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OPEN Associations of hyperthyroidism with epilepsy: a Mendelian randomization study

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Prior studies have revealed an increased susceptibility to epilepsy in hyperthyroid individuals, but the genetic basis of the hyperthyroidism-epilepsy relationship is not fully comprehended, prompting this study to explore this potential association. We conducted a two-sample Mendelian randomization (TSMR) study to explore the relationship between hyperthyroidism and epilepsy by utilizing aggregated statistics from Genome-Wide Association Studies (GWAS). Data for hyperthyroidism were derived from a GWAS encompassing 462,933 participants, while epilepsy data were sourced from the International League Against Epilepsy (ILAE) consortium. Five distinct methods were employed for TSMR analysis, which included the inverse variance weighting method, MR Egger method, weighted median method, simple model, and weighted model. In our sensitivity analysis, we employed the MR Egger and MR PRESSO methods to assess pleiotropy, and inverse variance weighting and MR Egger in Cochran's Q statistics to assess heterogeneity. In the IEU database, utilizing the MR-Egger method, we obtained an odds ratio (OR) of 2.631 (95% CI 0.608, 9.796) with a p-value of 0.122. Meanwhile, employing the Weighted Median method yielded an OR of 1.813 (95% CI 0.786, 4.181) with a p-value of 0.163. The IVW method exhibited an OR of 1.986 (95% CI 1.127, 3.502) with a p-value of 0.018. In the assessment of heterogeneity, the MR-Egger method produced a Q statistic of 65.205, accompanied by a p-value of 0.087, while the IVW method recorded a Q statistic of 66.668 with a p-value of 0.083. The multifactorial analysis results showed an intercept term with a standard error (SE) value of 0.009 and a p-value of 0.291. In the FinnGen database, employing the MR-Egger method for all epilepsy data, we observed an OR of 0.952 (95% CI 0.831, 1.093) with a p-value of 0.539. Simultaneously, the Weighted Median method produced an OR of 0.986 (95% CI 0.953, 1.021) with a p-value of 0.423. The IVW method indicated an OR of 0.992 (95% CI 0.965, 1.019) with a p-value of 0.541. The MR-Egger method's assessment of heterogeneity resulted in a Q statistic of 2.671, associated with a p-value of 0.445, while the IVW method generated a Q statistic of 3.011 with a p-value of 0.556. The multifactorial analysis results displayed an intercept term with a SE-value of 0.019 and a p-value of 0.601. Sensitivity analysis found no evidence of horizontal pleiotropy or heterogeneity. Hyperthyroidism was found to be causally related to all epilepsy but had no effect on other types of epilepsy.

Keywords Hyperthyroidism, Epilepsy, Mendelian randomization, Geno

Epilepsy is a prevalent neurological disorder characterized by sudden abnormal brain discharges¹. It impacts over 70 million people worldwide². This condition leads to substantial economic challenges and a compromised quality of life³.

Hyperthyroidism, or thyrotoxicosis, is a common endocrine disorder with a rising incidence and a tendency for an earlier onset^{4,5}. Thyroid hormones profoundly influence the development and function of the neuromuscular system⁶. Neurological complications are common in individuals with hyperthyroidism, and some present with symptoms like tremors when seeking medical attention. Neurological complications in hyperthyroidism encompass central nervous system (CNS) issues like movement disorders, corticospinal tract damage, epilepsy,

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emotional and cognitive impairments, cerebrovascular diseases, migraines, and sleep disorders, along with peripheral nervous system problems like tremors, myopathy, and peripheral nerve damage. These complications mainly stem from direct stimulatory effects of thyroid hormones, a hypermetabolic state, autoimmune factors, thyroid tissue enlargement, and compression of surrounding nerves by the extraocular muscles⁷. The incidence and severity of these neuromuscular complications may vary, often correlating with hyperthyroidism severity, and typically show marked improvement with antithyroid treatment⁸.

Thyroid disorders often present with reversible neurological manifestations affecting both the central and peripheral nervous systems, including seizures, as evidenced by idiopathic seizure reports in thyrotoxicosis patients⁹. Furthermore, experimental studies involving thyroxine administration in animal models of epilepsy suggest a reduction in seizure threshold, while thyroidectomy appears to confer protection against pharma-cologically induced seizures^{10–12}. Presently, meta-analyses provide insights into the potential effectiveness of thyroidectomy in reducing seizure recurrence¹³. Nevertheless, the precise relationship between thyroid hyper-activity and seizure risk remains enigmatic. The disparity in research findings can be attributed to the inherent complexity of observational studies, characterized by a multitude of confounding factors and potential reverse causality. The limitations of traditional statistical methods exacerbate these intricacies, posing challenges in precisely disentangling latent confounding factors or reverse causal links, thus impeding the establishment of a robust causal framework for the observed associations¹⁴.

Mendelian randomization (MR) appears to be a potential route in the effort to investigate the causal association between hyperthyroidism and epilepsy while overcoming confounding factors^{15–17}. MR mimics the design of randomized controlled trials (RCTs) by utilizing instrumental variables (IVs) obtained from genetic polymorphisms, allowing for a more thorough evaluation of causation¹⁶. The primary aim of this research endeavor is to explore the causal nexus between hyperthyroidism and epilepsy. To undertake this inquiry, we employ twosample Mendelian randomization (TSMR) analysis, leveraging summary-level data derived from Genome-Wide Association Studies (GWAS) to expound upon this intricate interconnection.

Materials and methods

Study design and data sources

This study employs the TSMR approach to investigate the impact of thyroid hyperactivity on epilepsy. Data on genetic variants associated with thyroid hyperactivity as an exposure variable were sourced from the MRC-IEU, encompassing 462,933 individuals of European lineage.

The dataset used for our study on genetic variations linked to epilepsy originates from the IEU OpenGWAS project and draws data from the International League Against Epilepsy Consortium on Complex Epilepsies (ILAE). This comprehensive dataset encompasses a range of epilepsy subtypes, offering valuable insights. It includes the following subtypes: (1) All epilepsy, with a substantial dataset comprising 15,212 cases and 29,677 controls. (2) Hereditary generalized epilepsy, with 3769 cases. (3) Focal epilepsy, a significant subset with 9671 cases. (4) Focal epilepsy with documented lesion absence, consisting of 2716 cases. (5) Juvenile absence epilepsy, represented by 415 cases. (6) Childhood absence epilepsy, providing insights from 793 cases. (7) Focal epilepsy with documented lesions other than hippocampal sclerosis, a subset with 803 cases. (8) Focal epilepsy with documented lesions other than hippocampal sclerosis, offering data from 3070 cases. (9) Generalized epilepsy with tonic–clonic seizures, a smaller subset comprising 228 cases. (10) Juvenile myoclonic epilepsy, with data available from 1181 cases¹⁸. This rich and diverse dataset allows for a comprehensive exploration of genetic factors associated with epilepsy across various subtypes, providing a robust foundation for our research (Fig. 1, Supplementary Table S1).

To assess the robustness of our MR estimations, we further employed an additional GWAS dataset, wherein the source of exposure data emanated from participants in the FinnGen (n = 473,681, European ancestry) (Supplementary Table S13).



Figure 1. Two-sample Mendelian randomization study: (1) Strong correlation between instrumental variables and the exposure factor; (2) Independence of instrumental variables from any potential confounding factors; (3) Lack of direct association between instrumental variables and the outcome.

Instrumental variable (IV) selection

By carefully selecting the genetic variations we've extracted as our instrumental variables, we embark on an endeavor to gauge the causal link between hyperthyroidism and the susceptibility to epilepsy. Our methodology hinges on adhering to three fundamental Mendelian randomization principles: (1) Predictive power We ensure that these genetic variations possess the predictive prowess to foretell the presence of hyperthyroidism, (2) Freedom from confounding We rigorously confirm that these genetic factors remain independent of any potential confounders that could cloud our causal assessment, (3) Pathway integrity We take extra precautions to ascertain that our results remain unaltered by any extraneous pathways unrelated to hyperthyroidism, thereby preserving the integrity of our causal inference framework¹⁹. In the initial phase of our study, we conducted a comprehensive assessment of single nucleotide polymorphisms (SNPs) associated with hyperthyroidism, subjecting them to rigorous scrutiny against a stringent genome-wide significance threshold ($P < 5 \times 10^{-8}$). Subsequently, we exercised prudence by excluding SNPs that demonstrated pronounced linkage disequilibrium (LD) $(r^2 < 0.001, distance < 10,000 \text{ kb})$ to uphold the analytical independence²⁰. Furthermore, to fortify our defenses against potential pleiotropic effects, we diligently explored secondary phenotypic associations for each SNP using PhenoScanner V2²¹. The application of the F-statistic served as a stringent criterion for the exclusion of SNPs exhibiting weak instrumental properties that might compromise the validity of Mendelian Randomization's first assumption; accordingly, only SNPs with instrument strengths (F) exceeding a threshold of 10 were retained for further analysis. Subsequently, the SNPs that remained after the initial screening were amalgamated into the outcomes Genome-Wide Association Study (GWAS) database. Palindromic SNPs characterized by intermediate allele frequencies were systematically excluded, and outlier SNPs were identified and removed through the application of the Mendelian randomization pleiotropy residual and outlier (MR PRESSO) test²⁰. Notably, proxy SNPs were not utilized in this process. Adhering to the aforementioned principles, a final set of multiple independent SNPs, each strongly associated with the respective exposure trait, were meticulously chosen to serve as instrumental variables (IVs).

Statistical analysis

Within this TSMR investigation, we employed a comprehensive suite of methodological approaches, encompassing Inverse Variance Weighting (IVW), Weighted Median (WM), MR Egger regression, Simple Mode, and Weighted Mode techniques, to conduct a rigorous assessment of the potential causal link between hyperthyroidism and epilepsy^{18,20,22}. Our primary analytical framework, predicated upon the Inverse Variance Weighting (IVW) method, amalgamates Wald estimates for individual single nucleotide polymorphisms (SNPs) through a meta-analysis framework, thereby deriving a comprehensive estimation. Subsequently, it facilitates a weighted linear regression, enforcing an intercept set at zero. When executed under the fulfillment of the three fundamental instrumental variable assumptions, this method enhances precision and statistical power, culminating in an overarching estimate of the causal effect²³. To enhance the resilience of our findings and mitigate potential sources of unmeasured confounding and unaccounted interference, we conducted supplementary analyses, employing the MR Egger regression, WM, Simple Mode, and Weighted Mode methodologies. Specifically, the MR Egger regression was utilized to scrutinize the presence of pleiotropy, incorporating an intercept term under the assumption that the strength of instrumental variables bore no correlation with the direct effect, thereby rectifying potential biases stemming from this phenomenon²². Should the intercept term equate to zero, this observation signifies the absence of horizontal pleiotropy. Furthermore, it is noteworthy that the weighted median (WM) method affords consistent estimations of causality, even in scenarios where up to 50% of genetic variants within the gene under consideration exhibit null effects²⁴.

In the evaluation of pleiotropy among instrumental variables (IVs) within the Genome-Wide Association Study (GWAS) dataset pertaining to outcomes, we employed the MR PRESSO approach and calculated the MR Egger intercept²⁰. Within the framework of these GWAS data, pleiotropy was deemed insubstantial when the p-values derived from the pleiotropy test surpassed the threshold of 0.05. To evaluate the heterogeneity of instrumental variables within the outcomes GWAS dataset, we employed the MR Egger method in conjunction with the IVW approach, incorporating Cochran's Q statistics²⁵. Heterogeneity was deemed absent if the P-value from the heterogeneity test exceeded 0.05. Furthermore, we employed scatter plots to examine the individual hypothesized causal effects.

The F-statistic was computed through the following mathematical expression: $F = [R^2(N - 2)]/[1 - R^2]$, wherein R^2 represents the proportion of variance explicated by each instrumental variable, and N signifies the sample size of the Genome-Wide Association Study (GWAS) regarding the linkage between the single nucleotide polymorphism (SNP) and the variable of interest. The determination of R^2 was achieved through the subsequent mathematical formula: $R^2 = 2 \times EAF \times (1 - EAF) \times \beta^2$, where EAF indicates the frequency of the effect allele, and β denotes the estimated effect magnitude on the variable. When the associated F-statistic exceeded P > 10, it indicated the absence of significant weak instrument bias.

Statistical analyses were conducted utilizing R version 4.2.1, as provided by the R Foundation for Statistical Computing. Mendelian Randomization (MR) analyses were executed employing both the two-sample MR (version 0.5.6) and MRPRESSO (version 1.0) methodologies^{18,20,26}.

Results

Results of the analysis of all epilepsy

Following a meticulous and discerning selection process, we judiciously chose a total of 53 SNPs as instrumental variables for inclusion in the study of hyperthyroidism. The results of Mendelian randomization consistently exhibit coherence across a range of analytical methodologies, including the Inverse Variance Weighted (IVW) method, MR-Egger method, Weighted Median (WM) method, Simple Mode method, and Weighted Mode

method. Specifically, IVW results reveal an odds ratio (OR) of 1.986 (95% CI 1.127, 3.502) with a p-value of 0.018, signifying a robust correlation between all epilepsy and hyperthyroidism. It's noteworthy that the Q-value for the IVW heterogeneity test is 66.668 with a p-value of 0.083, while the Q-value for the MR-Egger heterogeneity test is 65.205 with a p-value of 0.087, thus firmly establishing the absence of heterogeneity. Sensitivity analysis demonstrates that, in the context of the one-by-one exclusion approach, no SNPs exert a significant influence on the estimates of causal association. Furthermore, the results of gene pleiotropy analysis indicate an intercept term with a standard error(SE) value of 0.009 and a p-value of 0.291, once again confirming the absence of horizontal pleiotropy (Fig. 2, Supplementary Table S3, Supplementary Fig. 1).

To assess the elasticity of our MR estimates, we followed a rigorous selection process, incorporating five SNPs from the FinnGen database as instrumental variables for hyperthyroidism. Mendelian randomization was conducted on the dataset, once again utilizing the IVW method, MR-Egger method, WM method, Simple Mode method, and Weighted Mode method for analysis. Specifically, IVW results reveal an odds ratio of 0.992 (95% CI 0.965, 1.019) with a p-value of 0.541, indicating the absence of a substantial correlation between all epilepsy and hyperthyroidism. Furthermore, the Q-value for the IVW heterogeneity test is 3.011 with a p-value of 0.556, while the Q-value for the MR-Egger heterogeneity test is 2.671 with a p-value of 0.445, confirming the absence of heterogeneity. Sensitivity analysis demonstrates that, within the context of the one-by-one exclusion method, no SNPs significantly impact the estimates of causal association. Additionally, the results of gene pleiotropy analysis indicate an intercept term with a SE-value of 0.019 and a p-value of 0.601, consistently affirming the absence of horizontal pleiotropy (Fig. 3, Supplementary Table S15, Supplementary Fig. 11).

Lack of correlations between hyperthyroidism and various epilepsy

In the comprehensive Mendelian randomization analysis exploring potential associations between hyperthyroidism and diverse epilepsy subtypes such as focal epilepsy, hereditary generalized epilepsy, focal epilepsy with lesions other than hippocampal sclerosis, focal epilepsy with negative lesions, juvenile myoclonic epilepsy, focal epilepsy with hippocampal sclerosis, childhood absence epilepsy, juvenile absence epilepsy, and generalized epilepsy with tonic-clonic seizures, a prevalent finding emerged: the absence of significant correlations. Regarding

| All galapsy on hyperhypoidsm(EL) M.E.gar biorser vance weights Single rank 3 | Analysis | Method | N SNPs | | OR(95%CI) | P value |
|--|--|---------------------------|--------|---------------------------------------|---|---------|
| MK Egr Signer Automatical and automatical | all epilepsy on hyperthyroidism(IEU) | | | | | |
| Weigher mode 3 - - 11,00,79,41,10 0.01 Mice and the second se | | MR Egger | 53 | | \rightarrow 2.631(0.608,9.796) | 0.122 |
| Interest manage weighed 33 - - 1.08(1,12).303 0.01 Weighted max 33 - - 1.08(1,12).303 0.01 Bead epilepsy on hyperthynodism(EL) MR Egar 30 - - 0.0700.373,1270 0.73 Increase within example and mark withi | | Weighted median | 53 | | \rightarrow 1.813(0.786,4.181) | 0.163 |
| State State <td< td=""><td></td><td>Inverse variance weighted</td><td>53</td><td>· · · · · · · · · · · · · · · · · · ·</td><td>\rightarrow 1.986(1.127,3.502)</td><td>0.018</td></td<> | | Inverse variance weighted | 53 | · · · · · · · · · · · · · · · · · · · | \rightarrow 1.986(1.127,3.502) | 0.018 |
| Eval epileps on hyperhysodiam(IEU) ME gar Weight in mice winther winther winther bergins in the weight of the set unare winther bergins in the set unare weight of the set | | Simple mode | 53 | | \rightarrow 5.921(0.894,39.19) | 0.071 |
| MR Eggr 30 | food anilancy on hyperthyroidiem(IEU) | weighted mode | 55 | | → 1.688(0.382,7.461) | 0.493 |
| weights data 0 | ideal epitepsy on hyperthyroidism(120) | MR Egger | 30 | | $\rightarrow 0.144(0.001.15.86)$ | 0.426 |
| Increase variance vergined 30 | | Weighted median | 30 | · · · · · · · · · · · · · · · · · · · | 0.561(0.277.1.136) | 0.108 |
| Simple node 9 | | Inverse variance weighted | 30 | · · · · · · · · · · · · · · · · · · · | 0.907(0.539,1.527) | 0.714 |
| Weighied mode 30 | | Simple mode | 30 | | 0.391(0.091,1.692) | 0.219 |
| Interditing generalized epileps on hyperhynoidian(IEU) MR Egger 23 | | Weighted mode | 30 | | 0.381(0.094,1.546) | 0.187 |
| ME Eger Weighted median Simple nock 23 4 | hereditary generalized epilepsy on hyperthyroidism(IEU) | | | | | |
| Weight median 23 | | MR Egger | 23 | | → 3.212(0.071,16.94) | 0.191 |
| Inverse variance weighed 23 Single mode 23 Field epilepsy(documented lesion other than hippocampal sclerosis) on hyperthyroidism(IEU) field epilepsy(documented lesion negative) on hyperthyroidism(IEU) ficeal epilepsy(documented lesion negative) on hyperthyroidism(IEU) ME Rgsr 19 Weighted mode 29 ME Rgsr 20 ME Rgsr 20 ME Rgsr 30 ME | | Weighted median | 23 | • | $\rightarrow 0.831(0.248, 2.778)$ | 0.762 |
| Simple mode 23 | | Inverse variance weighted | 23 | | 0.858(0.361,2.041) | 0.731 |
| Weighted mode 23 | | Simple mode | 23 | | \rightarrow 2.731(0.254,29.41) | 0.416 |
| Biol epilepsy(documented lesion other than hippocampal sclerosis) on hyperthyroidism(EU) MR Egger biology (documented lesion negative) on hyperthyroidism(EU) 0 4470(108,2011) 23 biology (documented lesion negative) on hyperthyroidism(EU) 0 4470(108,2011) 24 biology (documented lesion negative) on hyperthyroidism(EU) 0 4470(108,2011) 24 biology (documented lesion negative) on hyperthyroidism(EU) 0 4470(108,2011) 24 biology (documented lesion negative) on hyperthyroidism(EU) 0 470(108,2011) 24 biology (documented hippocampal sclerosis) on hyperthyroidism(EU) 0 470(108,2011) 24 biology (documented hippocampal sclerosis) on hyperthyroidism(EU) 0 480(20,20,20) 44 biology (documented hippocampal sclerosis) on hyperthyroidism(EU) 0 980(20,22,20) 44 biology (do | | Weighted mode | 23 | | \rightarrow 2.618(0.249,27.56) | 0.432 |
| MR Egger 29 | focal epilepsy(documented lesion other than hippocampal sclerosis) on hyperthyroidism(IEU) | | | | | |
| weighted media 29 0.942(0.93/1.81) <td< td=""><td></td><td>MR Egger</td><td>29</td><td></td><td>0.467(0.108,2.011)</td><td>0.315</td></td<> | | MR Egger | 29 | | 0.467(0.108,2.011) | 0.315 |
| interest whatek weighted 29 | | Weighted median | 29 | | 0.922(0.739,1.151) | 0.474 |
| Simple mode 29 0.7400.89,1723 0.23 fical epilepsy(documented lesion negative) on hyperthyroidism(IEU) MR Eggr 34 | | Inverse variance weighted | 29 | | 0.904(0.769,1.063) | 0.223 |
| face of epilepsy (documented lesion negative) on hyperthyroidism(IEU) MR (Eggr Weighted make 1 0.77(0.550, 17(1)) 0.23 il verse variance veighted is user in the second s | | Simple mode | 29 | | 0.774(0.487,1.232) | 0.289 |
| Ideal cpin(sy)(decunication continue) MR Egger 34 3273(0) 53.0, 97.10, 00.25 3273(0) 53.0, 10.10, 00.25 3273(0) 53.0, 10.10, 00.25 3273(0) 53.0, 10.10, 00.25 3273(0) 53.0, 10.10, 00.25 3273(0) 53.0, 10.10, 00.25 3273(0) 53.0, 10.10, 00.25 3273(0) 53.0, 10.10, 00.25 3273(0) 53.0, 10.10, 00.25 3273(0) 53.0, 10.10, 00.25 3273(0) 53.0, 10.10, 00.25 3273(0) 53.0, 10.10, 00.25 3273(0) 53.0, 10.10, 00.25 3274(0) 53.0, 10.10, 00.25 3274(0) 53.0, 10.10, 00.25 3274(0) 53.0, 10.10, 00.25 3274(0) 53.0, 10.10, 00.25 3274(0) 53.0, 10.10, 00.25 3274(0) 53.0, 10.10, 00.25 3274(0) 53.0, 10.10, 00.25 3274(0) 53.0, 10.10, 00.25 3274(0) 53.0, 10.10, 00.25 3274(0) 53.0, 10.10, 00.25 3274(0) 53.0, 10.10, 00.25 3274(0) 53.0, 10.10, 00.25 3274(0) 53.0, 10.10, 00.25 3274(0) 53.0, 10.10, 00.25 <td>focal anilancy(documented lasion pacetive) on hyperthyroidism(IEU)</td> <td>weighted mode</td> <td>29</td> <td></td> <td>0.771(0.505,1.178)</td> <td>0.239</td> | focal anilancy(documented lasion pacetive) on hyperthyroidism(IEU) | weighted mode | 29 | | 0.771(0.505,1.178) | 0.239 |
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| increa versigned 34 | | Weighted median | 34 | | 1.035(0.845.1.266) | 0.742 |
| interest signer ander signer ander signer and | | Inverse variance weighted | 34 | | 1.021(0.881.1.183) | 0.787 |
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| juvenile myoclonic epilepsy on hyperthyroidism(IEU) MR Eggr 29 Inverse variance weighted 29 MR Eggr 32 Weighted median 32 MR Eggr 31 MR Eggr 32 MR Eggr 31 MR Eggr 31 MR Eggr 31 MR Eggr 32 MR Eggr 31 MR Eggr 32 MR Eggr 31 MR Eggr 32 MR Eggr 31 MR Eggr 32 MR Eggr 31 MR Eggr 32 MR Eggr 31 MR Eggr 31 MR Eggr 31 MR Eggr 32 MR Eggr 31 MR Eggr 32 MR Eggr 31 MR Eggr 32 MR Eggr 31 MR Eggr 31 MR Eggr 32 MR Eggr 32 MR Eggr 32 MR Eggr 32 MR Eggr 32 MR Eggr 31 MR Eggr 32 MR Eggr 33 MR | | Weighted mode | 34 | · · · · · · · · · · · · · · · · · · · | 1.051(0.696,1.584) | 0.819 |
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| Inverse variance weighted 29 | | Weighted median | 29 | | 0.981(0.839,1.144) | 0.796 |
| Simple mode 29 1.148(0.824,160) 0.421 Weighted mode 29 1.152(0.837,1,584) 0.393 focal epilepsy(documented hippocampal sclerosis) on hyperthyroidism(IEU) MR Egger 32 0.772(0.351,1687) 0.525 Weighted mode 32 1.014(0.931,1105) 0.743 0.710(0.931,1105) 0.743 Inverse variance weighted 32 1.014(0.931,105) 0.743 0.750(0.931,1105) 0.743 Childhood absence epilepsy on hyperthyroidism(IEU) MR Egger 31 1.29(0.937,0.886,1067) 0.555 Simple mode 31 0.973(0.886,1067) 0.555 0.753(0.886,1067) 0.555 Simple mode 31 0.973(0.886,1067) 0.555 0.555 0.451 0.452 0. | | Inverse variance weighted | 29 | | 0.964(0.861,1.081) | 0.523 |
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| focal epilepsy(documented hippocampal sclerosis) on hyperthyroidism(IEU) MR Eggr 32 0.772(0.351,169) 0.525 Weighted median 32 1.047(0.927,118) 0.461 Inverse variance weighted 32 1.014(0.931,105) 0.732 Simple mode 32 1.014(0.931,105) 0.752 Childhood absence epilepsy on hyperthyroidism(IEU) MR Eggr 31 1.21(0.922,158) 0.573 Weighted median 31 0.90(0.575,1177) 0.471 0.473 Simple mode 31 0.990(0.675,1177) 0.471 Weighted median 31 0.990(0.678,11.57) 0.471 Weighted median 29 0.990(0.678,1.167) 0.551 Simple mode 31 0.990(0.678,1.167) 0.551 Weighted median 29 0.990(0.678,1.162) 0.472 Weighted median 29 0.990(0.678,1.162) 0.452 Weighted median 29 0.910(0.711,1.188) 0.521 Weighted median 29 0.910(0.711,1.188) 0.541 Inverse variance weighted 29 0.910(0.841,1.029) 0.456 Weighted mode <td></td> <td>Weighted mode</td> <td>29</td> <td></td> <td>1.152(0.837,1.584)</td> <td>0.393</td> | | Weighted mode | 29 | | 1.152(0.837,1.584) | 0.393 |
| MR Egger 32 0.772(0.351,1679) 0.561 Weighted median 32 1.047(0.927,118) 0.646 Inverse variance weighted 32 1.014(0.931,169) 0.753 Simple mode 32 1.216(0.933,158) 0.175 Childhood absence epilepsy on hyperthyroidism(IEU) MR Egger 31 1.210(0.922,158) 0.575 Weighted median 31 0.973(0.885,107) 0.555 0.575 0.973(0.885,107) 0.555 Simple mode 31 0.899(0.675,1197) 0.471 0.471 0.899(0.675,1197) 0.471 juvenile absence epilepsy on hyperthyroidism(IEU) MR Egger 29 0.990(0.698,11.58) 0.521 Weighted median 29 0.990(0.698,11.58) 0.524 0.521 0.571 0.571 juvenile absence epilepsy on hyperthyroidism(IEU) MR Egger 29 0.990(0.698,11.58) 0.524 0.591 0.571 | focal epilepsy(documented hippocampal sclerosis) on hyperthyroidism(IEU) | | | | | |
| Weighted median 32 1047(0.927,1181) 0.61 Inverses variance weighted 32 121(0.933,1585) 0.18 Simple mode 32 121(0.922,1589) 0.175 childhood absence epilepsy on hyperthyroidism(IEU) MR Egger 31 129(0.933,1285) 0.575 Weighted mode 32 129(0.924,3223) 0.575 0.576 0.576 0.576 Weighted median 31 109(0.924,3223) 0.575 0.576 0.576 0.575 0.576 0.576 0.576 0.576 0.576 0.575 0.576 0.576 0.575 0.576 0.576 0.575 0.576 0.576 0.575 0.576 0.576 0.576 0.576 0.576 0.575 0.576 0.576 0.576 0.575 0.576 0.576 0.576 0.576 0.576 0.575 0.576 0.576 0.576 0.576 0.575 0.576 0.576 0.576 0.576 0.576 0.576 0.576 0.576 0.576 0.576 0.576 0.576 0.576 0.576 0.576 0.576 0.576 0.576 | | MR Egger | 32 | | 0.772(0.351,1.697) | 0.525 |
| Inverse variance weighted 32 1014(0.931,105) 0.158 Simple mode 32 121(0.922,1589) 0.158 Weighted mode 32 121(0.922,1589) 0.158 Weighted mode 32 129(0.524,3223) 0.577 Weighted median 31 0.963(0.851,1091) 0.551 Inverse variance weighted 31 0.973(0.886,1067) 0.555 Simple mode 31 0.999(0.675,1197) 0.471 juvenile absence epilepsy on hyperthyroidism(IEU) MR Egger 29 0.999(0.678,1158) 0.524 Weighted mode 31 0.999(0.678,1169) 0.524 0.999(0.678,1169) 0.524 generalized epilepsy on hyperthyroidism(IEU) MR Egger 29 0.999(0.678,1169) 0.524 Weighted mode 29 0.999(0.678,1169) 0.524 0.999(0.678,1169) 0.524 generalized epilepsy with tonic-clonic seizures on hyperthyroidism(IEU) MR Egger 29 0.999(0.81,102) 0.544 Mr Egger 29 0.990(0.841,102) 0.561 0.561 0.561 Weighted mode 29 0.990(0.841,102) 0.561 0. | | Weighted median | 32 | ++• | 1.047(0.927,1.181) | 0.461 |
| Simple mode 32 1216(0.933, 1585) 0175 Childhood absence epilepsy on hyperthyroidism(IEU) MR Egger 31 1211(0.922, 1589) 0175 Weighted mode 31 0950(0.851, 1091) 0.553 0.575 | | Inverse variance weighted | 32 | H - | 1.014(0.931,1.105) | 0.743 |
| Weighted mode 32 1,211(0,922,1389) 0,175 Childhood absence epilepsy on hyperthyroidism(IEU) MR Egger 31 1,290(0,524,322) 0,953(0,861,1001) 0,553 Simple mode 31 0,973(0,886,1067) 0,555 0,555 0,993(0,851,159) 0,471 juvenile absence epilepsy on hyperthyroidism(IEU) MR Egger 29 0,991(0,81,158) 0,412 Weighted median 29 0,964(0,874,1062) 0,458 0,964(0,874,1062) 0,458 Inverse variance weighted 29 0,964(0,874,1062) 0,458 0,964(0,874,1062) 0,458 Inverse variance weighted 29 0,964(0,874,1062) 0,458 0,964(0,874,1062) 0,458 generalized epilepsy with tonic-clonic seizures on hyperthyroidism(IEU) MR Egger 29 0,964(0,814,1078) 0,564 Weighted median 29 0,964(0,874,1062) 0,458 0,966(0,839,114) 0,668 Weighted median 29 0,964(0,814,1078) 0,564 0,966(0,839,112) 0,633 Weighted median 29 0,966(0,839,112) 0,633 0,668 0,966(0,839,112) 0,633 Weighted mode <td></td> <td>Simple mode</td> <td>32</td> <td>·</td> <td>1.216(0.933,1.585)</td> <td>0.158</td> | | Simple mode | 32 | · | 1.216(0.933,1.585) | 0.158 |
| MR Egger 31 1,299(0,524,3223) 0,577 Weighted median 31 0,953(0,851,1091) 0,555 Inverse variance weighted 31 0,899(0,675,1197) 0,471 juvenile absence epilepsy on hyperthyroidism(IEU) MR Egger 29 0,899(0,678,1168) 0,415 meterse variance weighted 31 0,899(0,678,1168) 0,415 0,415 juvenile absence epilepsy on hyperthyroidism(IEU) MR Egger 29 0,99(0,617,111,188) 0,524 Weighted mode 29 0,99(0,618,11,062) 0,458 0,99(0,011,11,188) 0,524 Weighted mode 29 0,99(0,011,11,188) 0,524 0,99(0,011,11,188) 0,524 Weighted mode 29 0,99(0,011,11,188) 0,524 0,99(0,011,11,188) 0,524 generalized epilepsy with tonic-clonic seizures on hyperthyroidism(IEU) MR Egger 29 0,99(0,011,141) 0,610 Meighted mode 29 0,99(0,088,1,102) 0,524 0,99(0,088,1,102) 0,524 Meighted mode 29 0,99(0,088,1,102) 0,524 0,99(0,088,1,102) 0,524 Weighted moda 29 0,99(0,0 | | Weighted mode | 32 | | 1.211(0.922,1.589) | 0.179 |
| Mit Rgger 31 | childhood absence epilepsy on hyperthyroidism(IEU) | MD Farme | 21 | | 1 200(0 524 2 222) | 0.577 |
| Weighted median 31 | | Waightad madian | 31 | | \rightarrow 1.299(0.324,3.223) | 0.577 |
| Interst engined 31 0.00000000000000000000000000000000000 | | Inverse variance weighted | 31 | | 0.903(0.831,1.091) | 0.559 |
| Of mode 31 0.00000000000000000000000000000000000 | | Simple mode | 31 | | 0.899(0.675.1.197) | 0.471 |
| ivenile absence epilepsy on hyperthyroidism(IEU) MR Egger 29 Weighted median 29 Mg Egger 20 Mg Egger 20 | | Weighted mode | 31 | | 0.899(0.698.1.158) | 0.415 |
| MR Egger 29 0.919(0.711,1.188) 0.524 Weighted median 29 0.964(0.874,1.052) 0.458 Inverse variance weighted 29 0.964(0.874,1.052) 0.458 Simple mode 29 0.965(0.817,1.141) 0.681 generalized epilepsy with tonic-clonic seizures on hyperthyroidism(IEU) MR Egger 29 0.961(0.841,1098) 0.561 Weighted mode 29 0.961(0.841,1098) 0.561 0.561 Weighted mode 29 0.966(0.839,1.112) 0.324 Weighted median 29 1.121(0.927,1.359) 0.246 Weighted median 29 1.011(0.941,102,002) 0.653 Simple mode 29 1.011(0.941,102,002) 0.653 Simple mode 29 1.011(0.955,1.156) 0.314 Weighted mode 29 1.051(0.955,1.156) 0.314 | iuvenile absence enilensy on hyperthyroidism(IEU) | in eighted mode | 5. | | 0.033(0.030,1.130) | 0.115 |
| Weighted median 29 0.964(0.874,1.062) 0.458 Inverse variance weighted 29 1.004(0.941,1.073) 0.964(0.874,1.062) 0.458 Simple mode 29 0.964(0.874,1.062) 0.458 0.964(0.874,1.062) 0.458 generalized epilepsy with tonic-clonic seizures on hyperthyroidism(IEU) MR Egger 29 0.961(0.841,1.098) 0.561 Weighted median 29 1.123(0.927,1.359) 0.246 Weighted median 29 1.011(0.942,1.062) 0.565 Inverse variance weighted 29 1.011(0.942,1.022) 0.563 Simple mode 29 1.011(0.962,1.026) 0.563 Weighted mode 29 1.011(0.962,1.0126) 0.563 Simple mode 29 1.051(0.955,1.156) 0.314 | juvenne uosenee epinepisj on nyperulytotalsin(120) | MR Egger | 29 | | 0.919(0.711.1.188) | 0.524 |
| Inverse variance weighted 29 1004(0.941,1073) 006(0.917,141) 068(0. | | Weighted median | 29 | | 0.964(0.874,1.062) | 0.458 |
| Simple mode 29 0,965(0,817,1141) 0.681 generalized epilepsy with tonic-clonic seizures on hyperthyroidism(IEU) MR Egger 29 1,123(0,927,1359) 0.246 Weighted mode 29 1,010(0,941,1098) 0.266 0.266 0.266 Weighted mode 29 1,011(0,962,1052) 0.256 0.266 0.266 Simple mode 29 1,011(0,962,1052) 0.655 0.366 0.366 0.366 0.314 Weighted mode 29 1,011(0,952,1152) 0.563 0.314 0.316 0.314 | | Inverse variance weighted | 29 | | 1.004(0.941,1.073) | 0.901 |
| Weighted mode 29 0.561 generalized epilepsy with tonic-clonic seizures on hyperthyroidism(IEU) MR Egger 29 1.123(0.927,1.359) 0.246 Weighted median 29 1.011(0.941,1087) 0.766 1.011(0.941,1087) 0.766 Inverse variance weighted 29 1.011(0.962,1026) 0.653 1.011(0.962,1026) 0.656 Simple mode 29 1.011(0.962,1026) 0.632 0.966(0.839,1.112) 0.633 Weighted mode 29 1.051(0.955,1.156) 0.946 0.946(0.839,1.112) 0.633 Weighted mode 29 1.051(0.955,1.156) 0.514 0.946(0.839,1.112) 0.633 Weighted mode 29 1.051(0.955,1.156) 0.514 0.514 0.514 | | Simple mode | 29 | | 0.965(0.817,1.141) | 0.681 |
| generalized epilepsy with tonic-clonic seizures on hyperthyroidism(IEU) MR Egger 29 1.123(0.927,1.359) 0.246 Weighted median 29 1.011(0.941,1.087) 0.766 Inverse variance weighted 29 1.011(0.942,1.062) 0.655 Simple mode 29 0.966(0.839,1.112) 0.633 Weighted mode 29 1.051(0.955,1.156) 0.314 | | Weighted mode | 29 | | 0.961(0.841,1.098) | 0.561 |
| MR Egger 29 1123(0.927,1359) 0.24 Weighted median 29 1011(0.941,102,00,00,768) 0.768 Inverse variance weighted 29 1011(0.942,102,00,00,768) 0.768 Simple mode 29 0.966(0.839,1.112) 0.633 Weighted mode 29 1051(0.955,1.156) 0.314 | generalized epilepsy with tonic-clonic seizures on hyperthyroidism(IEU) | | | | | |
| Weighted median 29 1.011(0.941,1.087) 0.768 Inverse variance weighted 29 1.011(0.962,1.062) 0.655 Simple mode 29 0.966(0.839,1.112) 0.633 Weighted mode 29 1.051(0.955,1.156) 0.314 | | MR Egger | 29 | · + • · · · | 1.123(0.927,1.359) | 0.246 |
| Inverse variance weighted 29 1.011(0.962,1.062) 0.655 Simple mode 29 0.966(0.839,1.112) 0.633 Weighted mode 29 1.051(0.955,1.156) 0.314 | | Weighted median | 29 | | 1.011(0.941,1.087) | 0.768 |
| Simple mode 29 0.966(0.839.1.12) 0.633 Weighted mode 29 1.051(0.955,1.156) 0.314 | | Inverse variance weighted | 29 | | 1.011(0.962,1.062) | 0.659 |
| Weighted mode 29 1 1 1.051(0.955,1.156) 0.314 0 0.65 1 1.55 1.051(0.955,1.156) 0.314 | | Simple mode | 29 | | 0.966(0.839,1.112) | 0.633 |
| | | Weighted mode | 29 | | 1.051(0.955,1.156) | 0.314 |
| | | | | | | |

0.5

Figure 2. Forest plot of the genetic causal relationship between hyperthyroidism (IEU) and epilepsy. CI confidence interval, N number, OR odds ratios, SNP single-nucleotide polymorphism.

| Add bit Mathod NS PA OR PORTO P Rest 14 prilipsy or hyperhysolametingsy) Waging and and a set of the set of t | | | | | | |
|--|---|---------------------------|--------|--|--------------------|---------|
| | Analysis | Method | N SNPs | | OR(95%CI) | P value |
| hear purpose on byerthyndam (ingen) inger and a set of the set o | all epilepsy on hyperthyroidism(finngen) | | | | | |
| Wighed meak S< S S | | MR Egger | 5 | → | 0.952(0.831,1.093) | 0.539 |
| Inter-structure usplate Second | | Weighted median | 5 | Here I | 0.986(0.953,1.021) | 0.423 |
| A provide a priori post priori p | | Inverse variance weighted | 5 | Hele Contraction of the Contract | 0.992(0.965.1.019) | 0.541 |
| Wight rank Control <thc< td=""><td></td><td>Simple mode</td><td>5</td><td></td><td>0.971(0.922.1.023)</td><td>0.336</td></thc<> | | Simple mode | 5 | | 0.971(0.922.1.023) | 0.336 |
| Beak optiops on hyperhyndim(fingen) Megin of set optiops on hyperhyndim(fingen) Megin of set optiops of set optis | | Weighted mede | 5 | | 0.971(0.922,1.023) | 0.330 |
| | | weighted mode | 5 | | 0.974(0.928,1.021) | 0.333 |
| MB Fight S< S S <ths< td=""><td>focal epilepsy on hyperthyroidism(finngen)</td><td></td><td></td><td></td><td></td><td></td></ths<> | focal epilepsy on hyperthyroidism(finngen) | | | | | |
| Wighed median 5 | | MR Egger | 5 | | 0.942(0.798,1.112) | 0.531 |
| | | Weighted median | 5 | + + | 0.977(0.939,1.015) | 0.234 |
| Single mode S 0.0720 0.071.001 0 | | Inverse variance weighted | 5 | | 0.995(0.964,1.027) | 0.741 |
| Weight op 5 0 <td< td=""><td></td><td>Simple mode</td><td>5</td><td></td><td>0.972(0.915,1.033)</td><td>0.416</td></td<> | | Simple mode | 5 | | 0.972(0.915,1.033) | 0.416 |
| heading generalized epidepo on hyperthyrodian (fingen) ME Egr Hold (100,00,0,1,00) 0.000 ME agr S 100,00,0,0,1,00 0.000 Single mode S 0.000,00,0,0,00 0.000 Single mode S 0.000,00,0,0,0,0 0.000 Single mode S 0.000,00,0,0,0,0 0.000,0,0,0,0 0.000,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0 | | Weighted mode | 5 | | 0.972(0.921.1.024) | 0.345 |
| Including path landing of information of production information ME Eggr information inform | haraditary generalized enilency on hyperthyroidicm(finngen) | | | | | |
| | hereanary generalized epilepsy on hyperallytolation (milligen) | MD Engag | 6 | | 1 110/0 995 1 415) | 0.419 |
| Merginal metal 1000 09.10.09 1000 | | WIK Eggei | 3 | | 1.119(0.885,1.415) | 0.418 |
| Image on the rest winter weighed 5 1007 0% 1.163 0.781 Single make 0 077 08 8.103 0.781 0.791 0.781 <td></td> <td>Weighted median</td> <td>5</td> <td></td> <td>1.015(0.957,1.076)</td> <td>0.627</td> | | Weighted median | 5 | | 1.015(0.957,1.076) | 0.627 |
| Simple mode 0.9710 (88.106) 0.81 Real epileps/documented lesion aber than hispecampal sclerosis) on hyperthysolism(finngen) 0.9710 (88.106) 0.81 Beed epileps/documented lesion aber than hispecampal sclerosis) on hyperthysolism(finngen) 0.9710 (88.106) 0.9710 (88.106) 0.9710 (88.106) 0.9710 (88.106) 0.9710 (88.106) 0.9710 (88.106) 0.9710 (88.106) 0.9710 (88.106) 0.9710 (88.106) 0.9710 (88.106) 0.9710 (88.106) 0.9710 (88.106) 0.9710 (88.106) 0.9710 (88.106) 0.9710 (88.106) 0.9710 (88.106) 0.9710 (88.106) 0.9710 (88.106) 0.9710 (89.106) 0.9710 (89.106) 0.9710 (89.106) 0.9710 (89.106) 0.9710 (89.106) 0.9710 (89.106) 0.9710 (89.106) 0.9710 (89.106) 0.9710 (89.106) 0.9710 (89.106) 0.9710 (89.106) 0.9710 (89.106) 0.9710 (89.106) 0.9700 (89.100) 0.9710 (89.100) 0.9710 (89.100) 0.9710 (89.100) 0.9710 (89.100) 0.9710 (89.100) 0.9710 (89.100) 0.9710 (89.100) 0.9710 (89.100) 0.9710 (89.100) 0.9710 (89.100) 0.9710 (89.100) 0.9710 (89.100) 0.9710 (89.100) 0.9710 (89.100) 0.9710 (89.100) 0.9710 (89.100) 0.9710 (89.100) 0.9710 (89. | | Inverse variance weighted | 5 | | 1.007(0.962,1.055) | 0.761 |
| Real epilepsy (documented lesion of the flam hispecample sterrors) on hyperthynodism(fingen) 0.83 Real epilepsy (documented lesion of the flam hispecample sterrors) on hyperthynodism(fingen) 0.933 Real epilepsy (documented lesion orgative) on hyperthynodism(fingen) 0.933 Mergine starting of the flam organization | | Simple mode | 5 | ⊢ • → | 0.977(0.896,1.066) | 0.634 |
| | | Weighted mode | 5 | · ↓ •→ | 1.032(0.963,1.105) | 0.423 |
| ME Eggr 0 0.98(0.941.10) 0.51 Weighed median 0.99(0.982.100) 0.23 Inverse variance weighed 0.99(0.982.100) 0.23 Simple mode 0.99(0.982.100) 0.23 Weighed mode 0.99(0.982.100) 0.81 Nead epileps/(documented lesion negative) on hyperthyroidism(fingen) 0.99(0.982.100) 0.81 Weighed mode 0.99(0.982.100) 0.81 Simple mode 0.99(0.982.100) 0.81 Weighed median 0.99(0.982.100) 0.81 Simple mode 0.99(0.982.100) 0.81 Weighed mode 0.99(0.982.100) 0.81 Weighed mode 0.99(0.982.100) 0.81 Weighed mode 0.99(0.982.100) 0.81 Weighed median 0.99(0.971.101) | focal epilepsy(documented lesion other than hippocampal sclerosis) on hyperthyroidism(finngen) | | | | | |
| Weighed median 0 0.9930.983.10.03 0.035 Simple mode 0.9930.983.10.03 0.035 Simple mode 0.9930.983.10.03 0.836 Weighed median 0 0.9930.983.10.10 0.836 Simple mode 0 0.9930.983.10.10 0.836 Weighed median 0 0.9930.983.10.10 0.836 Merge version 0 0.9930.983.10.10 0.836 Weighed median 0 0.9930.983.10.10 0.836 Merge version 0 0.9900.983.10.10 0.836 Merge version 0 0.9900.983.10.10 0.836 Merge version 0 0.9900.993.10.10 0.837 Merge version 0 | | MR Egger | 6 | | 0.985(0.943,1.031) | 0.551 |
| المعتدة بعد العنه العن العنه العن العنه العن المع المع المنه العنه ال | | Weighted median | 6 | | 0.993(0.982.1.004) | 0.238 |
| انتجاد المراكبة انت انتجاد المراكبة | | Inverse variance weighted | 6 | | 0.002(0.085.1.002) | 0.155 |
| Simple mode 0 0.0000 (% 1.0.000 % 1.0 | | Cimala made | 6 | 1 | 0.993(0.985,1.002) | 0.133 |
| Weighed mode 0 0.972(0.911, 100) 0.972 Inceal epilepsy(documented lesion negative) on hyperthyroidism(fingen) WE tagger 6 0.994(0.952, 10.9) 0.816 Weighed mode 0 0.972(0.911, 100) 0.872 0.979(0.911, 100) 0.872 Weighed mode 0 0.994(0.982, 10.9) 0.972(0.981, 100 | | Simple mode | 6 | T | 0.993(0.978,1.009) | 0.441 |
| Inceal epilepsy (documented lesion negative) on hyperthyroidsm(fingen) MR Egger 6 0.944(0.952,1.03) 0.69 Weighted media 6 0.944(0.952,1.03) 0.69 Burense variance weighted 6 0.944(0.952,1.03) 0.69 Simple mode 6 0.944(0.952,1.03) 0.69 Weighted mode 6 0.949(0.952,1.03) 0.69 Weighted mode 6 1.030(0.95,1.01) 0.83 Weighted mode 6 0.940(0.97,1.01) 0.43 Simple mode 6 0.940(0.97,1.01) 0.44 Keal epilepsy (documented hippocampal selensis) on hyperthyroidsm(fingen) MR Egger 6 0.940(0.97,1.01) 0.64 Weighted mode 6 0.940(0.97,1.01) 0.63 1.030(0.98,1.01) 0.53 Simple mode 6 0.940(0.97,1.01) 0.64 0.930(0.93,1.01) 0.52 <td></td> <td>Weighted mode</td> <td>6</td> <td>1</td> <td>0.993(0.981,1.007)</td> <td>0.372</td> | | Weighted mode | 6 | 1 | 0.993(0.981,1.007) | 0.372 |
| MR Egger 6 0.940(092,103) 0.86 Weighed median 6 0.940(092,103) 0.69 Inverse variance veighed 6 0.940(092,103) 0.69 juvenile myoclonic epilepsy on hyperthyroidism(finngen) Weighed mode 6 0.940(092,103) 0.69 Weighed median 6 0.940(092,103) 0.69 0.69 Weighed median 6 0.930(095,102) 0.474 Inverse variance veighed 6 0.920(095,101) 0.425 Single mode 6 0.920(095,101) 0.425 Weighed median 6 0.920(095,101) 0.425 Keiger 6 0.920(095,101) 0.425 Weighed median 6 0.920(095,101) 0.425 Keiger 6 0.920(095,101) 0.425 Weighed median 6 0.920(095,100) 0.425 Keiger 6 0.920(095,100) 0.425 Weighed median 6 0.920(095,100) 0.425 Me Egger 6 0.920(095,100) 0.425 Me Weighed median 6 0.920(095,100) <t< td=""><td>focal epilepsy(documented lesion negative) on hyperthyroidism(finngen)</td><td></td><td></td><td></td><td></td><td></td></t<> | focal epilepsy(documented lesion negative) on hyperthyroidism(finngen) | | | | | |
| Weighted mode 6 0.970(096,100) 0.69 Birnerse variance weighted 0.970(096,101) 0.64 Simple mode 6 0.976(097,101) 0.828 juvenie mycelonic epilepsy on hyperthyroidism(fingen) NR Egger 6 0.030(095,100) 0.828 Keighted mode 6 0.030(095,101) 0.828 0.030(095,101) 0.828 Simple mode 6 0.030(095,101) 0.744 0.970(095,101) 0.744 Neighted mode 6 0.920(075,101) 0.744 0.920(075,101) 0.744 Simple mode 6 0.920(075,101) 0.744 0.920(075,101) 0.744 Keighted mode 6 0.920(075,101) 0.744 0.920(075,101) 0.744 Meegited mode 6 1.020(096,101) 0.745 0.920(075,101) 0.749 Inverse variance weighted 6 1.020(096,101) 0.762 0.930(097,109) 0.740 Simple mode 6 0.930(097,109) 0.740 0.710(01) 0.750 Keighted mode 0.930(0 | | MR Egger | 6 | | 0.994(0.952,1.039) | 0.816 |
| Inverse variance weighted 6 0.9940 985,1003 0.104 Weighted mode 0.9940 995,1013 0.054 juvenile mycelonic epikepsy on hyperthyroidism(finngen) Weighted notion 0.0054 0.005400 0.00540 <t< td=""><td></td><td>Weighted median</td><td>6</td><td>+</td><td>0.997(0.986,1.009)</td><td>0.609</td></t<> | | Weighted median | 6 | + | 0.997(0.986,1.009) | 0.609 |
| Simple node 6 0.966(079,101,0) 0.074 juvenile myoclonic epilepsy on hyperthyroidism(fingen) 0.828 MK Eggr 6 0.930(0.951,002,0) 0.474 Invene vrainne/ weighted 6 0.909(0.951,012,0,0) 0.474 Invene vrainne/ weighted 6 0.909(0.951,012,0,0) 0.474 Invene vrainne/ weighted 6 0.909(0.971,010,0,0) 0.474 Invene vrainne/ weighted 6 0.909(0.971,010,0,0) 0.474 Invene vrainne/ weighted 6 0.999(0.971,010,0,0) 0.473 Invene vrainne/ weighted 6 0.999(0.971,010,0,0) 0.473 Invene vrainne/ weighted 6 0.999(0.991,100,0,0) 0.473 Invene vrainne/ weighted 6 0.999(0.991,00,0,0,0) 0.473 | | Inverse variance weighted | 6 | | 0.994(0.985,1.003) | 0.169 |
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| ivenile myockonie epilepsy on hyperthyroidism(finngen) | | Weighted mode | 6 | 1 | 0.998(0.986.1.011) | 0.828 |
| MR Egger 6 1033(1001,1066) 0.115 Weighted median 6 1003(0995,102) 0.74 Simple mode 0.0992(0975,101) 0.195 Weighted median 6 1003(0995,102) 0.74 Simple mode 0.0992(0975,101) 0.195 focal epilepsy(documented hippocampal sclerosis) on hyperthyroidism(fingen) Weighted median 6 1003(0996,1009) 0.431 Simple mode 0.0992(0975,101) 0.293 1003(0996,1009) 0.431 Simple mode 0.0992(0975,101) 0.293 1003(0996,1009) 0.431 Simple mode 0.0092(0973,101) 0.651 1002(0993,101) 0.651 Weighted median 6 1002(0993,101) 0.651 1002(0993,101) 0.651 Childhood absence epilepsy on hyperthyroidism(fingen) Weighted median 6 0.0992(0975,100) 0.62 Weighted median 6 0.0992(093,100) 0.651 0.0992(093,100) 0.557 Increas variance weighted 6 0.0992(093,100) 0.557 0.0992(093,100) 0.557 <t< td=""><td>iuvanile myzalonia anilanzy an hyperthyraidizm/finngan)</td><td>in eighted mode</td><td>0</td><td></td><td>0.550(0.500,1.011)</td><td>0.040</td></t<> | iuvanile myzalonia anilanzy an hyperthyraidizm/finngan) | in eighted mode | 0 | | 0.550(0.500,1.011) | 0.040 |
| Of the tigged 0 1.035 (1001, 1008) 0.191 Weighted median 0 1.000 (0993, 102) 0.744 Inverse variance weighted 0.992 (097, 1011) 0.429 Weighted median 0 0.992 (097, 1011) 0.429 Weighted median 0 0.992 (097, 1011) 0.429 Keral epilepsy (documented hippocampal sclerosis) on hyperthyroidism(fingen) 0.661 1.000 (099, 1001) 0.661 Weighted median 6 0.994 (097, 1019) 0.661 0.994 (097, 1019) 0.661 Inverse variance weighted 0.1000 (099, 1001) 0.632 0.994 (097, 1019) 0.661 Weighted median 6 0.1000 (099, 1010) 0.562 0.994 (097, 1019) 0.661 Simple mode 0.994 (097, 1019) 0.661 0.0994 (091, 1003) 0.567 Childhood absence epilepsy on hyperthyroidism(fingen) Weighted median 6 0.994 (097, 1019) 0.622 Weighted median 6 0.994 (098, 1003) 0.567 0.994 (098, 1003) 0.567 Jinvenie absence epilepsy on hyperthyroidism(fingen) Weighted median 6 0.994 (098, 1003) 0.567 Jin | juvenne myöciönic epitepsy on nypermytotaisin(ningen) | MD Farmer | 6 | | 1.022/1.001.1.0(() | 0.115 |
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| Image: A simple mode 6 1.001(0.93, 10.09) 0.764 Simple mode 6 0.920(.975, 10.10 0.429 Image: A simple mode 6 0.920(.975, 10.0 0.429 Image: A simple mode 6 0.940(.971, 10.19) 0.661 Weighted mode 6 0.940(.971, 10.19) 0.661 Image: A simple mode 6 0.902(.975, 10.00) 0.293 Simple mode 6 0.030(.998, 10.00) 0.203 Image: A simple mode 6 0.030(.998, 10.00) 0.203 Image: A simple mode 6 0.902(.975, 10.00) 0.203 Image: A simple mode 6 0.902(.903, 10.11) 0.653 Image: A simple mode 6 0.902(.903, 10.11) 0.653 Image: A simple mode 6 0.994(.903, 10.01) 0.567 Image: A simple mode 6 0.994(.903, 10.05) 0.567 Image: A simple mode 6 0.994(.903, 10.02) 0.250 Image: A simple mode 6 0.994(.908, 10.02) 0.250 Image: A simple mode 6 0.994(.993, 10.02) 0.251 Image: A si | | Weighted median | 6 | T T | 1.003(0.995,1.012) | 0.474 |
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| MR Egger 6 0.994(0.971, 1019) 0.661 Weighted median 6 1.002(0.994, 1009) 0.861 Simple mode 6 1.002(0.994, 1011) 0.653 Simple mode 6 1.002(0.994, 1011) 0.656 childhood absence epilepsy on hyperthyroidism(finngen) MR Egger 6 0.982(0.971, 1009) 0.626 Weighted mode 6 0.982(0.957, 1009) 0.262 Weighted mode 0.999(0.991, 1005) 0.570 Simple mode 6 0.999(0.991, 1005) 0.570 Inverse variance weighted 6 0.999(0.991, 1005) 0.570 Simple mode 6 0.999(0.991, 1005) 0.570 Simple mode 6 0.999(0.991, 1005) 0.570 Simple mode 6 0.999(0.991, 1004) 0.366 Simple mode 6 0.999(0.991, 1004) 0.366 Simple mode 6 0.997(0.992, 1004) 0.366 Simple mode 6 0.997(0.992, 1004) 0.366 Simple mode 6 0.997(0.992, 1003) 0.311 Inverse variance weighted 6 | focal epilepsy(documented hippocampal sclerosis) on hyperthyroidism(finngen) | | | | | |
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| $ \begin{array}{c c c c c c c c c c c c c c c c c c c $ | | Inverse verience weighted | 6 | | 1.002(0.008.1.009) | 0.282 |
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| Weighted mode 6 1002(0994,101) 0.52 childhood absence epilepsy on hyperthyroidism(finngen) MR Egger 6 0.982(0.957,1009) 0.262 Weighted median 6 0.998(0.991,1005) 0.709 Inverse variance weighted 6 0.999(0.993,1005) 0.709 Simple mode 6 0.999(0.993,1005) 0.709 Simple mode 6 0.999(0.993,1005) 0.709 juvenile absence epilepsy on hyperthyroidism(finngen) MR Egger 6 0.992(0.931,002) 0.154 Weighted modian 6 0.997(0.992,1003) 0.154 Weighted median 6 0.999(0.991,100) 0.55 generalized epilepsy with tonic-clonic seizures on hyperthyroidism(finngen) 1001(0.991,1009) 0.883 generalized epilepsy with tonic-clonic seizures on hyperthyroidism(finngen) MR Egger 6 1001(0.991,1009) 0.883 Inverse variance weighted 6 1001(0.991,1009) 0.893 1001(0.991,1003) 0.897 Weighted median 6 1001(0.991,1003) 0.897 1.001(0.991,1003) 0.893 <td></td> <td>Simple mode</td> <td>6</td> <td>T</td> <td>1.002(0.993,1.011)</td> <td>0.055</td> | | Simple mode | 6 | T | 1.002(0.993,1.011) | 0.055 |
| childhood absence epilepsy on hyperthyroidism(finngen) MR Egger 6 0.982(0.957, 100) 0.262 Weighted median 6 0.998(0.991, 1005) 0.567 Inverse variance weighted 6 0.999(0.992, 1005) 0.709 Simple mode 6 0.999(0.992, 1005) 0.709 juvenile absence epilepsy on hyperthyroidism(finngen) MR Egger 6 0.994(0.985, 1004) 0.366 Weighted median 6 0.994(0.985, 1004) 0.361 Inverse variance weighted 6 0.994(0.985, 1004) 0.51 Weighted median 6 0.994(0.992, 1003) 0.311 Inverse variance weighted 6 0.999(0.991, 1003) 0.859 generalized epilepsy with tonic-clonic seizures on hyperthyroidism(finngen) Weighted median 6 0.099(0.991, 1008) 0.859 MR Egger 6 1001(0.991, 1009) 0.953 1001(0.991, 1008) 0.859 Weighted median 6 1001(0.991, 1008) 0.951 1001(0.991, 1008) 0.951 generalized epilepsy with tonic-clonic seizures on hyperthyroidism(finngen) MR Egger 6 1001(0.991, 1008) 0.952 Weighte | | Weighted mode | 6 | T | 1.002(0.994,1.011) | 0.626 |
| MR Egger 6 0982(0957,1009) 0.25 Weighted median 6 0.998(0991,1005) 0.57 Inverse variance weighted 6 0.999(0991,1005) 0.709 Simple mode 6 0.999(0991,1005) 0.295 Weighted mediane 0.994(0.994,1005) 0.295 juvenile absence epilepsy on hyperthyroidism(finngen) 0.994(0.985,1004) 0.306 MR Egger 6 0.994(0.985,1002) 0.311 Inverse variance weighted 6 0.994(0.992,1003) 0.311 Inverse variance weighted mode 6 0.996(0.992,1003) 0.889 generalized epilepsy with tonic-clonic seizures on hyperthyroidism(finngen) MR Egger 6 0.999(0.991,1008) 0.889 Weighted mediane 6 0.999(0.991,1003) 0.891 0.983 generalized epilepsy with tonic-clonic seizures on hyperthyroidism(finngen) MR Egger 6 1.001(0.991,1003) 0.892 Weighted mediane 6 0.990(0.991,1003) 0.897 0.907 0.907 0.907 Weighted mediane 6 0.901(0.995,1003) 0.897 1.001(0.997,1003) 0.897 0.901 | childhood absence epilepsy on hyperthyroidism(finngen) | | | | | |
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| Inverse variance weighted 6 0.999(0.993,1.005) 0.709 Simple node 6 0.993(0.982,1.005) 0.295 juvenile absence epilepsy on hyperthyroidism(finngen) 7 7 MR Egger 6 0.992(0.963,1.002) 0.131 Weighted mode 6 0.992(0.963,1.002) 0.131 Inverse variance weighted 6 0.999(0.992,1.001) 0.66 Simple node 6 0.999(0.992,1.001) 0.66 Simple node 6 0.999(0.992,1.001) 0.66 Simple node 6 0.999(0.992,1.001) 0.96 Weighted medin 6 0.999(0.992,1.001) 0.96 Weighted medin 6 0.999(0.991,1.003) 0.879 Inverse variance weighted 6 1.001(0.991,1.009) 0.981 Inverse variance weighted 6 1.001(0.991,1.003) 0.891 Inverse variance weighted 6 1.001(0.991,1.003) 0.891 Inverse variance weighted 6 1.001(0.991,1.003) 0.891 Inverse variance weighted 6 0.990(0.991,0.003) 0.891 Inverse variance weighted | | Weighted median | 6 | • | 0.998(0.991,1.005) | 0.567 |
| Simple mode 6 0.993(0.982,1005) 0.295 Weighted mode 6 0.993(0.982,1005) 0.295 juvenile absence epilepsy on hyperthyroidism(finngen) MR Egger 6 0.997(0.992,1003) 0.154 Weighted median 6 0.997(0.992,1003) 0.154 Inverse variance weighted 6 0.999(0.992,1003) 0.311 Inverse variance weighted 6 0.999(0.992,1003) 0.859 generalized epilepsy with tonic-clonic seizures on hyperthyroidism(finngen) MR Egger 6 0.999(0.991,1008) 0.859 Weighted mode 6 1.001(0.991,1009) 0.953 1.001(0.991,1003) 0.859 MR Egger 6 1.001(0.991,1003) 0.859 1.001(0.991,1003) 0.859 Inverse variance weighted 6 1.001(0.991,1003) 0.859 1.001(0.991,1003) 0.897 Simple mode 6 1.001(0.991,1003) 0.897 1.001(0.991,1003) 0.897 Generalized epilepsy with tonic-clonic seizures on hyperthyroidism(finngen) MR Egger 6 1.001(0.991,1003) 0.897 Mrester variance weighted 6 1.001(0.991,1003) 0.897 | | Inverse variance weighted | 6 | • | 0.999(0.993,1.005) | 0.709 |
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Figure 3. Forest plot of the genetic causal relationship between hyperthyroidism (FinnGen) and epilepsy. *CI* confidence interval, *N* number, *OR* odds ratios, *SNP* single-nucleotide polymorphism.

focal epilepsy, whether with lesions other than hippocampal sclerosis or negative lesions, the findings revealed no significant associations with hyperthyroidism. Likewise, hereditary generalized epilepsy, juvenile myoclonic epilepsy, childhood absence epilepsy, juvenile absence epilepsy, and generalized epilepsy with tonic–clonic seizures demonstrated no significant correlations with hyperthyroidism. The robustness of these findings was established through the application of diverse analytical methods, such as the IVW method, MR-Egger method, WM method, Simple Mode method, and Weighted Mode method. Heterogeneity tests consistently indicated the absence of significant heterogeneity among instrumental variables, and sensitivity analyses, which systematically excluded SNPs, did not alter the non-significant associations. Gene pleiotropy analyses consistently revealed the absence of horizontal pleiotropy, underscoring the reliability of the results. For additional validation, an independent dataset from the FinnGen project was integrated, and the analysis confirmed the absence of significant associations between hyperthyroidism and each epilepsy subtype.

Discussion

Jabbari and Huott reported a 9% incidence of seizures among all admissions for thyrotoxicosis. Moreover, thyrotoxicosis was identified as the primary cause of initial seizures in 1.2% of thyrotoxicosis patients admitted²⁷. These findings underscore the relatively common occurrence of seizures in individuals with hyperthyroidism. Nevertheless, our understanding of the intricate mechanisms through which thyroid hormones influence brain excitability remains limited. The impact of elevated thyroid hormones on sodium–potassium adenosine triphosphatase activity, leading to significant alterations in neuronal sodium concentrations, has been acknowledged²⁸. However, a comprehensive grasp of the nuanced mechanisms through which thyroid hormones modulate brain excitability remains elusive. Notably, thyrotropin-releasing hormone (TRH) has emerged as a potential therapeutic target for managing seizures in thyrotoxicosis. Experimental evidence has shown that direct hippocampal infusion of TRH produces anticonvulsant effects in amygdale-kindled rats, as evidenced by reductions in after discharge activity and seizure duration²⁹. Further exploration of TRH's role in seizure management within the context of thyrotoxicosis merits ongoing investigation.

The comprehensive etiology of epilepsy remains enigmatic; however, the roles of mitochondrial dysfunction, oxidative stress, and GABAergic system dysregulation in its progression are evident. These factors are pivotal determinants contributing to this condition. Despite the blood-brain barrier curtailing the ingress of thyroid hormones into the central nervous system, with their concentrations therein maintaining a lower equilibrium compared to serum levels, recent research has unveiled the indispensable roles of thyroid hormones in various physiological realms of the central nervous system. These functions encompass the development of the central nervous system, the sustenance of normal cerebral function, and the intricacies of reparative mechanisms. Molecular evidence substantiates the active involvement of thyroid hormones in the orchestration of normative mitochondrial biogenesis. Their deficiency is intrinsically linked to mitochondrial dysfunction and oxidative stress, both of which are held in high regard as contributory factors in the pathogenesis of epilepsy. A critical interplay between thyroid hormones and the development and function of GABAergic neurons is noteworthy. It is imperative to underscore that the unimpeded functionality of thyroid hormones is the sine qua non for the proper execution of these neurons' functions³⁰.

In contrast to prior correlation analyses based on cross-sectional studies or limited sample data, the advent of public databases has provided us with the opportunity to employ Mendelian randomization on a large scale, enabling a comprehensive examination of the causal relationship between hyperthyroidism and all forms of epilepsy. The results robustly support a causal connection between hyperthyroidism and an increased risk of various epilepsy types. This study represents the first comprehensive investigation into the association between these two conditions, shedding light on the nature and extent of their respective relationships with distinct epilepsy categories. It serves as the foundation for a more profound and precise comprehension of the interplay between these two conditions.

Mendelian randomization, a method grounded in genetic variations as instrumental variables, effectively mitigates potential confounding factors and the impacts of reverse causality. It relies on three fundamental assumptions: a robust correlation between instrumental variables and exposure, the independence of instrumental variables from the outcome, and the unrelatedness of instrumental variables to confounding factors. Consequently, this approach finds widespread application in diverse studies of disease exposure and outcomes, facilitating a more precise analysis and enhanced understanding of disease relationships³¹.

Nevertheless, this study has certain limitations: (1) Mendelian randomization assumes a linear relationship between hyperthyroidism and epilepsy. If such a linear relationship does not exist, this method may not be applicable. (2) Mendelian randomization does not delve into the biological mechanisms underlying the association between hyperthyroidism and epilepsy. (3) Insufficient data, including age and gender, are available, which hinders in-depth analysis.

The present study is not without limitations. Firstly, in the Mendelian randomization (MR) analysis of the relationship between hyperthyroidism and epilepsy, the sample size is insufficient, resulting in lower statistical power. Although no anomalies were detected in other sensitivity analyses, this limitation compromises the robustness of the results, necessitating future investigations in larger databases and clinical studies to elucidate their relationship. Secondly, all participants in the Genome-Wide Association Studies (GWAS) datasets are of European descent, raising questions about the generalizability of the results to other populations, warranting further research. Thirdly, thyroid dysfunction is significantly influenced by gender, with the incidence in females being 8 to 9 times that in males³². However, the twin-sample design employed in this study did not stratify by gender and age, precluding an analysis of the relationship between hyperthyroidism and epilepsy across different genders and age groups. Lastly, although the GWAS data used in this study pertain to hyperthyroidism (congenital or acquired), a detailed stratification analysis for congenital and acquired hyperthyroidism was not conducted, demanding further comprehensive research to validate our findings.

Conclusions

This study found evidence for a possible link between hyperthyroidism and an increased risk of epilepsy.

Data availability

The data originates from the IEU OpenGWAS Project (specific URL detailed in Supplementary Table S1) and the Finn Gen database (specific URL detailed in Supplementary Table S13); for further inquiries, please contact the corresponding author.

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References

- 1. Fisher, R. S. *et al.* Epileptic seizures and epilepsy: Definitions proposed by the International League against epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). *Epilepsia* **46**, 470–472. https://doi.org/10.1111/j.0013-9580.2005.66104.x (2005).
- Thijs, R. D., Surges, R., O'Brien, T. J. & Sander, J. W. Epilepsy in adults. Lancet 393, 689–701. https://doi.org/10.1016/s0140-6736(18) 32596-0 (2019).
- de Boer, H. M., Mula, M. & Sander, J. W. The global burden and stigma of epilepsy. *Epilepsy Behav.* 12, 540–546. https://doi.org/ 10.1016/j.yebeh.2007.12.019 (2008).
- Scappaticcio, L., Maiorino, M. I., Maio, A., Esposito, K. & Bellastella, G. Neutropenia in patients with hyperthyroidism: Systematic review and meta-analysis. *Clin. Endocrinol.* 94, 473–483. https://doi.org/10.1111/cen.14313 (2021).
- 5. Scappaticcio, L. *et al.* Abnormal liver blood tests in patients with hyperthyroidism: Systematic review and meta-analysis. *Thyroid* **31**, 884–894. https://doi.org/10.1089/thy.2020.0715 (2021).
- 6. Lee, S. Y. & Pearce, E. N. Hyperthyroidism: A review. JAMA 330, 1472-1483. https://doi.org/10.1001/jama.2023.19052 (2023).

- 7. Ylli, D., Klubo-Gwiezdzinska, J. & Wartofsky, L. Thyroid emergencies. Polish Arch. Intern. Med. 129, 526-534. https://doi.org/10. 20452/pamw.14876 (2019).
- Sawicka-Gutaj, N., Zawalna, N., Gut, P. & Ruchała, M. Relationship between thyroid hormones and central nervous system metabolism in physiological and pathological conditions. Pharmacol. Rep. 74, 847-858. https://doi.org/10.1007/s43440-022-00377-w (2022).
- 9. Tonner, D. R. & Schlechte, J. A. Neurologic complications of thyroid and parathyroid disease. Med. Clin. N. Am. 77, 251-263. https://doi.org/10.1016/s0025-7125(16)30282-6 (1993).
- 10. Bakke, J. L., Lawrence, N. & Campbell, G. The effect of metronidazole on the synthesis of thyroid stimulating hormone in the hypothyroid rat. Metab. Clin. Exp. 14, 647-651. https://doi.org/10.1016/s0026-0495(65)80028-2 (1965).
- 11. Domino, E. F. & Minz, B. Influence of thyroidectomy and thyroid hormones on electrically induced seizures in rabbits. Arch. Int. Pharmacodyn. Ther. 94, 225-234 (1953).
- 12. Taubøll, E., Lindström, S., Stokke, K. T. & Gjerstad, L. Triiodothyronine and brain excitability. Epilepsia 31, 713-717. https://doi. org/10.1111/j.1528-1157.1990.tb05511.x (1990)
- 13. Song, T. J., Kim, S. J., Kim, G. S., Choi, Y. C. & Kim, W. J. The prevalence of thyrotoxicosis-related seizures. Thyroid 20, 955-958. https://doi.org/10.1089/thy.2009.0276 (2010).
- 14. Carreras-Torres, R. et al. Role of obesity in smoking behaviour: Mendelian randomisation study in UK Biobank. BMJ 361, k1767. https://doi.org/10.1136/bmj.k1767 (2018).
- 15. Davey Smith, G. & Hemani, G. Mendelian randomization: Genetic anchors for causal inference in epidemiological studies. Hum. Mol. Genet. 23, R89-R98. https://doi.org/10.1093/hmg/ddu328 (2014).
- 16. Smith, G. D. & Ebrahim, S. 'Mendelian randomization': Can genetic epidemiology contribute to understanding environmental determinants of disease? Int. J. Epidemiol. 32, 1-22. https://doi.org/10.1093/ije/dyg070 (2003)
- 17. Katan, M. B. Commentary: Mendelian randomization, 18 years on. Int. J. Epidemiol. 33, 10-11. https://doi.org/10.1093/ije/dyh023 (2004).
- 18. Luo, X., Ruan, Z. & Liu, L. The causal effect of serum 25-hydroxyvitamin D levels on epilepsy: A two-sample Mendelian randomization study. Epilepsia Open 8, 912-917. https://doi.org/10.1002/epi4.12758 (2023).
- 19. Larsson, S. C. Mendelian randomization as a tool for causal inference in human nutrition and metabolism. Curr. Opin. Lipidol. 32, 1-8. https://doi.org/10.1097/mol.000000000000721 (2021).
- 20. Verbanck, M., Chen, C. Y., Neale, B. & Do, R. Detection of widespread horizontal pleiotropy in causal relationships inferred from Mendelian randomization between complex traits and diseases. Nat. Genet. 50, 693-698. https://doi.org/10.1038/s41588-018-0099-7 (2018).
- 21. Kamat, M. A. et al. PhenoScanner V2: An expanded tool for searching human genotype-phenotype associations. Bioinformatics 35, 4851-4853. https://doi.org/10.1093/bioinformatics/btz469 (2019).
- 22. Bowden, J., Davey Smith, G. & Burgess, S. Mendelian randomization with invalid instruments: Effect estimation and bias detection through Egger regression. Int. J. Epidemiol. 44, 512-525. https://doi.org/10.1093/ije/dyv080 (2015).
- 23. Burgess, S., Butterworth, A. & Thompson, S. G. Mendelian randomization analysis with multiple genetic variants using summarized data. Genet. Epidemiol. 37, 658-665. https://doi.org/10.1002/gepi.21758 (2013).
- 24. Zhu, Z. et al. Causal associations between risk factors and common diseases inferred from GWAS summary data. Nat. Commun. 9, 224. https://doi.org/10.1038/s41467-017-02317-2 (2018).
- 25. Greco, M. F., Minelli, C., Sheehan, N. A. & Thompson, J. R. Detecting pleiotropy in Mendelian randomisation studies with summary data and a continuous outcome. Stat. Med. 34, 2926-2940. https://doi.org/10.1002/sim.6522 (2015)
- 26. Hemani, G., Tilling, K. & Davey Smith, G. Orienting the causal relationship between imprecisely measured traits using GWAS summary data. *PLoS Genet.* **13**, e1007081. https://doi.org/10.1371/journal.pgen.1007081 (2017). 27. Jabbari, B. & Huott, A. D. Seizures in thyrotoxicosis. *Epilepsia* **21**, 91–96. https://doi.org/10.1111/j.1528-1157.1980.tb04048.x
- (1980).
- 28. Hoffmann, G. & Dietzel, I. D. Thyroid hormone regulates excitability in central neurons from postnatal rats. Neuroscience 125, 369-379. https://doi.org/10.1016/j.neuroscience.2004.01.047 (2004).
- 29. Wan, R. Q., Noguera, E. C. & Weiss, S. R. Anticonvulsant effects of intra-hippocampal injection of TRH in amygdala kindled rats. Neuroreport 9, 677-682. https://doi.org/10.1097/00001756-199803090-00021 (1998).
- 30. Tamijani, S. M. et al. Thyroid hormones: Possible roles in epilepsy pathology. Seizure 31, 155-164. https://doi.org/10.1016/j.seizu re.2015.07.021 (2015).
- 31. Yuan, S. & Larsson, S. C. Assessing causal associations of obesity and diabetes with kidney stones using Mendelian randomization analysis. Mol. Genet. Metab. 134, 212-215. https://doi.org/10.1016/j.ymgme.2021.08.010 (2021).
- Chiovato, L., Magri, F. & Carlé, A. Hypothyroidism in context: Where we've been and where we're going. Adv. Ther. 36, 47-58. https://doi.org/10.1007/s12325-019-01080-8 (2019).

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Author contributions

L.D. conceived, initiated, and supervised the project. J.L. wrote a draft of the manuscript. H.Y., Q.W., J.Z., C.Y., and J.C. collected and analyzed the data. The authors read and approved the final manuscript.

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Competing interests

The authors declare no competing interests.

Additional information

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