Research Square

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Exploring the genetic link between hypothyroidism and osteoporosis in patients without cancer: a two-sample Mendelian randomization analysis

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Abstract

Background:

Osteoporosis (OP) is a global health issue. Essential for the metabolism of bone, thyroid function plays a crucial role. The connection between hypothyroidism and OP in individuals without cancer remains ambiguous. The aim of this study was to investigate the impact of hypothyroidism on the onset of OP in patients who did not have cancer.

Methods:

The exposures of individuals with non-cancer hypothyroidism were obtained from the publicly accessible MRC-IEU consortium of the UK Biobank, while the outcomes were derived from the GWAS of patients with OP included in the European Bioinformatics Institute (EBI) biobank. Furthermore, a two-sample Mendelian randomization (MR) method was employed to investigate the causal relationship between hypothyroidism and OP among non-cancer patients. This analysis identified single nucleotide polymorphisms (SNPs) that were closely associated with hypothyroidism in this population, which were then used as instrumental variables. Statistical analyses were conducted using four distinct approaches: inverse variance weighted (IVW), weighted median, MR Egger regression, and the weighted mode method.

Results:

We identified a total of 119 SNPs that exhibited strong associations with hypothyroidism in non-cancer patients ($P < 5 \times 10^{-8}$; $LDr^2 < 0.001$). The consistent association between hypothyroidism and OP in non-cancer patients was demonstrated through various analyses: IVW yielded an odds ratio (OR) of 1.017 with a 95% confidence interval (CI) of 1.003-1.031; MR-Egger regression produced an OR of 1.018 with a 95% CI of 0.989-1.049; the weighted median estimate indicated an OR of 1.021 with a 95% CI of 1.001-1.041; and the weighted mode analysis showed an OR of 1.039 with a 95% CI of 1.003-1.076. These findings suggest that hypothyroidism is associated with the development of OP in this population. Additionally, there was no evidence of horizontal pleiotropy affecting the relationship between hypothyroidism and OP among non-cancer patients, as indicated by an MR-Egger intercept of -5.9×10^{-6} ($P = 0.932$).

Conclusion:

The findings from the MR analysis indicate a potential causal relationship between hypothyroidism and the occurrence of OP in non-cancer patients.

Introduction

OP is recognized as the most prevalent metabolic bone disorder and has become a significant health concern worldwide. According to the World Health Organization, OP is defined by BMD at any skeletal

site that is 2.5 or more standard deviations (SD) below the peak BMD observed in young adults [1].Although there are preventive and therapeutic strategies in place for OP, its prevalence and the associated disease burden continue to escalate worldwide, particularly influenced by the growing aging population. The emergence and progression of osteoporotic conditions (OP) are closely linked to various metabolic and endocrine disorders [2], including diabetes [3], Cushing's syndrome [4], and thyroid dysfunction [5]. Thyroid hormones are crucial for the growth, development, and remodeling of bones [6], playing an essential role in maintaining the structural integrity and strength of adult bones. Consequently, any dysfunction of the thyroid inevitably impacts bone health to varying degrees. It is widely recognized that hyperthyroidism elevates the risk of OP and fractures due to enhanced bone turnover and loss [7]. Additionally, subclinical hyperthyroidism, whether stemming from endogenous causes or resulting from thyroid-stimulating hormone (TSH) suppression linked to excessive treatment of hypothyroidism, also adversely affects skeletal health. However, research indicates that increased levels of TSH may result in reduced BMD [8]. Currently, the causal relationship between hypothyroidism and OP in non-cancer patients remains unclear.

This study employs Mendelian randomization analysis of genome-wide association study (GWAS) data to enhance our understanding of the occurrence and prevention of OP. In Mendelian randomization, genetic variations serve as instrumental variables (IV) to explore causal relationships between exposure variables and outcomes. We utilized this approach in our study to minimize potential confounding variables by leveraging exposure and outcome data from distinct, non-overlapping samples [9]. To date, there have been no publications investigating the connection between hypothyroidism and OP in non-cancer patients through Mendelian randomization analysis. The objective of this study is to investigate whether hypothyroidism in individuals without cancer has a causal relationship with the onset of OP.

Materials and methods

Research Design

This study focuses on OP as the primary outcome. We conducted a two-sample Mendelian Randomization (MR) analysis to evaluate the causal relationship between hypothyroidism and OP (Fig. 1). The MR framework is based on three critical assumptions: (1) The genetic variations serving as influence variables must have a strong association with hypothyroidism; (2) There should be no linkage between these genetic variants and any potential confounding variables; and (3) The genetic variants impact the outcome solely through their effect on hypothyroidism, without any alternative causal mechanisms. Our analysis is mainly grounded in independent GWAS.

Data Source Description

Genetic Variants Linked to Hypothyroidism in Non-Cancer Patients

We utilized data obtained from the UK Biobank MRC-IEU consortium to identify genetic variants associated with hypothyroidism in individuals without cancer, specifically utilizing the MR-Base database

(http://www.mrbase.org/). The dataset comprised 462,933 participants, all of whom were of European descent, and included a total of 9,851,867 SNPs.. In our investigation of SNPs associated with hypothyroidism in non-cancer patients, we established the threshold for statistical significance at "$P < 5 \times 10^{-8}$; $LDr^2 < 0.001$" to minimize the impact of linkage disequilibrium (LD). Consequently, a total of 122 SNPs were incorporated into the analysis.

Genetic Variation Associated with OP

Summary statistics from the GWAS related to OP were sourced from the EBI, with the data made publicly available in 2021. This analysis encompassed a total of 484,598 participants, which included 7,751 cases alongside 476,848 controls. The study examined 9,587,836 SNPs, identifying 119 SNPs associated with hypothyroidism in non-cancer patients (Fig. 2). All data was at the summary level, devoid of any known sample overlap.

Assessment of the causal link between non-cancer hypothyroidism and OP

The data from the GWAS were sourced from the MR-Base platform and analyzed using the 'TwoSampleMR' package (version 0.5.5) within the R software, with a focus on hypothyroidism in non-cancer patients and OP.To evaluate the causal connection between hypothyroidism in non-cancer individuals and osteoporosis, various methods were employed, including IVW, weighted median estimation, MR-Egger regression, and weighted mode [10, 11, 12]. A meta-analysis Wald ratio of the included SNPs was utilized to apply the IVW method for examining causality. It is crucial to recognize that the IVW analysis relies on the assumption that all selected SNPs serve as valid instruments. If this assumption is not satisfied, MR-Egger regression provides an alternative statistical methodology. The MR-Egger slope represents the effect of exposure variables on the outcome, under the assumption that the intercept term is either zero or statistically insignificant [13]. The weighted median approach provides the median effect estimate of each SNP, arranged by their weight values. The beta values obtained from the weighted model should align directionally with the outcomes from the previous methods, serving as supplementary evidence. OR and their 95% confidence intervals (95% CI) were calculated to represent the estimated causal relationship between hypothyroidism and OP in non-cancer patients, with statistical significance defined as a P-value of less than 0.05 (Fig. 3).

Heterogeneity and Sensitivity Analyses

To begin with, we employed Cochran's Q statistic in conjunction with the I^2 index to assess the heterogeneity among the SNPs. Subsequently, we performed a 'leave-one-out' analysis to investigate the hypothesis of causality associated with individual SNPs. Furthermore, MR-Egger regression was conducted to evaluate genetic pleiotropy (Fig. 4).

Results

Instrumental Variables for Mendelian Randomization

Following the establishment of the statistical significance threshold ($P < 5 \times 10^{-8}$, linkage disequilibrium $r^2 < 0.1$) and the incorporation of SNP data from the EBI, we identified 119 unique SNPs from GWAS related to non-cancerous hypothyroidism as instrumental variables (IVs). These SNPs exhibited significant associations with non-cancer related hypothyroidism across the genome. For each variant, an F-test was performed, revealing that an F-value below 10 denotes a "weak IV" [14]. It was essential to address potential weak instrument bias. As the F-value for all 119 SNPs exceeded 10, all were included in the analysis.

Causal Effects of Hypothyroidism on OP in Non-Cancer Patients

The findings from the IVW method indicated a positive association between genetically predicted hypothyroidism in non-cancer patients and the likelihood of developing osteoporosis (OP) (OR 1.017, 95% CI 1.003–1.031). Similar results were observed using MR-Egger regression, weighted median estimation, and the weighted mode method. Consequently, hypothyroidism in non-cancer patients serves as a risk factor for OP, increasing the likelihood of the condition's onset (Table 1).

Table 1
All values are rounded to three decimal places.

Method	nsnp	Beta	SE	pval	OR	95%CI
Inverse variance weighted	119	0.017	0.007	0.011	1.017	1.003–1.031
MR Egger	119	0.018	0.015	0.216	1.018	0.989–1.049
Weighted median	119	0.021	0.010	0.033	1.021	1.001–1.041
Weighted mode	119	0.038	0.018	0.033	1.039	1.003–1.076

Heterogeneity and Sensitivity Analysis

The assessment of heterogeneity among SNPs was conducted using Cochran's Q statistic in conjunction with the I^2 statistic. Our data indicated a moderate degree of heterogeneity, as evidenced by a Q_p value of less than 0.05 for both analytical approaches. Despite the observed heterogeneity, the results obtained from the IVW method remained unaffected; thus, our conclusions can still be regarded as reliable (Table 2).

Table 2
$I^2 = (Q - df)/Q$

Method	Q	df	I^2	Q_p value
Inverse variance weighted	162.325	118	0.273	0.004
MR Egger	162.315	117	0.279	0.004

To investigate the hypothesis that a single SNP may be crucial for establishing causality, we conducted a 'leave-one-out' analysis. This approach revealed that none of the individual SNPs had a significant effect on the IVW outcomes.

Lastly, we conducted a horizontal pleiotropy analysis via MR-Egger regression (intercept = -5.9×10^{6}, SE = 6.9×10^{5}, P = 0.932), which indicated an absence of horizontal pleiotropy concerning SNPs linked to hypothyroidism in non-cancer patients and the risk of OP (Fig. 5).

Discussion

Thyroid hormone plays a crucial role in regulating metabolism and cellular differentiation throughout the human body. Variations in hormone levels can lead to widespread effects, including impacts on bone metabolism. The primary cause of hypothyroidism is typically dysfunction of the thyroid gland. While earlier research has largely established the detrimental effects of hyperthyroidism on bone metabolism, a consensus regarding the influence of hypothyroidism remains elusive. Nevertheless, some studies indicate that hypothyroidism may reduce BMD, and that TSH levels that fall above or below the normal range could also negatively impact BMD [15–19]. Investigations focusing on fracture rates among hypothyroid patients have identified an increased incidence of fractures in this population [20, 21]. This finding suggests that hypothyroidism may act as a contributing risk factor for osteoporotic fractures. Motivated by these insights, our research aimed to explore the causal link between hypothyroidism and the development of OP in non-cancer patients.

In this study, we aimed to investigate the causal relationship between hypothyroidism and the prevalence of OP in patients without cancer by conducting a comprehensive analysis of GWAS data. We utilized a two-sample MR approach for this analysis. We identified 119 SNPs as instrumental variables, selected for their strong association with hypothyroidism in non-cancer patients. Our analysis incorporated four distinct methodological approaches: inverse variance weighting (IVW), MR-Egger regression, weighted median estimation, and the weighted mode method. The results from the three alternative statistical approaches were consistent with those derived from the IVW method; however, only the IVW findings achieved statistical significance ($P < 0.05$), indicating that the results were both stable and positive. Consequently, our findings suggest a causal association between hypothyroidism and OP in non-cancer patients. This two-sample MR analysis provides novel insights into the causal relationship between hypothyroidism and OP within this specific patient population. While moderate heterogeneity was noted (Cochran’s Q statistic: $P < 0.05$), it did not affect the conclusions drawn from the IVW analysis. Furthermore, there was no evidence of horizontal pleiotropy (MR-Egger: intercept = -5.9×10^{6}, SE = 6.9×10^{5}, P = 0.932).

In order to enhance our comprehension of the connection between hypothyroidism and OP, we carried out a series of investigations and put forward several hypotheses. Bone experiences a continuous cycle of formation and resorption, recognized as the bone remodeling cycle [22]. Disruptions in the bone remodeling cycle can lead to osteopenia or OP. In addition to thyroid hormones, several systemic factors

influence this process, including calcitonin, parathyroid hormone, vitamin D3, estrogen, glucocorticoids, as well as growth hormone and serum iron levels [23]. A cross-sectional analysis revealed that women with hypothyroidism exhibited significantly lower serum levels of vitamin D and iron ($p < 0.01$) [24]. Vitamin D is essential for maintaining bone stability and regulating mineral balance, as it affects serum concentrations of calcium, phosphorus, and iron [25]. Iron, a critical component of hemoglobin and myoglobin, is vital for oxygen transport, and its deficiency can lead to anemia, which may indirectly affect bone health. Consequently, we hypothesize that hypothyroidism may influence the bone remodeling process by altering vitamin D and iron metabolism. Moderate supplementation of vitamin D and iron could be advantageous for female patients with hypothyroidism. Further research is necessary to elucidate the underlying mechanisms.

A different prospective study focused on postmenopausal women diagnosed with endometriosis found that higher levels of TSH and an increased average age at menopause were significantly correlated with a reduction in BMD [8]. While T4 levels were not examined in this research, elevated TSH is a characteristic indicator of hypothyroidism in laboratory assessments. Hypothyroidism is notably more common among females, particularly postmenopausal women, suggesting that this group should exercise extra caution regarding the risk of OP associated with this condition. Research indicates that childhood patients with abnormal TSH show lower BMD compared to those with normal levels [26]. These observations imply that an elevation in TSH may more likely contribute to a decline in BMD, aligning with the results of our investigation. Notably, various cross-sectional and longitudinal studies indicate that patients with hypothyroidism receiving thyroid hormone replacement therapy may face an increased likelihood of reduced BMD. This suggests that irregular thyroid function could lead to diminished BMD, subsequently raising the risk of OP and potential fractures. Consequently, it is essential to maintain stable thyroid hormone levels. As investigations into genes responsible for such diseases progress, future research may enable genetic testing for early assessment of OP risk in patients with hypothyroidism, potentially preventing fractures and significantly easing the disease burden.

We employed MR in our research, effectively controlling for reverse causality due to confounding factors. Both samples utilized in this analysis were derived from GWAS characterized by substantial sample sizes and significant genetic variability, which minimizes the potential impact of confounding variables. However, we recognize certain limitations inherent to this study.Firstly, the generalizability of the findings to other populations remains uncertain and necessitates validation through further studies. Secondly, the datasets concerning hypothyroidism and osteoporosis in non-cancer patients utilized in this analysis were obtained from different research institutions, potentially introducing bias associated with population stratification.

Conclusion

To summarize, our research indicates that specific SNPs associated with hypothyroidism in non-cancer individuals are linked to the progression of OP. Additional investigations in this area will enhance our understanding of prevention strategies and possible therapeutic approaches for OP.

Declarations

The authors have no relevant financial or non-financial interests to disclose.

Author Contribution

Z. Wrote the main manuscript text and drew figures and tables. L.Participated in manuscript writing and data management. S. Participated in manuscript writing and review. J. P.L. Co-contributed in data management. W.Q.Z. Y.H.C.X. M. Responsible for preliminary literature search. Y. Provide research ideas, funding acquisition and final review of manuscripts.All authors read and approved the final manuscript.All authors reviewed the manuscript.

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Data Availability

Our dataset is publicly accessible at the following URL: http://app.mrbase.org/.

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Figures

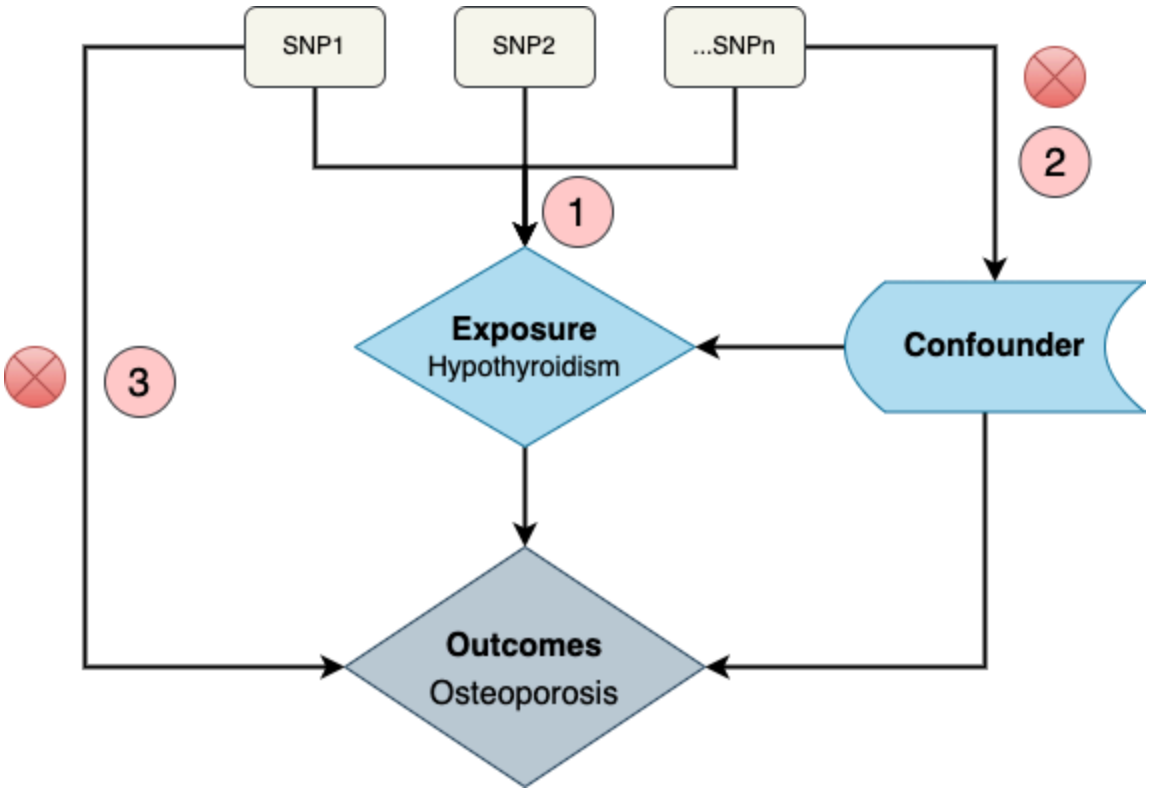

Figure 1

Study design

Sequence numbers represent 3 hypotheses; SNP (single nucleotide polymorphism)

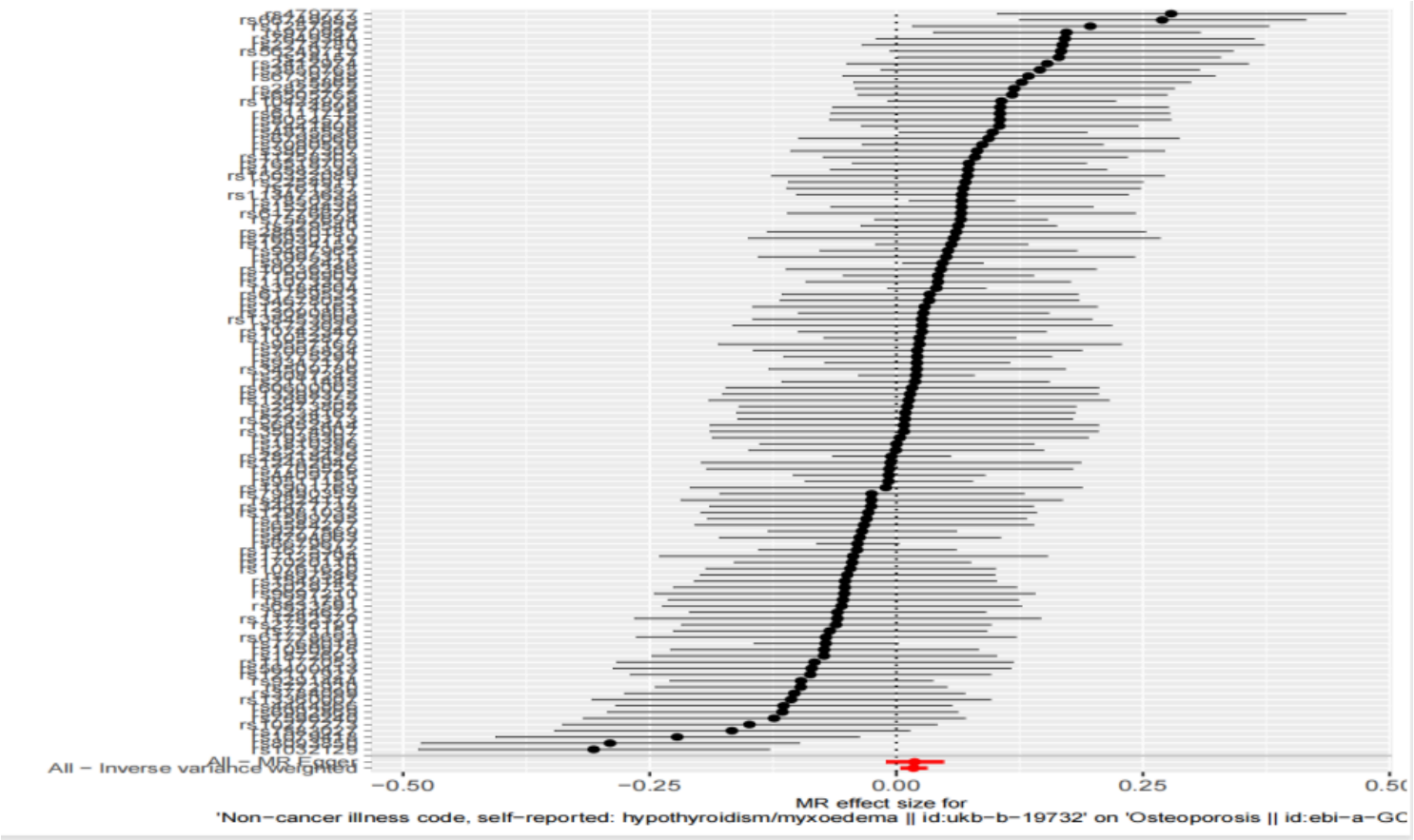

Figure 2

Forest plot of single SNPs

A forest plot illustrates the association between single nucleotide polymorphisms (SNPs) related to non-cancer hypothyroidism and the risk of osteoporotic fractures (OP). Each SNP is treated as an individual instrument and is represented by black dots, which indicate the log odds ratio (OR) for OP per standard deviation (SD) increase in non-cancer hypothyroidism. The overall causal estimate, derived from all SNPs considered as a unified instrument and assessed using two key methods—MR-Egger and the inverse-variance weighted (IVW) approach—is depicted as red dots. The horizontal line segments signify the 95% confidence intervals for these estimates.

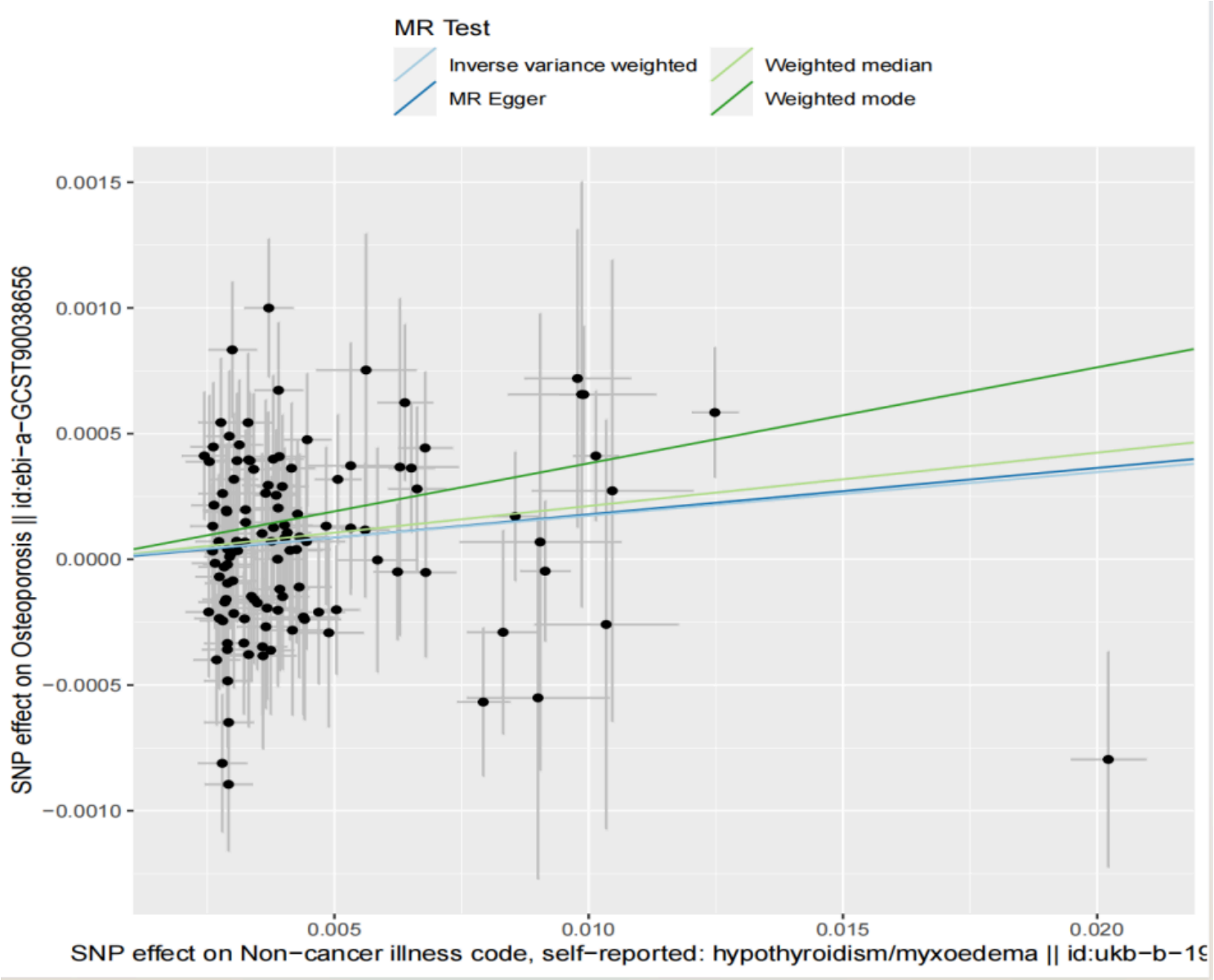

Figure 3

Scatterplot of non-cancer hypothyroidism and osteoporosis

The figure presents the effect sizes associated with the SNP-Non-cancer illness code, specifically highlighting the self-reported association of hypothyroidism/myxoedema, which is displayed on the x-axis in standard deviation units. In addition, the SNP-osteoporosis association is represented on the y-axis as log(OR), with accompanying 95 percent confidence intervals.

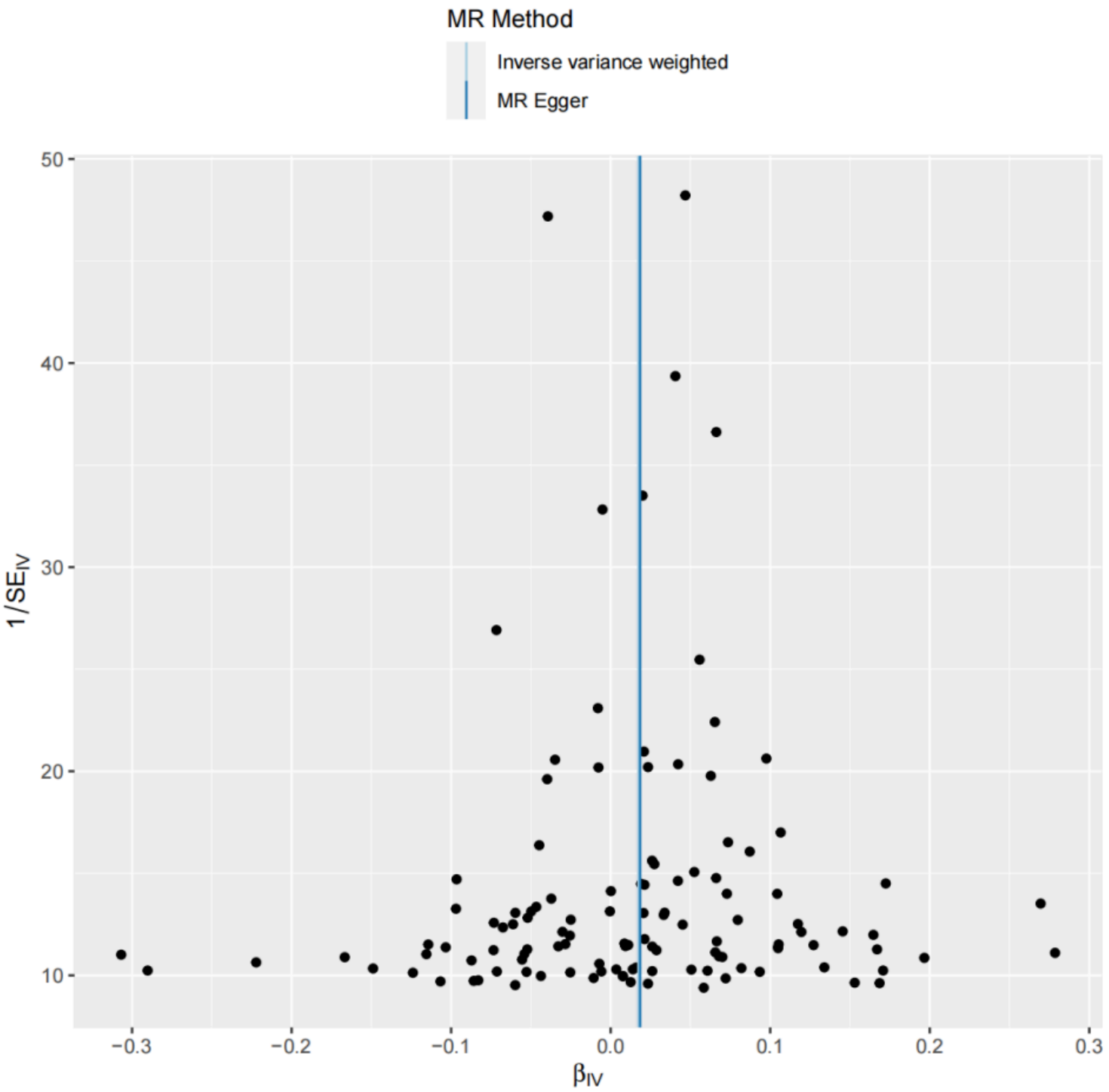

Figure 4

Funnel diagram

Heterogeneity was assessed using funnel plots. The dark blue line represents the MR-Egger estimate, while the blue line indicates the estimate weighted by inverse variance.

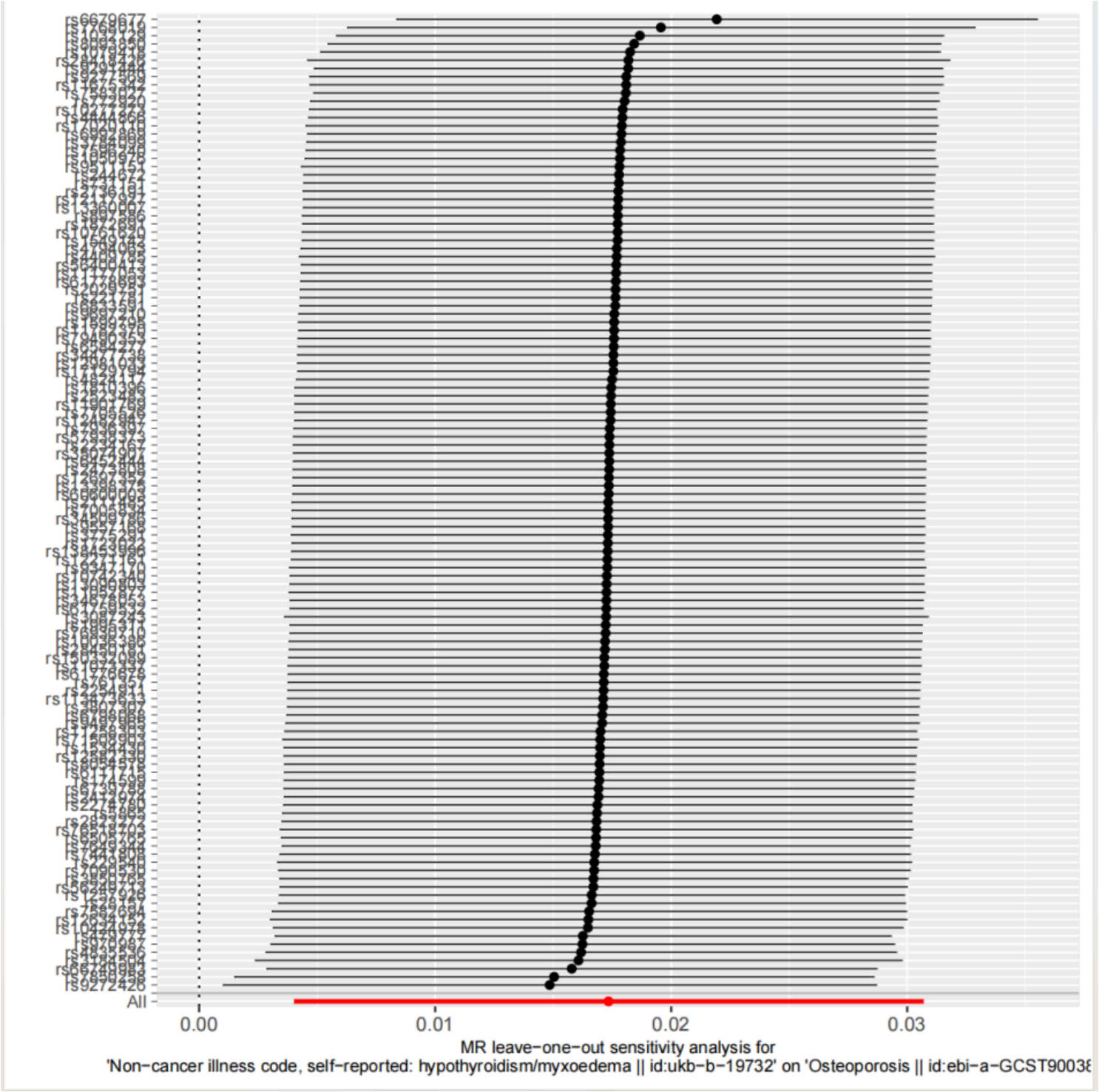

Figure 5

Leave-one-out test

Upon excluding specific SNPs from the analysis, the black dots illustrate the findings obtained from the Inverse Variance Weighted (IVW) and Mendelian Randomization (MR) methods, which were employed to assess the causal influence of hypothyroidism in non-cancer patients on osteoporosis (OP). Each red dot represents the IVW estimates derived from all included SNPs. Our sensitivity analysis revealed that

no individual SNP significantly affected the overall impact of hypothyroidism in non-cancer patients regarding OP.