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Nonlinear association of TSH with pulmonary ventilation: insights from bidirectional Mendelian randomization and cross-sectional study

Yuxin Wang[1], Jinmei Luo[1], Rong Huang[1] and Yi Xiao[1*]

Abstract

Background Thyroid hormones play a crucial role in numerous physiological processes, including pulmonary function. However, the relationship between thyroid function and different patterns of pulmonary ventilation remains unclear.

Methods This study employed a bidirectional two-sample Mendelian randomization (MR) approach combined with a cross-sectional study from the National Health and Nutrition Examination Survey (NHANES) to explore the relationship between thyroid function and pulmonary ventilation indicators. We used genomic data from the ThyroidOmics Consortium and the UK Biobank to derive instrumental variables for thyroid and pulmonary functions. Adults from the NHANES 2007–2012 were included to validate the MR findings through weighted generalized linear model (GLM) regression and restricted cubic spline (RCS) analysis.

Results Genetically predicted thyroid-stimulating hormone (TSH) was associated with pulmonary ventilatory function (forced expiratory volume in 1 s (FEV1): β = 0.0223, 95% confidence interval (CI) 0.0040—0.0406, p-value = 0.0170), particularly with a restrictive ventilatory pattern (forced vital capacity (FVC): β = 0.0237, 95% CI 0.0047—0.0427, p-value = 0.0143). This association was more robust in the low TSH subgroup. Additionally, the NHANES data revealed a nonlinear relationship between both FEV1% predicted and FVC% predicted and TSH, characterized by a positive relationship at lower TSH ranges and a negative relationship at higher TSH ranges.

Conclusions Our findings highlight a significant association between TSH levels and a restrictive ventilatory pattern, underscoring the importance of thyroid health in the clinical evaluation of certain pulmonary diseases. These insights may guide more personalized interventions in respiratory medicine.

Keywords Pulmonary function test, Thyroid stimulating hormone, Thyroid hormones, Mendelian randomization analysis, NHANES

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Background

Thyroid hormones, predominantly triiodothyronine (T3) and thyroxine (T4), are iodinated tyrosine derivatives synthesized and secreted by the thyroid gland. Their synthesis and secretion are regulated by thyroid-stimulating hormone (TSH) through a negative feedback mechanism, which can reflect early abnormalities in thyroid function [1]. The combination of TSH and free thyroxine (FT4), the bioactive form of T4, is essential for assessing thyroid function status [2, 3]. These hormones are vital for regulating key physiological processes, such as growth, development, and metabolism [4, 5], and alterations in their levels can indicate disease states [6]. Although there is a recognized connection between thyroid function and pulmonary development and pathology, it remains underexplored. Previous research has investigated the influence of thyroid hormones on various pulmonary conditions, including lung cancer, pulmonary fibrosis, alveolar damage, and chronic obstructive pulmonary disease (COPD) [7–9]. However, comprehensive research on the relationships among thyroid function, lung function and pulmonary diseases remains limited.

Pulmonary function tests are noninvasive tools critical for diagnosing and monitoring lung diseases [10]. These tests can differentiate patterns of pulmonary function changes associated with specific diseases. For example, obstructive ventilatory dysfunction in patients with COPD is typically indicated by a forced expiratory volume in 1 s/forced vital capacity (FEV1/FVC) ratio of less than 0.70, whereas a restrictive pattern, often seen in pulmonary fibrosis, is characterized by an FVC less than 80% of the predicted value [11].

Mendelian randomization (MR) is instrumental in establishing the causal impact of an exposure on an outcome by using genetic variants as instrumental variables. This method effectively addresses issues such as reverse causation and confounding which can affect the results [12, 13]. Bidirectional MR provides a more rigorous exploration of causality. The National Health and Nutrition Examination Survey (NHANES) is a population-based observational survey managed by the National Center for Health Statistics under the Centers for Disease Control and Prevention [14]. This study involves various activities, including physical examinations, laboratory tests, and the completion of questionnaires about health and nutritional practices, and is widely used in research related to population health and diseases.

Given the existing research gaps, this study aimed to elucidate the causal relationship between thyroid function and impaired pulmonary ventilation using an MR approach, which was further validated through analysis of NHANES data.

Methods

Study design

To investigate the causal relationships between thyroid function (represented by FT4 and TSH) and pulmonary ventilation function (measured by FEV1 for overall ventilatory function, FVC for restrictive ventilatory impairment, and FEV1/FVC for obstructive ventilatory impairment), we conducted a bidirectional two-sample MR approach. Our study adhered to the three core assumptions of MR: relevance, independence, and exclusion restriction, following the general protocols for conducting MR [15, 16]. We analyzed summary-level data from genome-wide association studies (GWASs), extracting single nucleotide polymorphisms (SNPs) associated with FT4 and TSH as instrumental variables (IVs) to investigate the effects of thyroid function on ventilatory function. Furthermore, SNPs associated with subclinical hyperthyroidism and hypothyroidism were also extracted as IVs for validation. To explore causal effects in the reverse direction, we used SNPs related to FEV1, FVC, and FEV1/FVC as IVs in reverse MR analyses. The reporting of this MR analysis work followed the Strengthening the Reporting of Observational Studies in Epidemiology using Mendelian Randomization (STROBE-MR) guidelines.

To corroborate the conclusions drawn from our MR analysis within a real-world population, we conducted a population-based observational survey utilizing data from the NHANES database [14]. The NHANES, administered by the National Center for Health Statistics under the Centers for Disease Control and Prevention, adopts a complex, stratified sampling design to ensure that the sample can represent the whole US population. The National Center for Health Statistics Ethics Review Board approved the survey, and every participant provided written informed consent. In this study, we extracted demographic data, laboratory data, examination data, and questionnaires from three NHANES cycles: 2007–2008, 2009–2010, and 2011–2012. These cycles were chosen because they included assessments of both spirometry and thyroid function, providing a comprehensive dataset to investigate the relationship between thyroid function and pulmonary ventilation.

GWAS data sources

SNPs related to thyroid function were derived from the GWAS meta-analysis results from the collaborative efforts of the ThyroidOmics Consortium (www.thyroidomics.com) [17]. The research includes GWAS meta-analyses of reference range thyroid function, encompassing up to 271,040 euthyroid individuals of European ancestry from 46 cohorts within the ThyroidOmics Consortium. The study excluded individuals under 18 years of age, those of non-European descent, those

using thyroid-related medications, and those who had undergone thyroid surgery. TSH and FT4 were analyzed as continuous variables. Subclinical hypothyroidism (characterized by TSH levels above the cohort-specific reference range) and subclinical hyperthyroidism (characterized by levels below the cohort-specific reference range) were analyzed as categorical variables. Data from 27 cohorts were included for subclinical hypothyroidism (6,712 cases and 146,529 controls) and 20 cohorts for subclinical hyperthyroidism (4,212 cases and 137,337 controls) [17]. The GWAS data from the ThyroidOmics Consortium are publicly accessible at https://transfer.sysepi.medizin.uni-greifswald.de/thyroidomics/datasets/.

Data on pulmonary ventilation function were sourced from a GWAS meta-analysis performed by Shrine N et al. [18], involving 321,047 participants of European ancestry from the UK Biobank. This analysis included measures of FEV1, FVC, and the FEV1/FVC ratio. Summary pulmonary function data are publicly available from the MRC Integrative Epidemiology Unit Open GWAS database (https://gwas.mrcieu.ac.uk/). The GWAS data for the exposure and outcome were derived from different populations.

Instrumental variable selection

To meet the assumptions of relevance in selecting SNPs related to thyroid function or pulmonary ventilation, we chose SNPs that demonstrated an association with the respective exposure at the genome-wide significance threshold, defined as p-value < 5 × 10^-8. This ensured that the SNPs were strongly associated with the exposures. Then, we implemented a clumping process for the selected SNPs for the assumptions of independence. The clumping window was set at 10,000 kb, and the threshold of r^2 was set at 0.001. This step minimized any potential overlap between SNPs, ensuring that each SNP provided independent information. To eliminate weakly associated variables, we computed the F statistic for each SNP to confirm the strength of its relationship with the exposure [19, 20]. SNPs with F statistics < 10 were excluded [19]. During the harmonization step, we excluded palindromic SNPs with a minor allele frequency exceeding 0.42. To reduce the potential for pleiotropic effects and ensuring that the SNPs would affect the outcome only through the IVs, we scrutinized the selected SNPs through the GWAS Atlas database, eliminating SNPs significantly associated with clinical phenotypes relevant to our outcomes, in line with the exclusion restriction assumption [21]. Ultimately, we identified a range of 4 to 150 IVs for thyroid function and 229 to 286 IVs for pulmonary ventilation. Further details of the IVs used can be found in Table S1 and Table S2.

NHANES study populations

The data from three NHANES cycles between 2007 and 2012 encompassed 30,442 individuals. We focused on adult participants aged 18 and older (n = 18,619). The exclusion criteria were as follows: (1) pregnant women (n = 182), (2) participants lacking a thyroid function assessment (n = 9,356), (3) participants without a spirometry test (n = 1930), (4) participants with unusable lung function test data, specifically those graded with a quality attribute of D or F (n = 272), (5) participants missing crucial covariates (n = 395), and (6) participants diagnosed with cancer, renal failure, or thyroid diseases (n = 1,062). To align with the focus of our MR study on individuals with FT4 within the normal reference range, we excluded those outside this range. Specifically, individuals diagnosed with hyperthyroidism (FT4 > 1.6 ng/dL) or hypothyroidism (FT4 < 0.6 ng/dL) were removed from the analysis (n = 138) [FT4 testing protocol: https://wwwn.cdc.gov/nchs/data/nhanes/2011-2012/labmethods/thyrod_g_met_free_t4.pdf]. Furthermore, as our MR analysis finally indicated the impact of TSH on restrictive ventilatory defects, we further excluded participants who demonstrated a definitive obstructive spirometry pattern (FEV1/FVC < 0.70) (n = 681) [11]. Finally, 4,603 individuals were included (Fig. S1).

Variates processing

The pulmonary function measurements of FEV1 and FVC were directly extracted from the NHANES database. The FEV1/FVC ratio was calculated by dividing FEV1 by FVC. To standardize these measurements, the raw data were converted into percentage-predicted values using the Hankinson equation, which adjusts for age, sex, race, and height [22]. We further categorized participants with normal FT4 levels based on TSH values into subclinical hyperthyroidism (TSH < 0.45 μIU/mL) and subclinical hypothyroidism (TSH > 4.5 μIU/mL) groups [23–25].

For covariates, we collected age, sex, race, body mass index (BMI), smoking status, activity intensity, and comorbidities, including hypertension, diabetes, and coronary heart disease. The smoking index is defined as the number of cigarettes smoked per day multiplied by the number of years smoked. Participants who had smoked fewer than 100 cigarettes in their lifetime were classified as nonsmokers, while those who had smoked 100 or more cigarettes were considered smokers. For former smokers, the number of cigarettes smoked per day was estimated based on the metric "cigarettes smoked per day when quit," while for current smokers, "cigarettes/day during the past 30 days" was used.

Statistical analysis

To investigate the relationship between thyroid function and pulmonary ventilation, we initially conducted MR analyses using TSH and FT4 as exposure factors and FEV1, FVC and FEV1/FVC as outcome measures. We utilized the random-effects inverse-variance weighted (IVW) method to integrate the causal effects of individual SNPs [26]. The IVW method is a widely used approach in MR that combines estimates from multiple IVs to calculate a weighted average of the causal effect. IVW assumes that IVs are valid, meaning they are associated with the exposure but only affect the outcome through the exposure. When these assumptions hold, IVW provides unbiased and stable causal estimates [26]. Cochrane's Q-statistic was utilized to assess heterogeneity among each SNP [27]. For sensitivity analyses, we applied various statistical approaches, including the weighted median, MR−Egger, and MR-PRESSO methods [28]. The weighted median method is another approach used to combine causal estimates from multiple IVs, with a different weighting scheme compared to IVW. When some IVs violate the key assumptions, such as horizontal pleiotropy, the weighted median method provides a more conservative yet reliable causal estimate. It complements the IVW method, offering additional robustness for causal inference, especially when some IVs may not be fully valid. The MR-PRESSO approach is a method that detects and corrects for pleiotropy in MR studies. It identifies outlier IVs that violate the exclusion restriction assumption due to horizontal pleiotropy. After removing these outliers, MR-PRESSO recalculates the causal effect using only valid IVs, providing a more accurate estimate by reducing pleiotropic bias. This approach assessed the robustness of the conclusions after outlier correction. The MR-Egger regression method is used to address potential bias when some IVs may not satisfy the exclusion restriction assumption. MR-Egger provides a bias-corrected estimate of the causal effect. The MR−Egger intercept test, with a p-value > 0.05, indicated no significant horizontal pleiotropy affecting our estimates [29]. Further analyses categorized thyroid function as a binary variable to explore its impact more granularly. To ascertain the causal impact of thyroid function on pulmonary ventilation, we also performed reverse-direction analyses. The results for continuous variables are presented as β with 95% confidence intervals (CIs), whereas estimates for binary variables are expressed as odds ratios (ORs) with 95% CIs. To address the potential for Type I errors arising from multiple testing, we implemented the Benjamini–Hochberg (BH) method to control the false discovery rate (FDR), setting the significance threshold at 5%. Results with adjusted p-values below this threshold were considered statistically significance. All the statistical analyses were performed using the TwoSampleMR package (version 0.5.8) in R (version 4.3.3, R Foundation for Statistical Computing).

The NHANES study adopted complex sampling surveys, including weighting, clustering, and stratification. Continuous variables are expressed as medians and interquartile ranges, while categorical variables are presented as counts and percentages. For continuous variables, we used the Wilcoxon rank-sum test for complex survey samples, and for categorical variables, we employed the chi-squared test with Rao & Scott's second-order correction. To further assess the relationship between TSH and ventilation function, we then implemented weighted generalized linear model (GLM) regression and restricted cubic spline (RCS) analyses adjusted for age, sex, race, BMI, smoking index, activity intensity and comorbidities. The RCS analysis was conducted to detect the nonlinear relationships. The number of knots was set between three and five to minimize overfitting while ensuring an optimal fit. The optimal number of knots was selected based on the lowest values of the Akaike information criterion and Bayesian information criterion. All analyses were conducted using R studio (version 4.3.3, R Foundation for Statistical Computing), with a two-sided p-value < 0.05 considered statistically significant.

Results

Bidirectional two-sample Mendelian randomization

Forward direction To explore the relationship between thyroid function and pulmonary ventilation function, we initially used TSH and FT4 as exposure factors and FEV1, FVC and FEV1/FVC as outcome factors. The primary results were obtained through the IVW method, as shown in Fig. 1 and Table S3. The genetic prediction of TSH was positively correlated with the overall ventilation function indicator FEV1 (β: 0.0223, 95% CI: 0.0040—0.0406, p-value = 0.0170) and the restrictive ventilation function indicator FVC (β: 0.0237, 95% CI: 0.0047—0.0427, p-value = 0.0143). However, no significant association was observed with the obstructive ventilation function indicators FEV1/FVC. This relationship remained significant after BH correction (FEV1: adjusted p-value = 0.0409; FVC: adjusted p-value = 0.0409). Genetically predicted levels of FT4 did not significantly correlate with any of the pulmonary function indicators. When TSH was treated as a categorical variable, IVW analysis revealed that genetically predicted subclinical hyperthyroidism (low TSH) was negatively correlated with FEV1 (β: -0.0126, 95% CI: -0.0204— -0.0046, p-value = 0.0016) and FVC (β: -0.0117, 95% CI: -0.0207— -0.0026, p-value = 0.0117). These findings also remained robust following BH correction (FEV1: adjusted p-value = 0.0097; FVC: adjusted p-value = 0.0409). No correlation was observed with FEV1/FVC. The genetic prediction of subclinical hypothyroidism (high TSH) was only positively correlated with FVC (β: 0.0612, 95% CI:

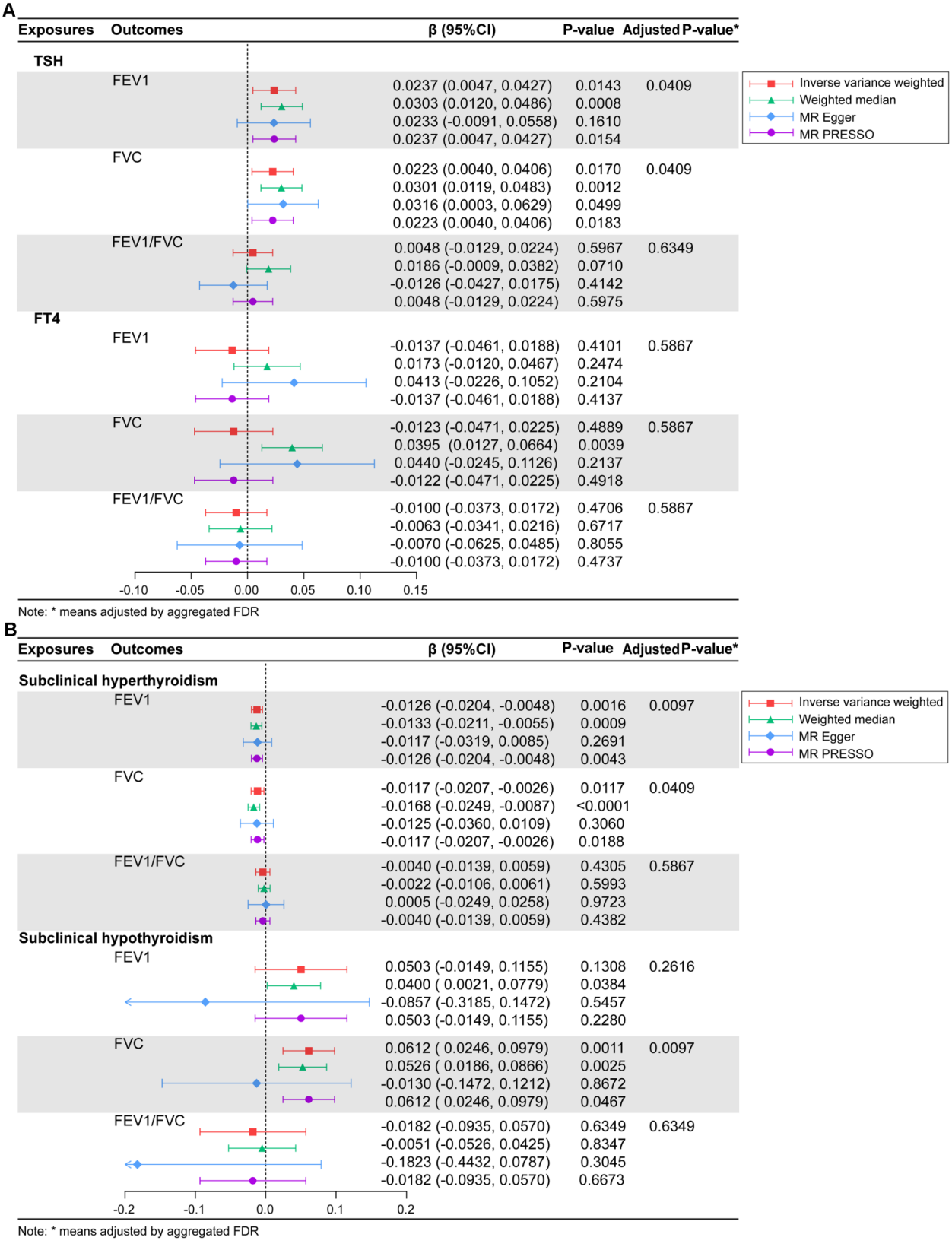

Fig. 1 Causal estimates for the effect of thyroid function on ventilation function. (**A**) Causal estimates for the effect of TSH and FT4 (as continuous variables) on FEV1, FVC and FEV1/FVC. (**B**) Causal estimates for the effect of subclinical hyperthyroidism and subclinical hypothyroidism (as categorical variables) on FEV1, FVC and FEV1/FVC. Estimates are presented as β and 95% CIs

0.0246—0.0979, p-value = 0.0011), which also remained significant after BH correction (adjusted p-value = 0.0097).

In sensitivity analyses, the effects of TSH and subclinical hyperthyroidism (low TSH) on ventilatory function were further evaluated using the weighted median and MR-PRESSO methods. These analyses yielded similar and consistent point estimates, reinforcing the reliability of our primary findings. Notably, while the MR–Egger method did not reach statistical significance, it displayed point estimates in alignment with those observed in other methods, supporting the consistency of the results (Fig. 1, Table S3). The relationship between subclinical hypothyroidism (high TSH) and FVC, although supported by weighted median and MR PRESSO results, showed opposite trends in MR–Egger's point estimates (Fig. 1, Table S3). MR–Egger's intercept test revealed no evidence of horizontal pleiotropy. Although Cochran's Q statistic and MR PRESSO detected heterogeneity, the removal of outliers had no significant impact on the results (Table S4).

Reverse direction We set FEV1, FVC, and the FEV1/FVC ratio as exposure factors and TSH, FT4, subclinical hyperthyroidism, and subclinical hypothyroidism as outcome factors. Through the IVW method, we only found a statistically significant positive effect of FEV1/FVC on TSH, but this effect was not significant after BH correction (Fig. 2, Table S5). Sensitivity analyses did not alter the relationship (Table S5 and Table S6).

Therefore, bidirectional two-sample MR analysis revealed that, in populations without clinical thyroid disease, genetically predicted TSH is associated with pulmonary ventilatory function, particularly with restrictive ventilatory patterns. Notably, the relationship was more pronounced in the low TSH subgroup. No significant genetic associations were detected between thyroid function and obstructive ventilatory patterns.

NHANES study

To further validate the conclusions from MR analysis, we used the NHANES database. This analysis focused on individuals without obstructive ventilatory patterns and without clinical thyroid disorders. A total of 4,603 participants were included and categorized based on TSH levels into three groups: normal TSH ($n = 4{,}349$), subclinical hyperthyroidism ($n = 117$), and subclinical hypothyroidism ($n = 137$), as detailed in Table 1. There were no significant differences among the groups in age, sex, BMI, smoking status, physical activity intensity or clinical comorbidities, although there were significant differences in racial composition. With respect to thyroid function, variations in TSH levels correlated with differences in FT4 levels, but no other thyroid function assessment indicators showed significant differences. In terms of ventilatory function, only FEV1% predicted (FEV1%pred) showed significant differences between groups. To address potential biases due to racial diversity, as the original MR study was based on individuals of European ancestry, we conducted further analyses within the subgroup of non-Hispanic White individuals. These analyses confirmed that similar significant variations in FEV1%pred were associated with different TSH levels, corroborating the MR findings (Table S7).

Our analysis showed that participants with higher TSH levels had lower FEV1 values. Given these findings and considering the results from our MR analysis where TSH was treated as a categorical variable, sensitivity analyses indicated that conclusions were particularly robust within the low TSH range. This pattern suggests the presence of a nonlinear relationship between TSH and pulmonary function. Regrettably, due to the unavailability of individual-level data that simultaneously included thyroid and ventilatory functions as well as GWAS data, we were unable to employ a nonlinear MR approach to further validate these findings. To address this limitation, we explored the potential nonlinear relationships using generalized linear regression combined with RCS. After adjusting for age, sex, race, BMI, smoking index, activity intensity, and comorbidities, both FEV1%pred and FVC%pred demonstrated a nonlinear relationship with TSH. Specifically, in lower TSH ranges (FEV1: TSH < 1.85 μIU/mL; FVC: TSH < 1.80 μIU/mL), FEV1%pred and FVC%pred were positively correlated with TSH (Fig. 3A-B), which aligns with our MR results. Conversely, in higher TSH ranges (FEV1: TSH ≥ 1.85 μIU/mL; FVC: TSH ≥ 1.80 μIU/mL), FEV1%pred and FVC%pred were negatively correlated with TSH (Fig. 3A-B). There was no significant correlation between FEV1/FVC and TSH (Fig. 3C). This relationship was also robust in the non-Hispanic White population (Fig. 3D-F).

Discussion

The present study offers novel insights into the complex interplay between thyroid function and pulmonary ventilation, filling a significant gap in the current medical literature. By employing bidirectional two-sample MR and validating findings with the NHANES database, our results strongly indicate a nonlinear relationship between TSH levels and restrictive ventilatory function, rather than obstructive ventilatory patterns, both genetically and clinically.

Past research on the relationship between thyroid function and lung diseases was various. Animal studies have revealed that administering T3 to experimental animals can reduce alveolar epithelial cell apoptosis and ameliorate lung tissue fibrosis. However, these studies did not provide specific in vivo thyroid function indicators; thus, the exact values of TSH, FT4, and FT3 in the

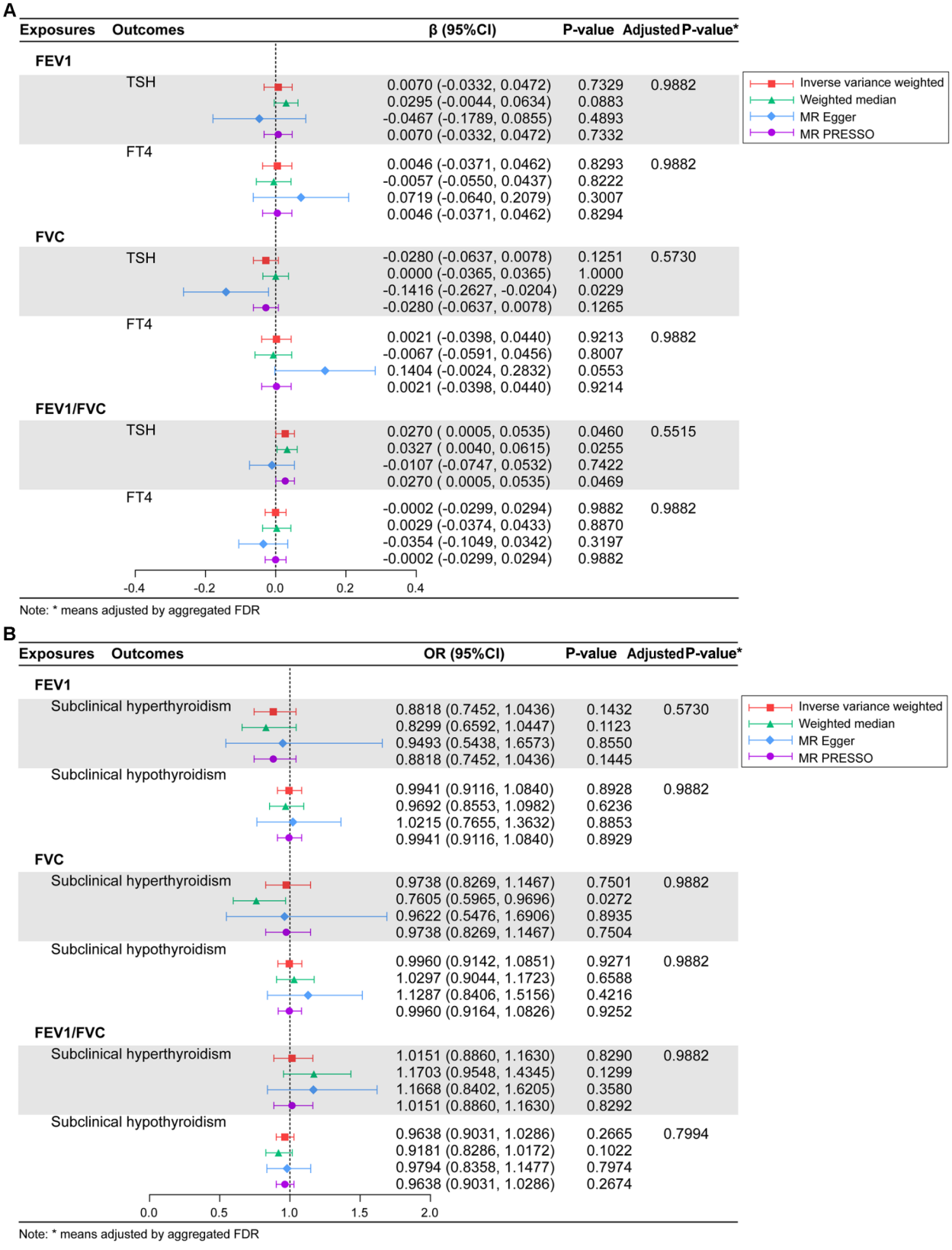

Fig. 2 Causal estimates for the effect of ventilation function on thyroid function. (**A**) Causal estimates for the effect of ventilation function on TSH and FT4 (as continuous variables). (**B**) Causal estimates for the effect of ventilation function on subclinical hyperthyroidism and subclinical hypothyroidism (as categorical variables). Estimates are presented as β and 95% CIs for continuous outcome variables and OR with 95% CIs for categorical outcome variables

Table 1 Baseline characteristics of participants with different TSH ranges

	Normol TSH (*n* = 4,349)*	Subclinical hyperthyroidism (*n* = 117)*	Subclinical hypothyroidism (*n* = 137)*	*P*-value
Age, years	40 (29, 51)	37 (29, 51)	41 (31, 52)	0.4
Male, n (%)	2264 (52%)	59 (45%)	66 (49%)	0.5
Race, n (%)				0.004
Mexican American	840 (10%)	18 (6.9%)	22 (7.8%)	
Non-Hispanic White	1722 (64%)	37 (63%)	77 (81%)	
Non-Hispanic Black	882 (11%)	44 (20%)	11 (3.1%)	
Other Hispanic	547 (7.1%)	12 (6.4%)	19 (3.7%)	
Other/multiracial	358 (7.9%)	6 (3.9%)	8 (4.7%)	
BMI, kg/m^2	27 (24, 32)	27 (24, 30)	28 (23, 32)	0.5
Smoking status				0.4
Current smoker	914 (20%)	40 (28%)	22 (17%)	
Former smoker	889 (20%)	25 (24%)	27 (21%)	
Never smoker	2546 (60%)	52 (48%)	88 (62%)	
Smoking index	0 (0, 76)	1 (0, 205)	0 (0, 35)	0.2
Activity intensity				0.016
high	1152 (31%)	37 (51%)	29 (29%)	
medium	1101 (28%)	22 (15%)	45 (34%)	
low	2096 (41%)	58 (34%)	63 (37%)	
HTN, n (%)	1110 (22%)	24 (11%)	45 (32%)	0.055
DM, n (%)	383 (6.1%)	10 (12%)	7 (2.1%)	0.14
CHD, n (%)	66 (1.4%)	2 (0.5%)	2 (0.7%)	0.3
FEV1%pred, %	99 (90, 107)	99 (92, 106)	95 (90, 101)	0.017
FVC%pred, %	100 (91, 108)	99 (92, 107)	97 (90, 105)	0.14
FEV1/FVC, %	80.4 (76.4, 84.3)	80.8 (76.1, 84.7)	80.1 (74.9, 82.6)	0.3
FT3, pg/mL	3.20 (3.00, 3.44)	3.20 (3.00, 3.50)	3.10 (2.90, 3.47)	0.8
FT4, ng/dL	0.80 (0.70, 0.88)	0.80 (0.72, 0.90)	0.70 (0.68, 0.80)	0.006
TT3, ng/dL	114 (102, 128)	112 (98, 129)	114 (102, 134)	0.6
TT4, ug/dL	7.64 (6.82, 8.59)	8.00 (6.92, 9.02)	7.60 (6.35, 8.67)	0.3
TSH, μIU/mL	1.52 (1.08, 2.14)	0.36 (0.24, 0.40)	5.29 (4.83, 6.59)	< 0.001

*n: Unweighted numbers are shown, and the statistics are all under complex sampling design conditions

BMI: body mass index, CHD: coronary heart disease, DM: diabetes mellitus, FEV1%pred: percent-predicted FEV1, FVC%pred: percent-predicted FVC, FT3: free triiodothyronine, FT4: free thyroxine, HTN: hypertension, TT3: total triiodothyronine, TT4: total thyroxine, TSH: thyroid stimulating hormone

experimental animals remain undetermined [8]. Nevertheless, it can be deduced that thyroid function can indeed impact lung alveolar elasticity by affecting the basic structure of the lungs, thereby leading to restrictive ventilatory function. In human studies, Li L et al. reported that patients with TSH levels above the reference range (> 4.94 μIU/mL) were more prone to radiation-induced pulmonary fibrosis [30]. This observation aligns with previous meta-analyses and trends observed in our study using the NHANES database [31]. Although Ittermann T et al. did not find a positive relationship between TSH and lung function, they speculated that the lack of association might be due to the small number of patients with abnormal TSH levels [32]. In our study, we expanded the sample size by utilizing the NHANES database for weighted analysis. In our research, thyroid function was not significantly related to the presence of obstructive ventilatory patterns. Although some studies have focused on the relationship between thyroid disease and COPD, the current research findings are inconsistent [33, 34]. It is currently believed that non-thyroidal illness syndrome is the most common disorder in COPD patients [35], reflecting the state of the body under chronic disease conditions. There are no definitive studies currently linking thyroid-related hormones to airway structure. Our findings underscore the importance of considering thyroid function as a potential factor in pulmonary diseases with a restrictive pattern, such as pulmonary fibrosis, and highlight the need for clinicians to be vigilant about pulmonary complications in patients with thyroid dysfunctions.

Currently, the mechanisms underlying the relationship between thyroid-related hormones and pulmonary diseases or lung function are not fully understood. From the perspective of early lung development, thyroid hormones promote lung maturation [36]. Single-cell studies indicate that thyroid hormones can enhance alveolar regeneration by comprehensively regulating the cellular states and

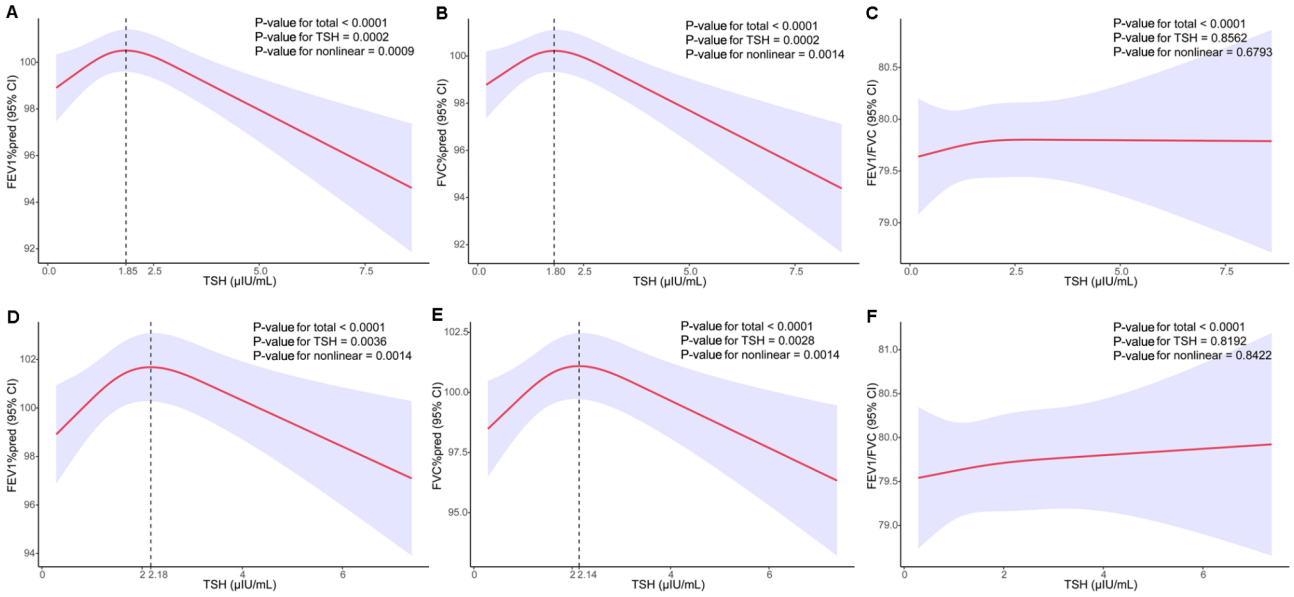

Fig. 3 Analysis of TSH in relation to ventilation function using restricted cubic spline analysis in a weighted generalized linear model. Relationships between TSH and FEV1%pred, FVC%pred, and FEV1/FVC after adjusting for age, sex, race, BMI, smoking index, activity intensity and comorbidities in all participants (**A-C**) and in non-Hispanic White individuals (**D-F**)

intercellular communication of mouse alveolar epithelial cells, macrophages, and fibroblasts [37]. However, these studies lack specific research on the effects of TSH, FT4, and FT3 on lung tissue, and they lack human clinical research results. The observation of a nonlinear relationship between TSH levels and FEV1%pred and FVC%pred, particularly across different TSH ranges, opens new avenues for understanding thyroid-pulmonary interactions. This finding suggests that both low and high levels of TSH might differentially affect lung function, suggesting the need for a more individualized approach when evaluating patients with thyroid and pulmonary disorders. A deeper understanding of the intricate relationship between thyroid function and pulmonary ventilation could lead to more personalized treatment strategies in respiratory medicine. Future studies, particularly randomized controlled trials (RCTs), are needed to confirm these findings.

Although the findings are significant, they are not without limitations. A key strength of our study is the combination of MR and large-scale observational study results, which is the first of its kind in the field of thyroid and lung function. However, a limitation is that the nonlinear relationships observed in observational studies are difficult to reflect in MR. Nonlinear MR offers a method to explore nonlinear genetic relationships, which could complement linear MR results [38]. Regrettably, due to the unavailability of individual-level data on both thyroid function and ventilatory function, along with corresponding GWAS data, we were unable to use this method to validate our findings at the genetic level. Additionally, MR was based on a European population sample, and although we conducted a subgroup analysis within this population in the observational study, future research involving other ethnic groups is needed. Finally, the relationship between thyroid hormones and pulmonary diseases or ventilatory function requires further investigation through high-quality clinical studies, such as RCTs, to provide clearer insights and implications.

Conclusions

In our bidirectional two-sample MR study combined with NHANES database analysis, we found that TSH is associated with pulmonary ventilatory function, particularly in a restrictive ventilatory pattern, with a nonlinear relationship. These findings significantly enhance the clinical understanding of the interplay between thyroid function and pulmonary diseases. They highlight the importance of considering thyroid function in the assessment of pulmonary abnormalities, potentially facilitating the early and personalized treatment of pulmonary disorders. This study underscores the need for a nuanced approach to patient care, where thyroid health is integrally considered in the diagnosis and management of respiratory diseases.

Abbreviations

BH	Benjamini-Hochberg method
BMI	Body mass index
CHD	Coronary heart disease
CIs	Confidence intervals
COPD	Chronic obstructive pulmonary disease
DM	Diabetes mellitus
FDR	False discovery rate
FEV1	Forced expiratory volume in one second

FVC	Forced vital capacity
FT3	Free triiodothyronine
FT4	Free thyroxine
GLM	Generalized linear model
GWAS	Genome-wide association studies
HTN	Hypertension
IVs	Instrumental variables
IVW	Inverse-variance weighted
MR	Mendelian randomization
NHANES	National Health and Nutrition Examination Survey
OR	Odds ratio
RCS	Restricted cubic spline
RCT	Randomized controlled trial
SNPs	Single nucleotide polymorphisms
T3	Triiodothyronine
T4	Thyroxine
TT3	Total triiodothyronine
TT4	Total thyroxine
TSH	Thyroid stimulating hormone

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12890-025-03584-2.

Additional file 1: Table S1: Instrumental variables of thyroid function. Table S2: Instrumental variables of ventilation function. Table S3: Summary of the MR results on the effect of thyroid function on ventilation function. Table S4: Heterogeneity and horizontal pleiotropy tests results for the MR analysis on the effect of thyroid function on ventilation function. Table S5: Summary of the MR results on the effect of ventilation function on thyroid function. Table S6: Heterogeneity and horizontal pleiotropy tests results for the MR analysis on the effect of ventilation function on thyroid function. Table S7: Baseline characteristics of non-Hispanic white participants with different TSH ranges

Additional file 2: Figure S1: Flowchart for NHANES participants selection

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Author contributions
YW designed the research, conducted the statistical analysis and wrote the manuscript. JL and RH interpreted the data and revised the manuscript. YX designed the research, interpreted the data and revised the manuscript. All authors made a significant contribution to the work reported, gave final approval of the version to be published, agreed on the journal to which the article has been submitted and agreed to be accountable for all aspects of the work.

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Data availability
Publicly available datasets were analyzed in this study. These data can be found at https://gwas.mrcieu.ac.uk/, https://transfer.sysepi.medizin.uni-greifswald.de/thyroidomics/datasets/, http://www.cdc.gov/nchs/nhanes/.

Declarations

Ethics approval and consent to participate
Data utilized in the cross-section study came from the NHANES database. The NCHS Institutional Review Board approved the survey protocol, and all participants provided written informed consent. Data utilized in the MR study were sourced from existing research, thus not requiring additional ethical approval.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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