,[2,4,5] with approximately 15% of pregnant women in the United States suffering from SCH, a nearly five-fold increase in prevalence, and the global prevalence of thyroid autoimmunity in women of childbearing age ranges from approximately 8% to 14%,[6] and has become the most common endocrine disorder in women of childbearing age.[7] Pregnancy is a natural physiologic process accompanied by changes in hormone and metabolic levels in the body, and it also leads to pathophysiologic changes in various organs, and one of the organs that undergoes physiologic changes during pregnancy is the thyroid gland.[8] Many observational studies have speculated that SCH may be associated with adverse pregnancy outcomes such as miscarriage, preterm delivery, gestational hypertension, and poor fetal growth.[5,7,9–12] Hypothyroidism that occurs during pregnancy affects the

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body's metabolism of sugars and fats, among other things, and may lead to adverse maternal and foetal pregnancy outcomes if not well controlled with hormones,[8] affecting the health of the mother and child. Still, some studies have shown that hypothyroidism has no adverse effect on perinatal outcomes.[13,14] Thyroid anti-peroxidase antibodies, when isolated and studied, are linked to an elevated risk of placental abruption but not to other unfavorable pregnancy outcomes. Approximately one-third of women with SCH have abnormally high levels of these antibodies.[8] No consistent conclusions have been reached about whether SCH increases the risk of adverse pregnancy outcomes. It has been hypothesised that levothyroxine supplementation in patients with SCH may reduce the likelihood of adverse pregnancy outcomes if it is administered prior to the start of the IVF-ET cycle.[15] Therefore, exploring whether there is a genetic relationship between hypothyroidism and adverse pregnancy is instructive for hormone use and gynaecological clinical management.

The effect of SCH on pregnancy outcomes is unclear, and while some observational studies have explored the association, Reverse causation and other potential confounding variables could skew the results. Consequently, we employ Mendelian randomization (MR) analysis to infer the causal relationship between exposure and outcome using single nucleotide polymorphism (SNP) as an instrumental variable. It can compensate for the limitations of observational research by producing an impact that is comparable to random grouping without the intervention of outside environmental factors.[16] In this study, MR Integrated bioinformatics was used to explore the causal association between hypothyroidism and six adverse pregnancy outcomes (ectopic pregnancy, spontaneous abortion, fetal dysplasia, placental abruption, gestational hypertension, and gestational diabetes), while revealing the disease's fundamental molecular pathways.

Material and Methods

Research Design

The goal of the current investigation was to determine whether there was a causal relationship between the two once it was established that the exposure and outcome factors in the Genome-wide Association investigation (GWAS) pooled data were independent of one another, using hypothyroidism as the exposure variable and the six adverse pregnancy outcomes (ectopic pregnancy, spontaneous abortion, poor fetal growth, placenta previa, gestational hypertension, and gestational diabetes mellitus) as the outcome variables to explore whether there was a causal effect between the two, with the specific design shown in Figure 1. The MR analysis was guided by the following three key assumptions:[17] first, the instrumental variable is a valid proxy for the exposure variable (hypothyroidism); second, the instrumental variable is not

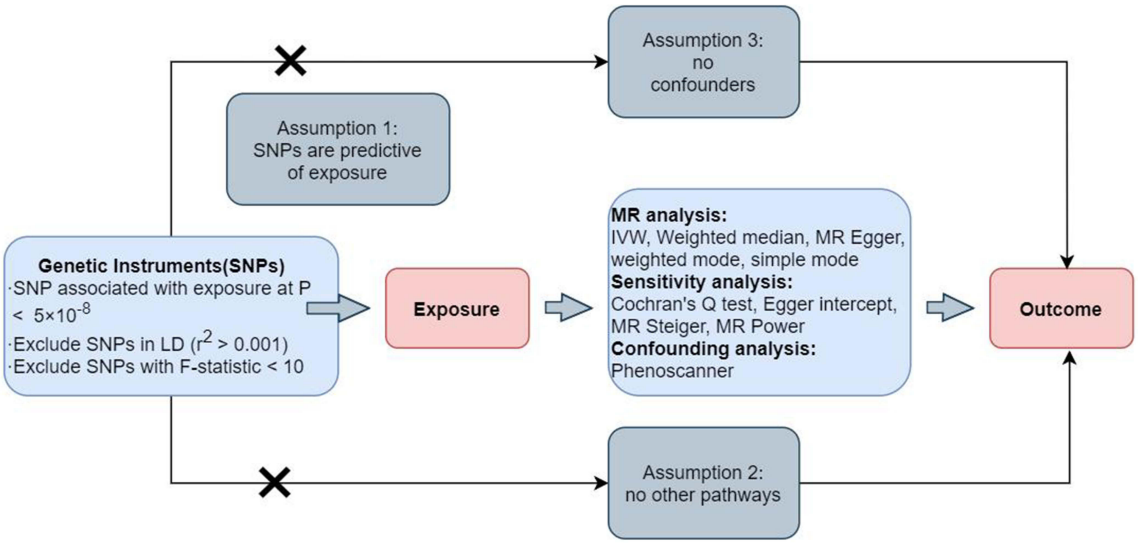

Figure 1 Flowchart of instrumental variable screening for MR method analysis. SNPs: single nucleotide polymorphisms.

associated with other confounders that may affect the outcome; and third, the instrumental variable affects the outcome (the six adverse pregnancy outcomes) only through exposure.

Data Source

Combined GWAS data for hypothyroidism (N=410,141) were obtained from a study by Masahiro Kanai et al.[18] Ectopic pregnancies (N=149,622), spontaneous abortions (N=149,622), poor fetal growth (N=207,312), placental abruption (N=168,929), gestational hypertension (N=194,266), and gestational diabetes (N=197,831) GWAS pooled data were obtained from Finnish databases. To avoid the chance of duplicate data samples, pooled exposure and outcome data were gathered from two distinct databases. For further details, refer to Table S1. All of the samples were of European descent.

Instrumental Variable Selection

(1) Relevant Settings of instrumental variables (IVs). To obtain strongly correlated exposure data, relevant SNPs of hypothyroidism are screened with P<5×;10−8[19](2) To ensure that the SNPs were independent of one another, the linkage disequilibrium (LD) between them was determined using the PLINK aggregation method, where the linkage disequilibrium coefficient R2 > 0.001; SNPs with a physical distance of bases less than 10,000 kb were removed;[20,21] (3) Weak instrumental variables with F < 10 were eliminated, and statistical strength was determined to determine the validity of instrumental variables using the statistic.[22] Ultimately, SNPs that were associated with confounding variables or findings were eliminated using the PhenoScanner database (http://www.phenoscanner.medschl.cam.ac.uk/).

Mendelian Randomization Analysis

The primary analytical technique for establishing causality was the inverse variance weighted (IVW),[23] which produced the most accurate results when heterogeneity and horizontal pleiotropy were absent. Furthermore, we used other supplementary techniques, such as plurality-based weighted mode (WM), weighted median (WME), and MR-Egger regression, to evaluate causality in various scenarios. Using the Multiple Effectiveness Residuals and Outliers Test (MR pleiotropy residual sum and outlier, MR-PRESSO),[24] potential outliers were removed and reanalyzed if heterogeneity was found. Heterogeneity was first evaluated using the Cochran's Q test. The horizontal pleiotropy was tested using the MR-Egger intercept, and the lack of horizontal pleiotropy (P>0.05) suggests that the MR analysis's findings are trustworthy.[25] In order to ascertain whether the results are resilient, "leave-one-out" (LOO) analysis conducts a sensitivity analysis in order to guarantee the reliability of the results and to eliminate particular SNPs that might alter the causal effect.[26]

Pilot Bioinformatics Analysis

A vast amount of functional genomics data and quantitative trait loci are integrated by Open Targets Genetics (https://genetics.opentargets.org/) to produce overall variant-gene (V2 G) scores, which are useful for choosing the best candidate genes. After building protein interaction networks and performing enrichment analyses using Kyoto Encyclopedia of Genes and Genomes (KEGG) and Gene Ontology (GO), the genes with the highest overall V2 G scores were chosen.

Results

Causal Effect of Gut Microbiota on Cervical Cancer

After selection and coordination of IVs, 58 (ectopic pregnancy), 58 (spontaneous abortion), 58 (poor fetal growth), 58 (placental abruption), 58 (hypertension in pregnancy), and 56 (gestational diabetes mellitus) SNPs were obtained, respectively, and detailed information on each SNP is provided in Table S2. The results of the IVW analysis were used as the primary reference indicator because of the absence of heterogeneity and horizontal pleiotropy. As shown in Figure 2, hypothyroidism increased the risk of developing gestational hypertension (OR=1.054, 95% CI: 1.002~1.110 P=0.042) and poor fetal growth (OR=1.081, 95% CI:1.005~1.162 P=0.035). Cochran's Q test showed that there was no heterogeneity in

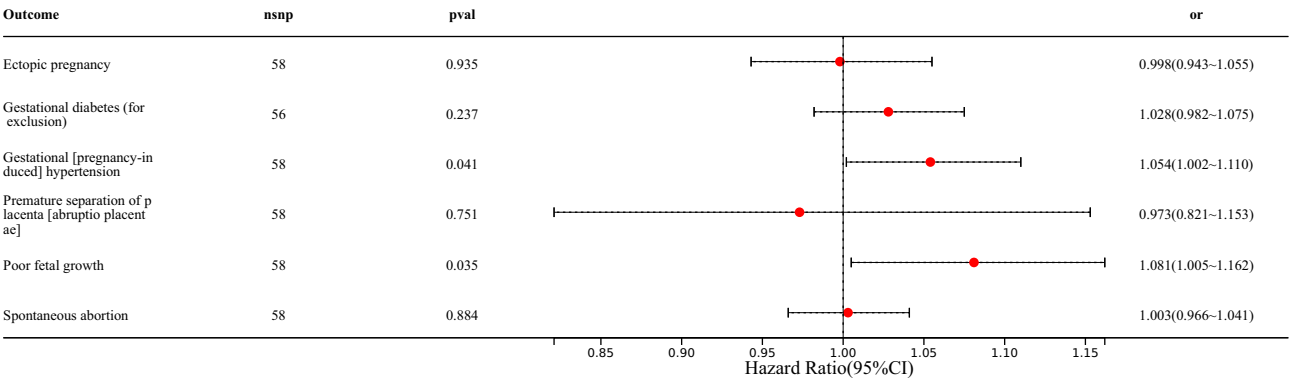

Figure 2 Forrest plot for causal associations of hypothyroidism with adverse pregnancy outcomes based on IVW method.

any of the SNPs. The test for pleiotropy showed that the p-values of MR Egger's test were greater than 0.05, suggesting that there was no horizontal pleiotropy. LOO analysis showed robust results, see Table S3 and Figure S1.

Genetic Architecture Mediating Causal Effects

We mapped the mutation loci of hypothyroidism-hypertension in pregnancy and hypothyroidism-fetal dysplasia, respectively, to the Open Targets Genetics database based on their location on the chromosome. Based on the V2G scores and after removing duplicates, we finally matched 58 independent SNPs in hypothyroidism-hypertension in pregnancy and hypothyroidism-fetal dysplasia to 57 independent genes with the highest V2 G scores (Table S4).

35 interacting genes were evaluated using PPI network analysis (Figure 3A). The next step involved identifying the top ten hub genes with the highest degree: CTLA4, MYC, CD44, IL7R, CD247, STAT4, BACH2, FLT3, TLR3, and SH2B3. The KEGG analysis revealed that the Hub genes were predominantly enriched in the Toll-like receptor signaling pathway, the NOD-like receptor signaling pathway, and the Necroptosis pathway. Hub genes were predominantly found to be enriched in pathways associated with leukocyte activation, lymphocyte activation, lymphocyte proliferation, endosome membranes, protein kinase binding, protein tyrosine kinase binding, transcription factor binding, DNA-binding, and clathrin-coated vesicles (Figure 3B).

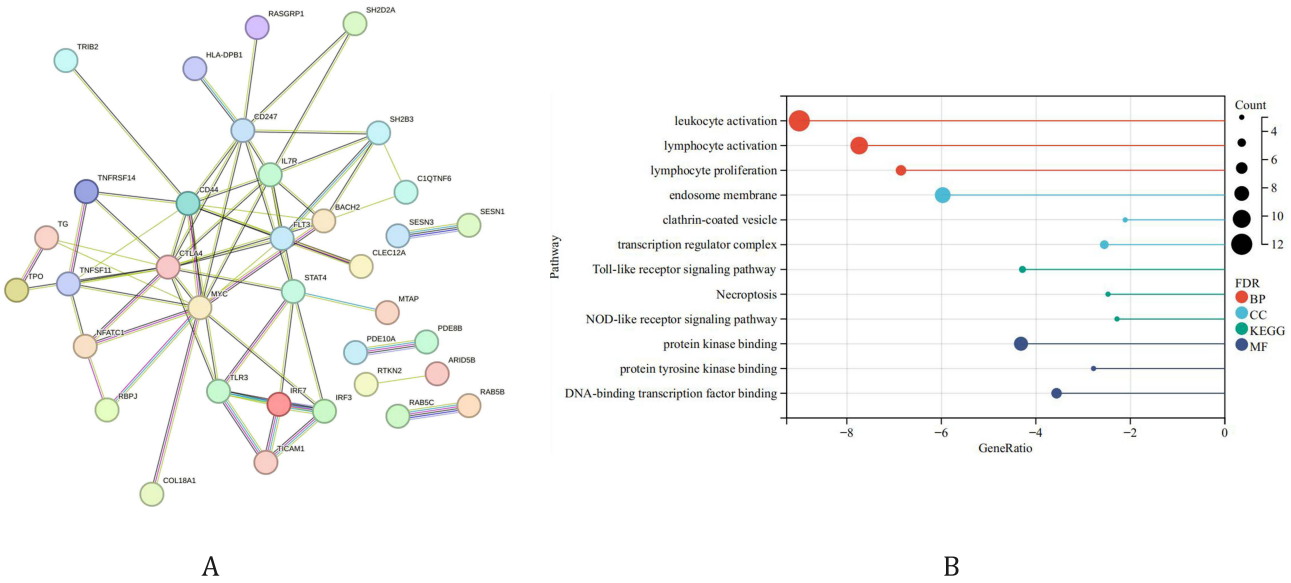

Figure 3 The biological functions and Interactions of mediator genes. (**A**) Interaction network of genes was constructed using the STRING database. (**B**) The top 3 GO and KEGG enriched pathways.

Discussion

In this study, MR and bioinformatics methods were applied to investigate the causal relationship and biological mechanisms between hypothyroidism and six adverse pregnancy outcomes. The results showed that hypothyroidism increased pregnancy hypertension in women (OR=1.054, 95% CI: 1.002~1.110 P=0.042) and fetal dysplasia (OR=1.081, 95% CI:1.005~1.162 P=0.035), which may be related to toll-like receptor and NOD-like receptor signaling pathways. There is no causal relationship between hypothyroidism and ectopic pregnancy, spontaneous abortion, placental abruption, and gestational diabetes mellitus.

During embryonic development, thyroid development in the fetus starts at 10–12 weeks and continues until delivery, with the mother supplying the fetus with the required thyroxine,[27–29] and maternal-fetal transfer of thyroxine accounting for approximately 50% of serum thyroxine in term fetuses, Maternal thyroid insufficiency leads to poor thyroxine status in the offspring fetus, which further leads to disruption of the fetal neonatal pituitary- thyroid axis development disruption,[30] disruption of fetal pituitary GH secretion,[31] and disruption of in utero cardiovascular homeostasis,[32] which leads to fetal low birth weight, neurodevelopmental delay, and other growth deficits. In addition, fetal brain development depends on maternal iodine supply, which delivers T4 to the fetus for normal fetal development.[33,34] The effectiveness of placental nutrition transfer is a critical element in fetal growth.[35] Studies have found that hypothyroidism in rats can reduce placental efficiency, induce placental morphological changes and placental dysfunction, and decreased placental transport results in less availability of maternal T4 and reduced maternal lipolysis, resulting in lower availability of triglycerides and free fatty acids. Thus, inadequate nutrition in the body interferes with the fetus's ability to grow and develop normally.[36]

Pregnancy-related hypertension problems are the primary cause of maternal, fetal, and neonatal mortality globally, with a concentration in low- and middle-income nations.[37,38] Low thyroid hormone levels may be relevant in the development of hypertensive diseases during pregnancy since thyroid hormones are involved in the regulation of blood pressure, endothelial function, and placental development.[39–41] Triiodothyronine (T3) is a thyroid hormone molecule that is biologically significant in cardiomyocytes. These cells have specific transport proteins for T3, which changes the functionality of different sodium, potassium, and calcium channels in the heart.[39] This is because a thyroxine deficiency causes the body to retain water and sodium, which is one of the mechanisms that leads to the pathophysiology of hypertension. The body increases arterial constriction, which raises blood pressure and increases peripheral vascular resistance in order to prevent increased cardiac output, tissue overperfusion, etc.[40] In addition, due to the increase in blood volume after pregnancy, hypothyroidism causes lipid metabolism and vascular abnormalities, and free T3 in serum can directly act on smooth muscle cells of blood vessels, leading to systemic vasospasm and causing hypertension in pregnancy. It has been found that VSMC proliferation in the spiral arteries of the uterus in patients with gestational hypertension leads to narrowing of the lumen of the arteries, causing ischaemia and hypoxia in the uteroplacental placenta, and giving rise to a series of pathological changes in hyperemesis gravidarum. Expression of the C-myc gene is correlated with uterine spiral arterial VSMC, and the C-myc antisense deoxidative oligodeoxynucleotide reduces the expression of C-myc mRNA and the level of the corresponding proteins, inhibiting vascular VSMC proliferation. In this experiment, we showed that C-myc gene expression was significantly higher in expectant mothers than in normal pregnant women.[42]

While MR studies combine the techniques of functional enrichment and protein-interaction networks to provide new insights into the specific mechanisms underlying the association between hypothyroidism and unfavorable pregnancy outcomes, they also minimize the inherent bias due to confounding factors or reverse causality, in contrast to previous observational studies that were vulnerable to these issues and the drawbacks of large-scale, clinically conducted RCT experiments. Our study still has a number of shortcomings, though. First, the MR Analysis is limited to the use of genetic data that is currently available; second, more comprehensive cohort data, such as age, are not available for additional subgroup analysis; and third, all of the study's data are from European populations. Non-genetic factors that may influence the onset and progression of the disease, such as lifestyle, cannot be excluded. When extrapolating the findings to other people with distinct lifestyles and cultural customs, care should be taken.

Conclusions

Larger experimental studies are necessary to clarify the intricate interactions at the epigenetic level of hypothyroidism for gestational hypertension and poor fetal growth. In summary, these results support a causal relationship between hypothyroidism and gestational hypertension and poor fetal growth, as well as the idea that hypothyroidism increases the risk of both conditions.

Abbreviations

MR, Mendelian randomization; RCT, Randomized Controlled Trial; SNPs, single nucleotide polymorphisms; IVs, instrumental variables; GWAS, Genome Wide Association Study; LD, linkage disequilibrium; IVW, inverse variance weighted; WME, weighted median; SCH, hypothyroidism.

Data Sharing Statement

The study's data can be accessed through the publication and its Supplementary Information PDF.

Ethics Approval and Informed Consent

Mendelian randomization analysis was performed using pooled data obtained from GWAS. These data were collected in compliance with the principle of written informed consent and ethical approval was obtained.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflict of interest.

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