Causal relationship between hypothyroidism and the risk of hearing loss: A bidirectional two-sample Mendelian randomization study

Zhu Zhengxin
The Second Affiliated Hospital of Nanchang University
Yuehui Liu (liuyuehuiclark@21cn.com)
The Second Affiliated Hospital of Nanchang University

Research Article

Keywords: Mendelian randomization, genome-wide association studies, hypothyroidism, hearing loss, single nucleotide polymorphisms

Posted Date: April 25th, 2023

DOI: https://doi.org/10.21203/rs.3.rs-2798037/v1

Additional Declarations: No competing interests reported.

Abstract

Background

Hypothyroidism's causal direction and the magnitude of its association with hearing loss is uncertain due to the limitations of observational studies. This study aims to investigate the relationship between hypothyroidism and hearing loss using bidirectional two-sample mendelian randomization (MR).

Materials and Methods

The genetic variants of 462,933 participants in the hypothyroidism study and 323,978 participants in the hearing loss study were used for bidirectional two-sample MR. Independent genetic variants that were significantly ($P < 5\times10^{-8}$) associated with each exposure were considered as instruments. To test for sensitivity, Cochran's Q test, the MR-Egger intercept test, and leave-one-out analysis were applied apart from the multiplicative random effects-inverse variance weighted (MRE-IVW) approach used as the main MR analysis.

Results

The forward MR revealed a significant causal estimate for the genetically predicted hypothyroidism with the high risk of hearing loss [MRE-IVW: odds ratio (OR) = 1.092, $P = 0.003$]. However, the reverse MR analysis found no significant correlation between genetically predicted hearing loss and hypothyroidism (MRE-IVW: OR = 1.04, $P = 0.113$). Sensitivity analyses showed that the causal association estimations were stable and reliable.

Conclusion

In this MR study, we demonstrated hypothyroidism was causally associated with a high risk of hearing loss. However, there was no evidence to support the causality of hearing loss on hypothyroidism.

Introduction

Hearing loss is a common sensory dysfunction often unrecognized by patients and physicians and undertreated. By the time people are aware of having hearing difficulties, the hearing loss is often severe (1). World Health Organization(WHO) believe the key fact that, by 2050 nearly 2.5 billion people are projected to have some degree of hearing loss and at least 700 million will require hearing rehabilitation (2). Therefore, it is imperative to identify potential risk factors for hearing loss and develop timely and effective prevention strategies.

Hypothyroidism, also known as underactive thyroid disease, refers to the common pathological condition of thyroid hormone (TH) deficiency. The prevalence of overt hypothyroidism in the general population varies between 0–7% in the USA and between 0–5% in Europe depending on the definition used(3). And TH has been shown to be associated with a variety of diseases, including cardiovascular system

diseases(4, 5), digestive system diseases(6, 7), nervous system disease (8–10) and other diseases(11–13). Numerous observational studies have suggested that congenital hypothyroidism is associated with an increased risk of hearing loss(14–16). And some observed that patients with sudden sensorineural hearing loss (SSNHL) were more likely to have hypothyroidism than normal individuals (17, 18). However, the causal association between hypothyroidism and hearing loss remains uncertain because these observational results are inevitably affected by other potential confounding effects and reverse causation.

Mendelian randomization (MR) study is a data analysis method mainly applied to etiology inferences in epidemiological studies during recent years. It advanced that differences in genotypes are major determinants of differences in intermediate phenotypes, if the association between genotype and disease can represent the effect of exposure factors on disease, then the phenotype represents an individual's exposure characteristics. Alleles follow the principle of random allocation, so this effect is unaffected by confounding factors and reverse causal associations in traditional studies (19). Mendelian randomization can thereby demonstrate the true causal relationship between exposure and outcome.

In order to give theoretical support for clinical practice, we intend to carry out a bidirectional two-sample MR research in the current study to determine if hypothyroidism and hearing loss are directly causally related. We predicted that there would be a directed causal relationship between hypothyroidism and the high risk of hearing loss.

Materials And Methods

Study Design

In MR analysis, the instrumental variables (IVs) were employed to reduce the impact of confounders and evaluate the causal association between exposure and particular outcome. The three main assumptions upon which MR was based: (1) the IVs are significantly related to exposure; (2) the IVs must not be related to confounders; and (3) the IVs should only be related to the risk of overcome through exposure (20). The MR schematic was shown in Fig. 1. This analysis was reported according to the STROBE-MR guidelines (21).

Data Sources

The MR analysis was based on summary-level genome wide association study(GWAS) data from the Integrative Epidemiologic Unit(IEU) Open GWAS database (22). Individual data were obtained from the UK Biobank, a large-scale biomedical database comprising half a million participants aged 40 to 73 years, recruited between 2006 and 2013 from across the United Kingdom (23). In the current study, we utilized publicly accessible datasets from studies that had been published, in which individuals had given formal consent and the study had received ethical approval from the appropriate committees, informed consent and additional ethical approval were thus not necessary. Details of all GWAS datasets used in this study were listed in Supplementary Table 1.

The hearing loss GWAS summary dataset (GWAS ID: ukb-a-257) included the GWAS analysis results of 323,978 samples (84,839 cases and 239,139 controls) and 10,894,596 single-nucleotide polymorphisms (SNPs). Participants were assigned to case or control groups based on their answer for the questionnaire about hearing difficulties.

The hypothyroidism GWAS summary dataset (GWAS ID: ukb-b-19732) contained 462,933 samples (including 22,687 cases and 440,246 controls) and 9,851,867 SNPs. Hypothyroidism cases were self-reported by participants via a touch screen questionnaire.

Instrumental Variables Selection

SNPs closely associated with hypothyroidism or hearing loss were extracted from published GWAS data as IVs, with $P < 5\times10^{-8}$ as the main screening condition. To ensure that SNPs for hypothyroidism or hearing loss were independent, SNPs in linkage disequilibrium ($r^2 < 0.001$ and distance > 10,000 kb) were excluded. And the F statistic was used to assess the weak instrumental variable bias, $F < 10$ indicates that the instrumental variable may be subject to weaker instrumental variable bias (24), which in turn was removed to avoid any effect on the results. Final valid SNPs associated with hypothyroidism or hearing loss were obtained as IVs. Then, the IVs in GWAS for outcome data were extracted based on the SNPs of the previous exposure data. F statistics for each SNP were calculated by the following equation: $F = \beta^2/SE^2$ (25), where β indicates the allele effect value of exposure and SE indicates the standard error of β. The main information for the final valid SNPs (including effect allele, other allele, β, standard error and P value) were collected systematically for further analysis.

Statistical Analysis

After reconciling effect alleles in the exposure data and outcome data, the strength of the association between hypothyroidism and HL was calculated by using the multiplicative random effects-inverse variance weighted (MRE-IVW) method as the main analysis, meanwhile using the MR-Egger, weighted median estimator (WME), simple mode (SM), and weight mode (WM) methods as complementary analyses. Because IVW is the most widely used method among the five methods in MR studies, and could provide the most precise results when all selected SNPs were valid IVs. The causal effects were measured in the odds ratio (OR). Then, Cochran's Q statistic was employed to estimate heterogeneity from each SNP (26). The P value of Cochran's Q test was used to test for heterogeneity. The MR-Egger intercept test was utilized to evaluate the potential horizontal pleiotropy. In addition, the “leave-one-out” sensitivity analysis was performed to determine whether the result was affected by a single SNP. The funnel plot and forest plot were constructed to visualize the presence of horizontal pleiotropy in the MR analysis. $P < 0.05$ was considered statistically significant. All statistical analyses were performed using the "TwoSampleMR" package(27) in R software version 4.2.2.

Results

Characteristics of Instrumental Variables

Following the IVs selection steps, a total of 118 valid IVs strongly associated with hypothyroidism on hearing loss, and 22 valid IVs strongly associated with hearing loss on hypothyroidism were included into MR estimates, respectively. None of these IVs' *F* statistics were less than 10, indicating that no weak IVs were employed. An overview of the IVs included in each MR analysis was provided in Supplementary Table 3–4.

Mendelian Randomization Analysis

The MR analysis estimates from different methods for the causal effects among hypothyroidism and hearing loss were presented in Fig. 2. MRE-IVW evaluation of 118 valid IVs effects for hypothyroidism on hearing loss provided evidence to support that causal relationship existed (OR = 1.092, 95% CI = 1.031–1.156, $P = 0.003$), and results estimated by WME and WM were consistent with MRE-IVW. However, the evaluation of 22 valid IVs effects for hearing loss on hypothyroidism showed the consistent results that hearing loss was not causally associated with hyperthyroidism (OR = 1.042, 95% CI = 0.990–1.096, $P = 0.113$). *P* values of all five MR estimate tests were more than 0.05. Full information of each MR analysis results was provided in Supplementary Table 2. The scatter plots of valid IVs causal effects estimate for each MR analysis were shown in Fig. 3.

Sensitivity Analysis

We conducted several sensitivity analyses to evaluate the robustness of our findings. The sensitivity analyses included Cochran's Q test, the MR-Egger intercept test, leave-one-out analysis, and the funnel plot. We used IVW and MR-Egger regression methods to calculate Cochran's Q statistics. The results of the Cochran's Q test and the MR-Egger intercept test can be found in Supplementary Table 5–6. Despite the existence of heterogeneities between IVs used to estimated effect between hypothyroidism and hearing loss ($P < 0.05$), MRE-IVW estimated results were still valid, as indicated by the results of the Cochran's Q test. Furthermore, no horizontal pleiotropy existed between IVs and outcomes, as confirmed by the MR-Egger intercept test ($P > 0.05$). Additionally, the outcome of the leave-one-out test showed that the causal estimates of hypothyroidism and hearing loss were not driven by any single SNP (Fig. 4). More detailed results of leave-one-out tests were displayed in Supplementary Table 7–8. Finally, the funnel plots for MR analysis demonstrated that the data points were distributed equally around the funnel (Fig. 5). This indicated that our study had sufficient statistical power and the MR results withstand the test of sensitivity analysis.

Discussion

Our study firstly investigated the causal effects between hypothyroidism and hearing loss by bidirectional two-sample MR analysis. The results of the study indicated that genetically predicted hypothyroidism causally associated with an increased risk of hearing loss. Furthermore, no evidence was found to support causal relationship of hearing loss on hypothyroidism. our findings provided a better

understanding of the role of hypothyroidism in hearing loss, indicating that regular hearing assessments for hypothyroidism patients are required, in order to prevent them from severe hearing loss.

Hearing loss is reported frequently associated with hypothyroidism, ranging from mild disturbances to severe disability. A case-control study conducted by Tsai et al. (18) in Taiwan demonstrated that after adjusting for confounders, associations were identified between a history of hypothyroidism and an elevated risk of SSNHL (adjusted odds ratio [AOR], 1.54; 95% CI, 1.02–2.32; p = 0.042). Similar results were obtained in a retrospective cohort study including 8658 SSNHL patients and 34,632 controls conducted by Kim et al. (17) in Korean. Meanwhile, A prospective observational study conducted by Almagor et al. (28) in Israel indicated a high prevalence of hearing impairment among patients with congenital hypothyroidism, predominantly of the conductive type. Unlike the above study, however, more observed that sensorineural hearing loss was most common in congenital hypothyroidism, higher frequencies in particular(29–32), and this phenomenon was not associated with THS and free T4 levels(33–35). There was also a contradictory conclusion, François et al. (36) found no significant difference for the auditory thresholds at high frequencies between congenital hypothyroidism treated with L-thyroxine and control group, regardless of the cause of the thyroid failure or hormone level and the age at the start of treatment.

These contradiction between observational studies could be due to confounding bias or reverse causality. For instance, some genetic or chromosomal disorders can also present with hypothyroidism and hearing loss at the same time, including Pendred syndrome variants in the SLC26A4 gene (37–39), Woodhouse-Sakati Syndrome variants in the DCAF17 gene(40), Down syndrome(41), and TBL1X mutations(42). In animal experiments, Oliveira et al. (43) observed that perinatal hypothyroidism leads to irreversible damage to cochlear function in offspring rats. Others found that the congenital hypothyroid mouse displayed consistent morphologic abnormalities of the stereocilia on both inner and outer hair cell systems. The surrounding and supporting cells showed no significant histologic abnormalities in hypothyroid mouse and control animals (44).

Despite an abundance of evidence from observational studies support the association between hypothyroidism and hearing loss, there still remain a question about their causative relationships. The present Mendelian randomization study employs IVs to eliminate confounders and offers a new perspective on the causality between hypothyroidism and hearing loss. We provided more statistically significant results through bidirectional two-sample MR analysis. It is possible be that the presence of hypothyroidism leads to the increasing risk of hearing loss, as opposed to hearing loss promoting the occurrence of hypothyroidism.

The current study has several strengths. First, the data we used containing 323,978 and 462,993 individuals of European ancestry, allowing us to gain more precise estimates and detect slight statistical differences, meanwhile preventing the simple error in previous cohort studies. Second, bidirectional two-sample MR methods were firstly applied to explore the causal associations with hypothyroidism and hearing loss, and these methods tend to be less biased than conventional observational studies. Third,

the MR method took advantage of GWAS summary data on hypothyroidism and hearing loss that were derived from two different populations, which reduced the interference of sample overlap.

Nevertheless, there are still several limitations in our study. First, our conclusions were based on data from GWASs that were solely conducted in people with European ancestry, with relatively little variety in ethnicity or culture. Thus, the results may not be fully representative of the entire population and might not be generalizable. However, the participants' consistency assures that there is little chance of population admixture confounding the results. Second, as our study used summarized data for MR analysis, stratification based on gender, age or subtypes was not applicable. Third, we found that the two samples were somewhat heterogeneous. However, because the MRE-IVW that used as the primary analysis in this work can balance the pooled heterogeneity, the presence of heterogeneity did not render the MR estimates invalid.

Conclusion

In conclusion, our bidirectional two-sample MR study investigated the controversial relationship between hypothyroidism and hearing loss, and revealed that hypothyroidism was causally associated with hearing loss, but no evidence was found to support reverse causally associated. Further investigation is required to determine whether this result is replicated in other environments and to uncover the potential underlying mechanisms.

Declarations

Ethics approval and consent to participate

Not applicable. In the current study, we utilized publicly accessible datasets from studies that had been published, in which individuals had given formal consent and the study had received ethical approval from the appropriate committees, informed consent and additional ethical approval were thus not necessary.

Availability of data and materials

Our study used publicly available summary-level data of GWAS. The summary statistics of GWAS for hypothyroidism and hearing loss can be accessed at IEU Open GWAS database (https://gwas.mrcieu.ac.uk/); Each IDs were presented in Supplementary Table 1.

Acknowledgements

We would like to acknowledge the participants and investigators of the IEU Open GWAS database and UK biobank.

Consent for publication

Not applicable.

Author contributions

ZZ contributed to the preparation and writing of the manuscript. YL contributed to the editing of the manuscript.

Funding

The study was supported by the National Natural Science Fund of China (grant No. 81760184 and 82060185) and Natural Science Fund of Jiangxi Province (grant No. 20192ACB20027).

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.

References

1. Nieman CL, Oh ES. Hearing Loss. Ann Intern Med. 2020;173(11):ITC81-ITC96. doi.org/10.7326/AITC202012010.
2. World Health Organization. Deafness and hearing loss. https://www.who.int/news-room/fact-sheets/detail/deafness-and-hearing-loss [Accessed March 10, 2023].
3. Chaker L, Bianco AC, Jonklaas J, Peeters RP. Hypothyroidism. Lancet. 2017;390(10101):1550-62. doi.org/10.1016/S0140-6736(17)30703-1.
4. Jabbar A, Pingitore A, Pearce SH, Zaman A, Iervasi G, Razvi S. Thyroid hormones and cardiovascular disease. Nat Rev Cardiol. 2017;14(1):39-55. doi.org/10.1038/nrcardio.2016.174.
5. Razvi S, Jabbar A, Pingitore A, Danzi S, Biondi B, Klein I, et al. Thyroid Hormones and Cardiovascular Function and Diseases. J Am Coll Cardiol. 2018;71(16):1781-96. doi.org/10.1016/j.jacc.2018.02.045.
6. Sinha RA, Bruinstroop E, Singh BK, Yen PM. Nonalcoholic Fatty Liver Disease and Hypercholesterolemia: Roles of Thyroid Hormones, Metabolites, and Agonists. Thyroid. 2019;29(9):1173-91. doi.org/10.1089/thy.2018.0664.
7. Sinha RA, Singh BK, Yen PM. Direct effects of thyroid hormones on hepatic lipid metabolism. Nat Rev Endocrinol. 2018;14(5):259-69. doi.org/10.1038/nrendo.2018.10.
8. Baksi S, Pradhan A. Thyroid hormone: sex-dependent role in nervous system regulation and disease. Biol Sex Differ. 2021;12(1):25. doi.org/10.1186/s13293-021-00367-2.
9. Schiera G, Di Liegro CM, Di Liegro I. Involvement of Thyroid Hormones in Brain Development and Cancer. Cancers (Basel). 2021;13(11):2693. doi.org/10.3390/cancers13112693.
10. Charoenngam N, Rittiphairoj T, Ponvilawan B, Prasongdee K. Thyroid Dysfunction and Risk of Parkinson's Disease: A Systematic Review and Meta-Analysis. Front Endocrinol (Lausanne). 2022;13:863281. doi.org/10.3389/fendo.2022.863281.

11. Petranovic Ovcaricek P, Verburg FA, Hoffmann M, Iakovou I, Mihailovic J, Vrachimis A, et al. Higher thyroid hormone levels and cancer. Eur J Nucl Med Mol Imaging. 2021;48(3):808-21. doi.org/10.1007/s00259-020-05018-z.
12. Bassett JH, Williams GR. Role of Thyroid Hormones in Skeletal Development and Bone Maintenance. Endocr Rev. 2016;37(2):135-87. doi.org/10.1210/er.2015-1106.
13. Gauthier BR, Sola-Garcia A, Caliz-Molina MA, Lorenzo PI, Cobo-Vuilleumier N, Capilla-Gonzalez V, et al. Thyroid hormones in diabetes, cancer, and aging. Aging Cell. 2020;19(11):e13260. doi.org/10.1111/acel.13260.
14. Andrade CLO, Alves CAD, Ramos HE. Congenital Hypothyroidism and the Deleterious Effects on Auditory Function and Language Skills: A Narrative Review. Front Endocrinol (Lausanne). 2021;12:671784. doi.org/10.3389/fendo.2021.671784.
15. Braga H, Duarte JL, da Cruz Fernandes L, Salles IC, Oliveira de Andrade CL, Ramos HE, et al. Congenital hypothyroidism as a risk factor for hearing and parents' knowledge about its impact on hearing. J Otol. 2021;16(2):71-9. doi.org/10.1016/j.joto.2020.09.003.
16. Bruno R, Aversa T, Catena M, Valenzise M, Lombardo F, De Luca F, et al. Even in the era of congenital hypothyroidism screening mild and subclinical sensorineural hearing loss remains a relatively common complication of severe congenital hypothyroidism. Hear Res. 2015;327:43-7. doi.org/10.1016/j.heares.2015.04.018.
17. Kim SY, Song YS, Wee JH, Min C, Yoo DM, Choi HG. Association between SSNHL and Thyroid Diseases. Int J Environ Res Public Health. 2020;17(22):8419. doi.org/10.3390/ijerph17228419.
18. Tsai YT, Chang IJ, Hsu CM, Yang YH, Liu CY, Tsai MS, et al. Association between Sudden Sensorineural Hearing Loss and Preexisting Thyroid Diseases: A Nationwide Case-Control Study in Taiwan. Int J Environ Res Public Health. 2020;17(3):834. doi.org/10.3390/ijerph17030834.
19. Katan MB. Apolipoprotein E isoforms, serum cholesterol, and cancer. Lancet. 1986;1(8479):507-8. doi.org/10.1016/s0140-6736(86)92972-7.
20. Davies NM, Holmes MV, Davey Smith G. Reading Mendelian randomisation studies: a guide, glossary, and checklist for clinicians. BMJ. 2018;362:k601. doi.org/10.1136/bmj.k601.
21. Skrivankova VW, Richmond RC, Woolf BAR, Yarmolinsky J, Davies NM, Swanson SA, et al. Strengthening the Reporting of Observational Studies in Epidemiology Using Mendelian Randomization: The STROBE-MR Statement. JAMA. 2021;326(16):1614-21. doi.org/10.1001/jama.2021.18236.
22. IEU. OpenGWAS Database. https://gwas.mrcieu.ac.uk/datasets [Accessed March 10, 2023].
23. Sudlow C, Gallacher J, Allen N, Beral V, Burton P, Danesh J, et al. UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. PLoS Med. 2015;12(3):e1001779. doi.org/10.1371/journal.pmed.1001779.
24. Pierce BL, Ahsan H, Vanderweele TJ. Power and instrument strength requirements for Mendelian randomization studies using multiple genetic variants. Int J Epidemiol. 2011;40(3):740-52. doi.org/10.1093/ije/dyq151.

25. Qin Q, Zhao L, Ren A, Li W, Ma R, Peng Q, et al. Systemic lupus erythematosus is causally associated with hypothyroidism, but not hyperthyroidism: A Mendelian randomization study. Front Immunol. 2023;14:1125415. doi.org/10.3389/fimmu.2023.1125415.
26. Huedo-Medina TB, Sanchez-Meca J, Marin-Martinez F, Botella J. Assessing heterogeneity in meta-analysis: Q statistic or I2 index? Psychol Methods. 2006;11(2):193-206. doi.org/10.1037/1082-989X.11.2.193.
27. MRC Integrative Epidemiology Unit. TwoSampleMR. https://github.com/MRCIEU/TwoSampleMR [Accessed March 10, 2023].
28. Almagor T, Rath S, Nachtigal D, Sharroni Z, Elias-Assad G, Hess O, et al. High Prevalence of Hearing Impairment in Primary Congenital Hypothyroi dism. Eur Thyroid J.10(3):215-21. doi.org/10.1159/000509775.
29. Vanderschueren-Lodeweyckx M, Debruyne F, Dooms L, Eggermont E, Eeckels R. Sensorineural hearing loss in sporadic congenital hypothyroidism. Archives of disease in childhood. 1983;58(6):419-22. doi.org/10.1136/adc.58.6.419.
30. Lichtenberger-Geslin L, Dos Santos S, Hassani Y, Ecosse E, Van Den Abbeele T, Léger J. Factors Associated With Hearing Impairment in Patients With Congenital Hypothyroidism Treated Since the Neonatal Period: A National Populati on-Based Study. The Journal of Clinical Endocrinology & Metabolism. 2013;98(9):3644-52. doi.org/10.1210/jc.2013-1645.
31. Anand VT, Mann SB, Dash RJ, Mehra YN. Auditory investigations in hypothyroidism. Acta Otolaryngol. 1989;108(1-2):83-7. doi.org/10.3109/00016488909107396.
32. Singh R, Aftab M, Jain S, Kumar D. Audiological Evaluation in Hypothyroid Patients and Effect of Thyroxin e Replacement Therapy. Indian journal of otolaryngology and head and neck surgery : official publication of the Association of Otolaryngologists of India. 2019;71(Suppl 1):548-52. doi.org/10.1007/s12070-018-1395-3.
33. Rodríguez-Valiente A, Álvarez-Montero Ó, Górriz-Gil C, García-Berrocal JR. l-Thyroxine does not prevent immunemediated sensorineural hearing loss in autoimmune thyroid diseases. Acta Otorrinolaringol Esp (Engl Ed). 2019;70(4):229-34. doi.org/10.1016/j.otorri.2018.06.001.
34. Santos KTPd, Dias NH, Mazeto GMFdS, Carvalho LRd, Lapate RL, Martins RHG. Audiologic evaluation in patients with acquired hypothyroidism. Braz J Otorhinolaryngol. 2010;76(4):478-84. doi.org/10.1590/S1808-86942010000400012.
35. Thakur PK, Nishad RK, Jain AK. Evaluation of Hearing Loss in Congenital Hypothyroid Children at a Ter tiary Care Hospital in Central India. Indian journal of otolaryngology and head and neck surgery : official publication of the Association of Otolaryngologists of India. 2022;74(Suppl 3):4393-8. doi.org/10.1007/s12070-021-03063-0.
36. François M, Bonfils P, Leger J, Czernichow P, Narcy P. Role of congenital hypothyroidism in hearing loss in children. The Journal of Pediatrics. 1994;124(3):444-6. doi.org/10.1016/s0022-3476(94)70373-6.

37. Pelzl L, Fakhri H, Umbach AT, Gawaz M, Paulmichl M, Lang F. Sgk1 sensitive pendrin expression in murine platelets. Cell Physiol Biochem. 2013;32(7):210-20. doi.org/10.1159/000356640.
38. Ishii J, Suzuki A, Kimura T, Tateyama M, Tanaka T, Yazawa T, et al. Congenital goitrous hypothyroidism is caused by dysfunction of the iod ide transporter SLC26A7. Commun Biol. 2019;2:270. doi.org/10.1038/s42003-019-0503-6.
39. Tesolin P, Fiorino S, Lenarduzzi S, Rubinato E, Cattaruzzi E, Ammar L, et al. Pendred Syndrome, or Not Pendred Syndrome? That Is the Question. Genes. 2021;12(10):1569. doi.org/10.3390/genes12101569.
40. Louro P, Durães J, Oliveira D, Paiva S, Ramos L, Macário MC. Woodhouse–Sakati Syndrome: First report of a Portuguese case. Am J Med Genet. 2019;179(11):2237-40. doi.org/10.1002/ajmg.a.61303.
41. Stirn Kranjc B. Ocular abnormalities and systemic disease in Down syndrome. Strabismus. 2012;20(2):74-7. doi.org/10.3109/09273972.2012.680234.
42. Heinen CA, Losekoot M, Sun Y, Watson PJ, Fairall L, Joustra SD, et al. Mutations in TBL1X Are Associated With Central Hypothyroidism. The Journal of clinical endocrinology and metabolism. 2016;101(12):4564-73. doi.org/10.1210/jc.2016-2531.
43. Oliveira PFd, Trindade BBS, Reis PFM, Santos TFdC, Alves JCS, Santana DSd, et al. The Induction of Hypothyroidism during Gestation Decreases Outer Hair Cell Motility in Rat Offspring. Int Arch Otorhinolaryngol. 2022;26(4):e712-e7. doi.org/10.1055/s-0042-1745856.
44. O'Malley BW, Jr., Li D, Turner DS. Hearing loss and cochlear abnormalities in the congenital hypothyroid (hyt/hyt) mouse. Hear Res. 1995;88(1-2):181-9. doi.org/10.1016/0378-5955(95)00111-g.

Figures

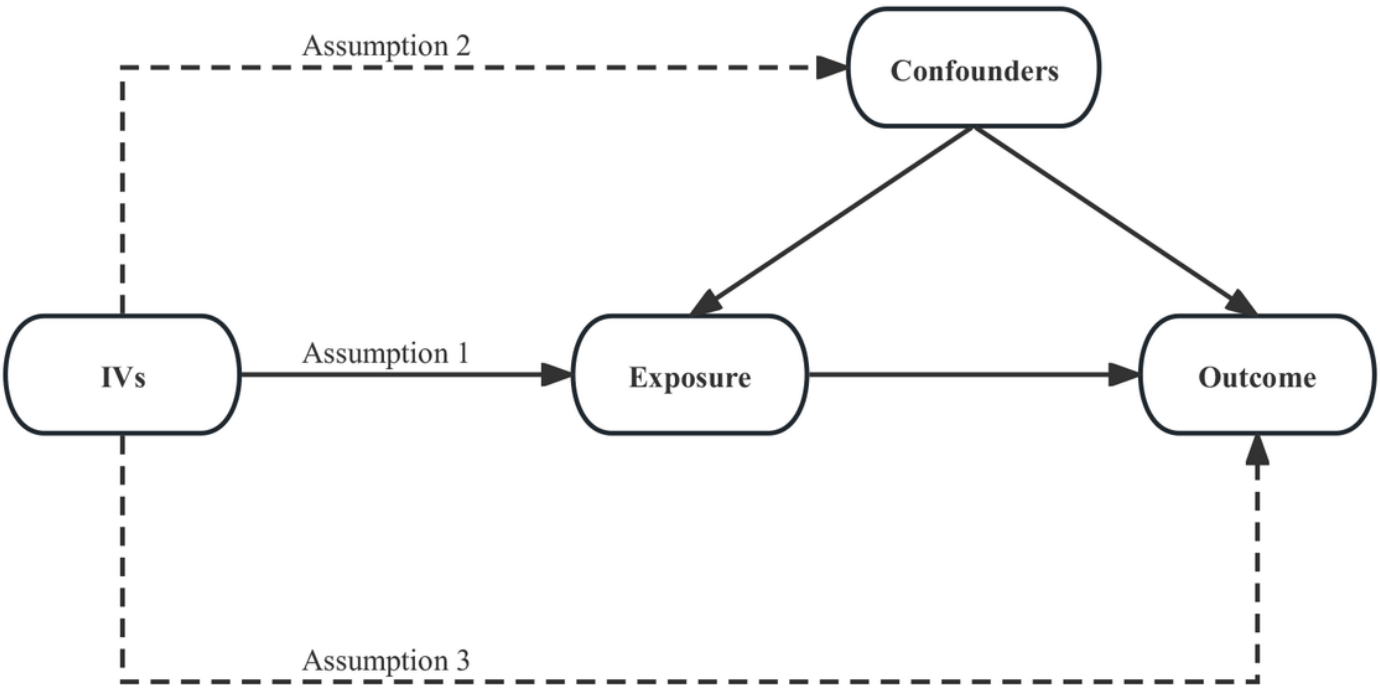

Figure 1

The design flow chart for the MR study. MR assumptions: assumption 1, 2, and 3. The solid line represents direct putative causal effects in assumption 1. The dotted line represents exposure are not associated with any measured and unmeasured confounders and do not influence the outcome through other pathways in assumptions 2 and 3, respectively. IVs, instrumental variables.

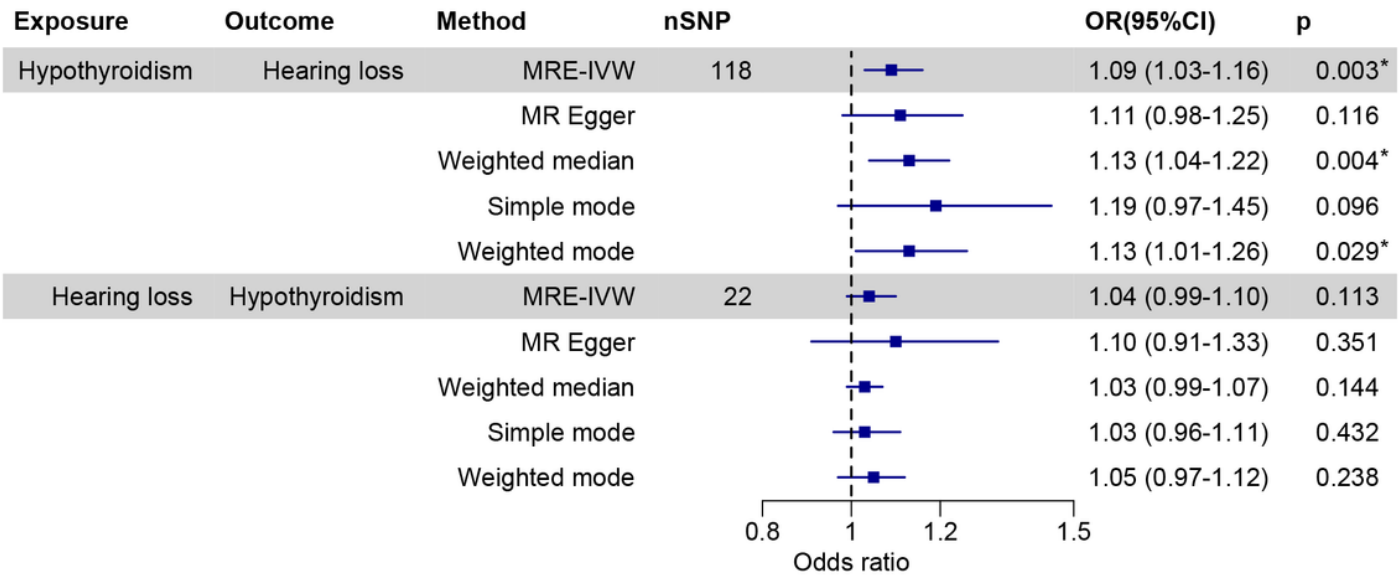

Figure 2

Forest plot of the MR analyses for the association between hypothyroidism and hearing loss using various analysis methods. *Statistically significant P-value.

MRE-IVW, multiplicative random effects-inverse variance weighted; SNP, single nucleotide polymorphism; OR, odds ratio; CI, confidence interval.

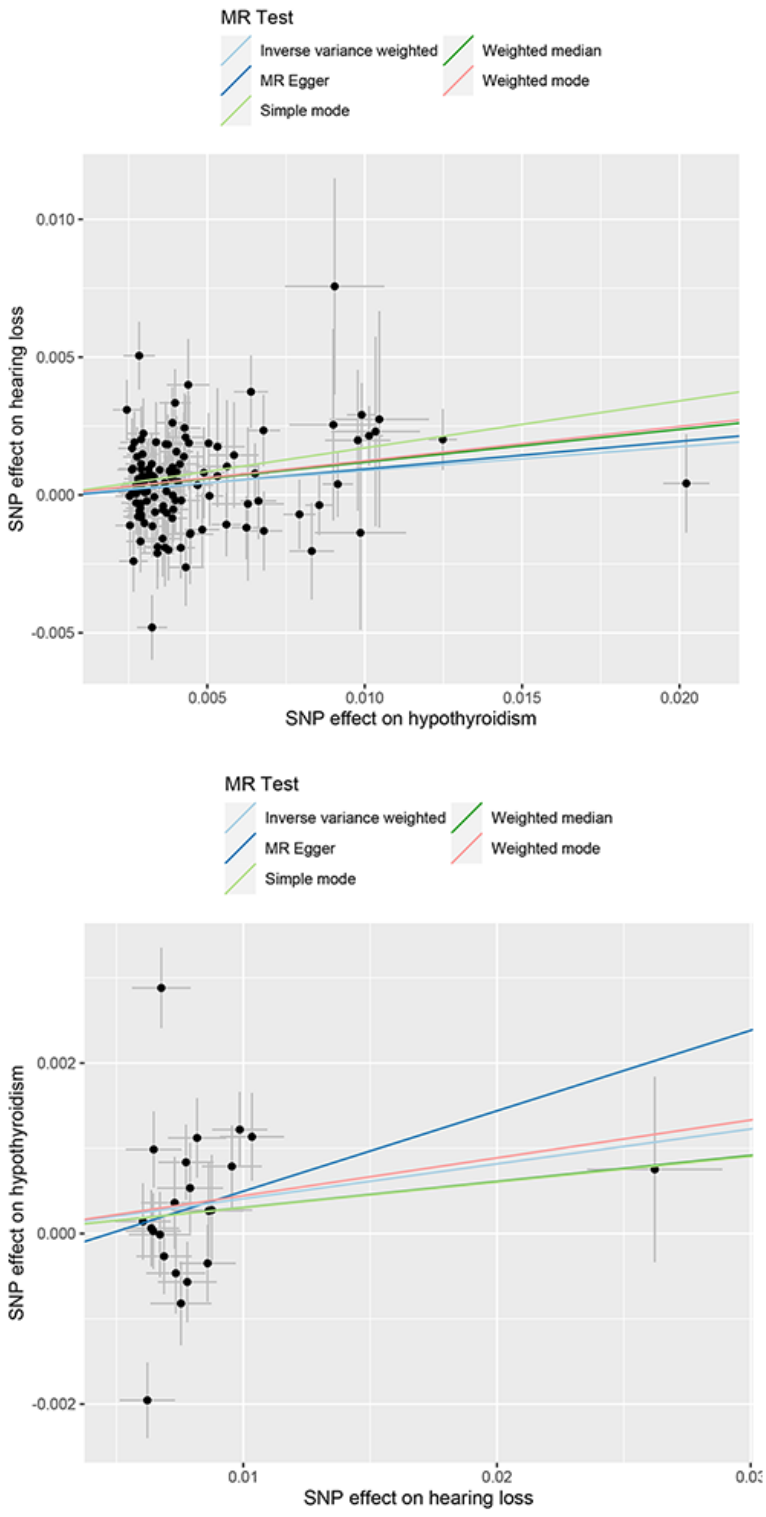

Figure 3

Scatter plots of causal effect estimates for hypothyroidism on hearing loss (A) and hearing loss on hypothyroidism (B), with all 118 and 22 valid instrumental variables. SLE, systemic lupus erythematosus. SNP, single nucleotide polymorphism.

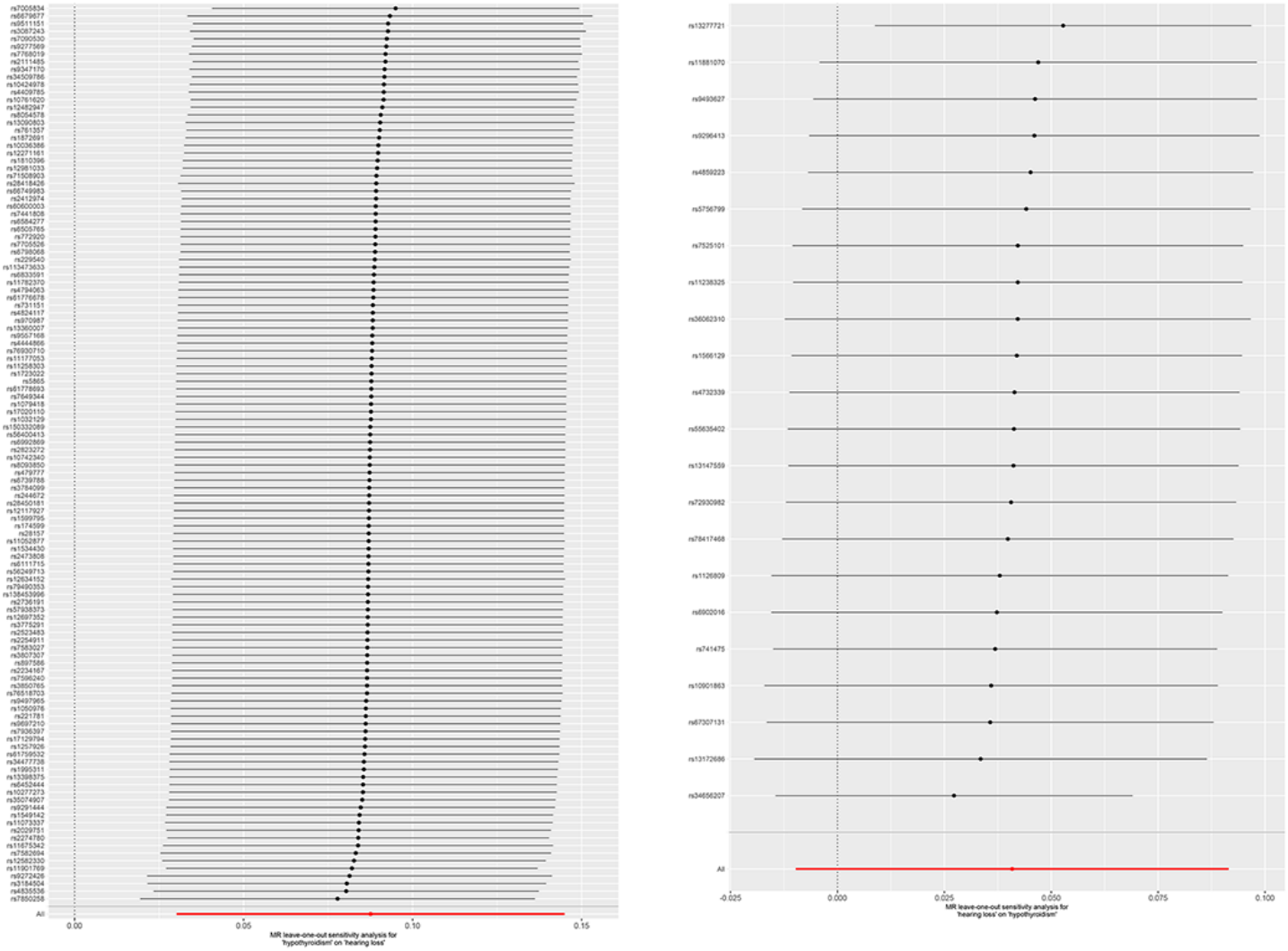

Figure 4

Forrest plots of leave-one-out test for hypothyroidism on hearing loss (A) and hearing loss on hypothyroidism (B), with all 118 and 22 valid instrumental variables. SLE, systemic lupus erythematosus.

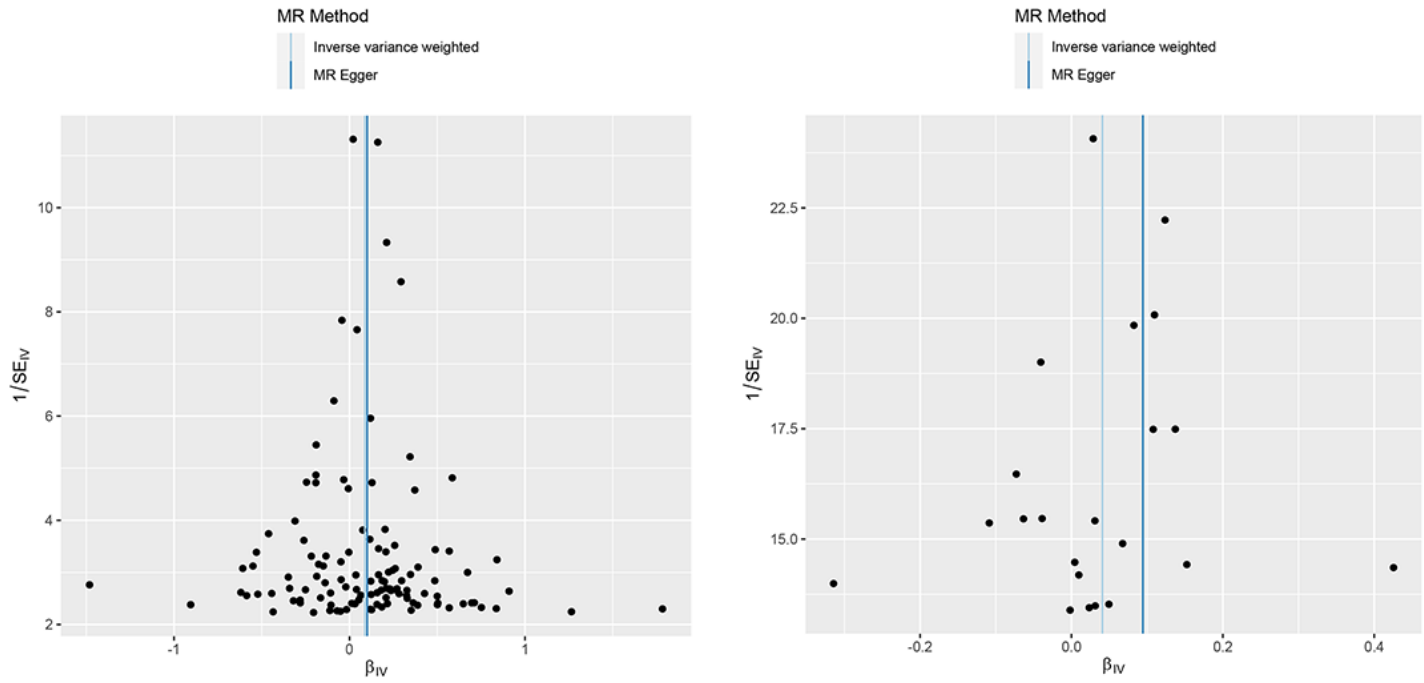

Figure 5

Funnel plots for hypothyroidism on hearing loss (A) and hearing loss on hypothyroidism (B). *β*, the allele effect value of exposure; SE, standard error of *β*; IV, instrumental variable.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryTable.xlsx