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Research article

Reduced sensitivity to thyroid hormones is associated with lung function in euthyroid individuals

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ABSTRACT

Background: The thyroid gland exhibits a subtle interconnection with the lungs. We further investigated the correlation between thyroid hormone sensitivity and lung function in euthyroid individuals.

Methods: Data on spirometry and mortality for participants aged 19–79 years were extracted from the NHANES database. Obstructive lung function was defined as a forced expiratory volume in 1 s to forced vital capacity ratio (FEV_1/FVC) < 0.70, while restrictive lung function was considered when $FEV_1/FVC \geq 0.70$ and baseline FVC <80 % predicted. Central and peripheral sensitivities to thyroid hormones were mainly evaluated by Thyroid Feedback Quantile-based Index (TFQI) and Free Triiodothyronine/Free thyroxine (FT3/FT4) ratio. Logistic regression and subgroup analysis were used to examine potential associations between thyroid hormone sensitivity and lung function. The association between TFQI and all-cause mortality risk was also investigated.

Results: A total of 6539 participants were analyzed, 900 with obstructive lung function and 407 with restrictive lung function. The prevalence of impaired lung function, both obstructive and restrictive, increased with higher TFQI levels. Logistic regression analysis showed that increased TFQI and decreased FT3/FT4 levels were independent risk factors for obstructive and restrictive lung function ($\boldsymbol{P} < 0.05$). After adjusting for the impact of lung function, TFQI (HR = 1.25, 95 % CI 1.00–1.56, $\boldsymbol{P} = 0.048$) was an independent risk factor for all-cause mortality.

Conclusion: Reduced sensitivity to thyroid hormones has been linked to impaired lung function. TFQI and FT3/FT4 are potential epidemiological tools to quantify the role of central and peripheral thyroid resistance in lung function.

1. Introduction

The thyroid gland is a crucial endocrine gland that produces thyroid hormones, playing a vital role in metabolic regulation [1]. Conversely, the lung is primarily responsible for facilitating gas exchange, allowing oxygen to diffuse into the blood while removing

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carbon dioxide. Despite seeming dissimilar, research suggests a potential connection between thyroid function and lung health. Altered levels of thyroid hormones, including hypothyroidism or hyperthyroidism, may influence respiratory outcomes and lung function. Studies have shown that hypothyroidism may lead to weakened respiratory muscles and reduced lung capacity, while hyperthyroidism may result in increased airway resistance and decreased lung volume [2–4]. Moreover, thyroid hormone imbalance has been linked to numerous respiratory disorders such as chronic obstructive pulmonary disease (COPD), asthma, lung chronic fibrotic, and sleep-disordered breathing [5–10]. Treatment of thyroid dysfunction has shown substantial positive outcomes in respiratory symptoms and patient outcomes [3,11].

However, it is currently unclear whether the above risks apply to individuals without thyroid dysfunction (hypothyroidism or hyperthyroidism). Previous research has suggested that mild thyroid hormone resistance may be present in the general population, and a new metric called Thyroid Feedback Quantile-based Index (TFQI) has been proposed to assess deviations from the average suppression of thyroid hormone in the pituitary gland within the population [12]. Notably, TFQI demonstrated superior clinical applicability and diagnostic value compared to the previous central resistance indices, such as Thyrotroph Thyroxine Resistance Index (TT4RI) and Thyrotropin Index (TSHI) [12–14]. Additionally, compared to peripheral resistance (FT3/FT4), central resistance is easier to evaluate, and it can be quantified by observing the concentration of thyroid hormones and serum thyrotropin (TSH) or their derived indicators, without being affected by other factors [12,15,16].

Currently, no studies have investigated the association between thyroid hormone sensitivity and risk of impaired lung function. The present study assessed the correlation between central and peripheral sensitivities to thyroid hormones, mainly measured by TFQI and FT3/FT4, respectively, with the risk of obstructive and restrictive lung function among euthyroid participants from the National Health and Nutrition Examination Survey (NHANES) database.

2. Methods

2.1. Study population

This was a population-based study obtained from the NHANES database, which is conducted by the Centers for Disease Control and Prevention's National Center for Health Statistics [17]. NHANES is a stratified, multi-stage survey with good national representation and participants are selected at random through a complex statistical process each year. Participants underwent physical examinations, laboratory assessments, as well as questionnaires related to their health and nutrition. The NHANES study was approved by the Ethics Review Board of the National Center for Health Statistics, and written informed consent was obtained from all participants.

We combined data from the 2007–2008, 2009–2010, and 2011–2012 NHANES cycles for analysis, resulting in 6539 eligible participants. All subjects were between the ages of 19 and 79, underwent medical examinations, were not pregnant, had complete thyroid function indicators, and completed lung function tests with acceptable data quality (grade C or above) [18]. According to the medical guidelines for clinical practice provided by the American Association of Clinical Endocrinologists, TSH levels within the range of 0.4–4.5mUI/L are considered normal [19]. We excluded subjects with TSH levels $<$0.4mUI/L or $>$4.5mUI/L. In addition, individuals with abnormal reference ranges for both FT3 (2.5–3.9 pg/mL) and FT4 (7.74–20.64 pmol/L) were also excluded, as well as those receiving thyroid hormone replacement therapy (such as levothyroxine, liothyronine, thyroid desiccated, or any other form) [12,20].

2.2. Calculation of thyroid hormone sensitivity

The central sensitivity to thyroid hormones was measured using three indices: TT4RI, TSHI, and TFQI. TT4RI was calculated as FT4 (pmol/L) $\cdot$ TSH (mIU/L). TSHI $=$ ln TSH (mIU/L) $+$ 0.1345 $\cdot$ FT4 (pmol/L). The formula for calculating TFQI was cumulative distribution function (cdfFT4) – (1 – cdfTSH). The peripheral sensitivity to thyroid hormones was evaluated by FT3/FT4 ratio.

2.3. Lung function measures

From 2007 to 2012, the NHANES study invited individuals ages 6–79 to undergo spirometry, excluding those on supplemental oxygen, who had recently undergone eye, chest, or abdominal surgery, or who had experienced a recent heart attack or stroke [21]. Pre-bronchodilator spirometry was performed by using Ohio 822/827 dry-rolling volume seal spirometers according to American Thoracic Society (ATS) guidelines. The NHANES spirometry data with quality A exceeds ATS data collections standards, B meets ATS data collection standards, and C is potentially useable but does not meet all ATS standards. The FEV_1 and FVC metrics were measured and then converted into percent-predicted values based on the Global Lung Function Initiative (GLI-2012) equation [22,23]. According to previous studies on lung function based on the NHANES database, obstructive lung function was defined by an $FEV_1/FVC < 0.70$ and restrictive lung function by an FVC $<$80 % of predicted with $FEV_1/FVC \geq 0.70$ [21,24,25]. Obstructive lung function categories were established as: severe obstructive impairment ($FEV_1/FVC < 0.70$ and $FEV_1 <$ 50 % predicted), moderate obstructive impairment ($FEV_1/FVC < 0.70$ and FEV_1 50 %–80 % predicted), and mild obstructive impairment ($FEV_1/FVC < 0.70$ and $FEV_1 \geq$ 80 % predicted) [21].

2.4. Covariate definitions

We obtained demographic data including age, gender, race/ethnicity, and annual income. We calculated the body mass index (BMI) for each participant by dividing their weight in kilograms by their measured height in meters squared. Smoking status was

assessed as never, former, or current. Self-reported diabetes was defined. Hypertension was defined as systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg, or the use of antihypertensive medication. Cardiovascular disease was determined based on a patient's reported history of heart attack, stroke, congestive heart failure, coronary artery disease, or angina. Medication history refers to the use of medications in the past month for the treatment of respiratory conditions, primarily categorized as bronchodilators, anti-asthmatics, and inhalers.

2.5. Mortality data

Public-use files for continuous NHANES 2007–2012 with linked mortality data are available. Follow-up time extends from the medical examination date until December 31, 2019. Mortality status is determined by matching NHANES participant records with death certificates in the National Death Index using a probabilistic algorithm.

2.6. Statistical analysis

Population-weighted descriptive statistics were computed and presented. Mean with standard error (SE) was used to express continuous variables, while proportions (SE) were utilized for categorical variables. For comparing continuous variables between two groups, the weighted *t*-test is employed. For multiple groups, weighted Kruskal-Wallis tests is utilized. The comparison of categorical variables across groups is conducted using the weighted chi-square test. Logistic models were utilized to estimate the associations of TT4RI, TSHI, TFQI, and FT3/FT4 with obstructive and restrictive lung function among participants based on the baseline spirometry evaluation. Restricted cubic spline (RCS) analysis was used to further elucidate the correlation between thyroid hormone sensitivity quantified by TFQI, FT3/FT4 and lung function. Subgroup analyses were performed according to age, gender, BMI, race, smoking, diabetes, hypertension, and cardiovascular disease. Finally, the survival curves were constructed using Kaplan-Meier survival analysis, and the log-rank test was used to assess the difference in survival between different TFQI groups. The Cox proportional hazards models

Table 1
Baseline characteristics of study participants with and without impaired lung function, weighted.

Variables	Normal Lung Function (n = 5232)	Obstructive Lung Function (n = 900)	Restrictive Lung Function (n = 407)
Age (years), %			
19–39	47.16 (1.28)	14.49 (2.25) ***	25.31 (3.18) ***
40–59	38.98 (0.97)	44.91 (2.68)	45.31 (4.25)
60–79	13.86 (0.75)	40.60 (2.26)	29.38 (3.34)
Male, %	48.60 (0.85)	61.11 (2.14) ***	49.78 (2.74)
Race, %			
White	66.76 (2.25)	83.41 (2.15) ***	63.26 (5.02) **
Black	10.70 (1.19)	7.14 (1.07)	16.16 (2.90)
Mexican American	9.47 (1.05)	2.44 (0.46)	8.80 (1.70)
Other Hispanic	6.17 (0.80)	2.59 (0.69)	2.91 (0.82)
Other	6.89 (0.77)	4.43 (1.18)	8.86 (2.55)
BMI (kg/m2)	28.42 ± 0.15	27.50 ± 0.25**	32.84 ± 0.47***
Under $20,000, %	12.40 (0.92)	13.73 (1.33)	22.50 (2.67) ***
Smoking, %			
Never	58.98 (1.17)	30.22 (2.42) ***	55.63 (4.61)
Former	21.35 (0.77)	33.54 (1.87)	25.24 (2.42)
Current	19.67 (0.75)	36.24 (2.23)	19.13 (3.23)
Respiratory Medication, %	5.43 (0.59)	15.42 (1.55) ***	9.77 (1.95) *
Diabetes, %	7.08 (0.49)	11.78 (1.06) ***	31.20 (3.60) ***
Hypertension, %	23.16 (0.94)	38.41 (2.12) ***	45.31 (2.46) ***
Cardiovascular Disease, %	3.62 (0.32)	10.48 (1.32) ***	13.58 (2.11) ***
FEV_1 (mL)	3415.51 ± 0.02	2659.33 ± 0.04***	2387.46 ± 0.05***
FVC (mL)	4255.33 ± 0.02	4164.77 ± 0.05	2897.57 ± 0.06***
ppFVC	1.023 (0.00)	1.005 (0.01) *	0.731 (0.00) ***
$ppFEV_1$	1.007 (0.00)	0.813 (0.01) ***	0.750 (0.01) ***
FEV_1/FVC	0.804 (0.00)	0.634 (0.00) ***	0.822 (0.00) ***
FT3 (pg/mL)	3.22 ± 0.01	3.14 ± 0.02***	3.14 ± 0.03**
FT4 (pmol/L)	10.15 ± 0.07	10.22 ± 0.07	10.43 ± 0.13*
TSH (mIU/L)	1.71 ± 0.02	1.82 ± 0.04**	1.85 ± 0.05*
TT4RI	17.26 ± 0.18	18.53 ± 0.46**	19.00 ± 0.58**
TSHI	1.78 ± 0.01	1.86 ± 0.02**	1.91 ± 0.03***
TFQI	0.05 ± 0.01	0.10 ± 0.02**	0.16 ± 0.03***
FT3/FT4	0.33 ± 0.00	0.32 ± 0.00***	0.31 ± 0.00***
Mortality, %	3.85 (0.34)	18.53 (1.93) ***	14.36 (2.54) ***

Note: Values for categorical variables are given as weighted percentage (standard error); for continuous variables, as weighted mean ± standard error. *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$ (Normal lung function was used as reference).
BMI – body mass index; FEV_1 – forced expiratory volume in 1 s; FVC - forced vital capacity; $ppFEV_1$– percent predicted FEV_1; ppFVC– percent predicted FVC; TT4RI - Thyrotroph Thyroxine Resistance Index; TSHI - Thyrotropin Index; TFQI - Thyroid Feedback Quantile-based Index; FT3/FT4 -Triiodothyronine/Free thyroxine.

were employed to estimate the hazard ratios (HRs) and 95 % confidence interval (CI) of all-cause for each standard deviation (SD) increment of TFQI. All statistical analyses were carried out in compliance with Centers for Disease Control and Prevention guidelines. The complex multistage cluster survey design was considered, and weights combined with three cycles were applied. Statistical significance was assessed at a two-sided P value < 0.05.

3. Results

3.1. Baseline characteristics of study population

Out of the total number of 6, 539 participants surveyed, 900 (13.8 %) individuals had obstructive lung function, while 407 (6.2 %) had restrictive lung function. We compared the general information and clinical indicators of participants with normal, obstructive, and restrictive lung function (Table 1). The obstructive and restrictive lung function groups demonstrated a statistically significant increase in various factors including age, use of respiratory medication, prevalence of diabetes, hypertension, and cardiovascular disease, as well as mortality, and TSH levels when compared to the normal lung function group ($P < 0.05$). Conversely, FT3, FEV_1, percent predicted FEV_1 ($ppFEV_1$), and percent predicted FVC (ppFVC) exhibited a significant decrease ($P < 0.05$). Additionally, obstructive lung function is more common in males, smokers, and individuals with a low BMI and FEV_1/FVC ($P < 0.01$). Participants with restrictive lung function showed significant increases in annual income under $20,000, BMI, FEV_1/FVC, and FT4 levels, whereas FVC decreased significantly ($P < 0.05$). Race distribution also demonstrated significant differences among the three groups ($P < 0.01$). Importantly, our study revealed significantly higher levels of T4RI, TSHI and TFQI in participants with obstructive and restrictive lung function compared to those with normal lung function ($P < 0.01$). On the other hand, the level of FT3/FT4 is significantly lower ($P < 0.001$).

Table 2
Baseline characteristics of study population in TFQI tertiles, weighted.

Variables	TFQI-Tertile 1	TFQI-Tertile 2	TFQI-Tertile 3	P-value
Age (years), %				<0.001
19–39	45.76 (1.55)	43.13 (1.66)	35.64 (1.86)	
40–59	43.13 (1.62)	38.76 (1.40)	38.59 (1.61)	
60–79	11.11 (0.80)	18.11 (1.33)	25.77 (1.21)	
Male, %	49.60 (1.47)	49.96 (1.34)	51.67 (1.20)	0.568
Race, %				<0.001
White	64.98 (2.49)	69.97 (2.54)	71.70 (2.30)	
Black	14.86 (1.48)	9.54 (1.25)	7.15 (1.04)	
Mexican American	8.76 (1.09)	8.23 (1.00)	8.38 (1.12)	
Other Hispanic	6.04 (0.87)	5.22 (0.76)	5.27 (0.85)	
Other	5.37 (0.72)	7.03 (0.98)	7.49 (1.04)	
BMI (kg/m2)	28.13 ± 0.18	28.64 ± 0.21	28.76 ± 0.20	0.031
Under $20,000, %	13.39 (1.16)	12.66 (0.89)	13.23 (1.19)	0.782
Smoking, %				<0.001
Never	52.29 (1.83)	56.30 (1.59)	55.64 (1.84)	
Former	20.78 (1.16)	23.69 (1.12)	25.22 (1.25)	
Current	26.93 (1.51)	20.01 (1.24)	19.14 (1.58)	
Respiratory Medication, %	6.44 (0.82)	6.90 (0.71)	7.79 (0.86)	0.393
Diabetes, %	6.99 (0.63)	8.50 (0.79)	11.29 (0.87)	<0.001
Hypertension, %	23.61 (1.15)	25.39 (1.52)	30.17 (1.49)	0.002
Cardiovascular Disease, %	4.09 (0.52)	3.90 (0.56)	7.24 (0.70)	<0.001
FEV_1 (mL)	3308.41 ± 0.02	3263.31 ± 0.03	3204.79 ± 0.03	0.039
FVC (mL)	4228.35 ± 0.03	4174.95 ± 0.03	4123.02 ± 0.03	0.096
ppFVC	1.015 (0.00)	1.005 (0.00)	0.999 (0.01)	0.022
$ppFEV_1$	0.974 (0.00)	0.966 (0.01)	0.960 (0.01)	0.097
FEV_1/FVC	0.784 (0.00)	0.783 (0.00)	0.776 (0.00)	0.020
Lung Function, %				0.003
Normal	84.18 (1.00)	80.95 (1.46)	77.90 (0.90)	
Mild Obstructive	7.41 (0.82)	7.76 (0.86)	9.21 (0.69)	
Moderate Obstructive	4.68 (0.54)	5.09 (0.71)	5.62 (0.53)	
Severe Obstructive	0.48 (0.18)	0.84 (0.25)	0.98 (0.23)	
Restrictive	3.25 (0.46)	5.36 (0.76)	6.30 (0.65)	
FT3 (pg/mL)	3.20 ± 0.01	3.19 ± 0.01	3.22 ± 0.01	0.148
FT4 (pmol/L)	9.01 ± 0.05	10.21 ± 0.08	11.26 ± 0.06	<0.001
TSH (mIU/L)	1.13 ± 0.01	1.67 ± 0.03	2.39 ± 0.03	<0.001
TT4RI	9.91 ± 0.09	16.07 ± 0.22	26.42 ± 0.28	<0.001
TSHI	1.25 ± 0.01	1.79 ± 0.01	2.33 ± 0.01	<0.001
FT3/FT4	0.36 ± 0.00	0.32 ± 0.00	0.29 ± 0.00	<0.001
Mortality, %	5.58 (0.64)	5.08 (0.75)	8.65 (0.78)	<0.001

Note: Values for categorical variables are given as weighted percentage (standard error); for continuous variables, as weighted mean ± standard error.

3.2. Clinical features according to TFQI tertiles

Study participants were classified into three groups based on their TFQI levels, ranging from low to high (Table 2). The prevalence of older age, white ethnicity, BMI, diabetes, hypertension, cardiovascular disease, and the levels of FT4, TSH, TT4R, and TSHI were significantly greater in the second and third tertile groups than in the first tertile group. In contrast, FEV_1, ppFVC, and FEV_1/FVC were significantly lower ($P < 0.05$). Notably, as TFQI levels gradually increased, there was a consequent gradual increase in the number of participants experiencing obstructive and restrictive lung function ($P < 0.01$). Race and smoking status distribution also demonstrated significant differences among the three groups ($P < 0.001$). Additionally, the TFQI-Tertile 3 group demonstrated significant mortality rates ($P < 0.001$).

3.3. Associations between sensitivity to thyroid hormones and obstructive lung function

The association between thyroid hormone sensitivity and obstructive lung function was shown in Table 3. In unadjusted models, TT4RI, TSHI, and TFQI exhibited positive associations with a heightened risk of obstructive lung function, in contrast to FT3/FT4, which demonstrated a negative association with obstructive lung function prevalence. The correlation between thyroid hormone sensitivity-related indices and obstructive lung function remained significant even after adjusting for multiple covariates. TFQI had a higher correlation with obstructive lung function compared to other central resistance indices (TT4RI and TSHI). The adjusted model supported a 34 % escalated risk of impaired obstructive lung function per unit increase in TFQI (OR = 1.34, 95 % CI 1.05–1.70, $P = 0.017$). The classification of TFQI revealed that high TFQI tertiles (2 and 3) had a higher prevalence of obstructive lung function than the lowest tertile, as observed in both the unadjusted (Teritle 3, OR = 1.36, 95 % CI 1.14–1.62, $P < 0.001$) and adjusted models (Teritle 3, OR = 1.26, 95 % CI 1.05–1.52, $P = 0.015$). RCS analysis substantiated the existence of a positive correlation between TFQI and obstructive lung function (Fig. 1a). In addition, a reduced FT3/FT4 level was associated with an increased risk of obstructive lung function (Fig. 1b).

3.4. Associations between sensitivity to thyroid hormones and restrictive lung function

Table 4 explored the association between central and peripheral sensitivity to thyroid hormone and restrictive lung function. Consistent with the above results on obstructive lung function, the unadjusted model indicates a positive association between TT4RI, TSHI, and TFQI and restrictive lung function. In turn, FT3/FT4 showed a negative association with the prevalence of restrictive lung function. After controlling for covariates, TT4RI (OR = 1.01, 95 % CI 1.00–1.02, $P = 0.036$), TSHI (OR = 1.32, 95 % CI 1.08–1.60, $P = 0.005$), TFQI (OR = 1.61, 95 % CI 1.15–2.25, $P = 0.005$), and FT3/FT4 (OR = 0.04, 95 % CI 0.01–0.23, $P < 0.001$) continued to be significantly correlated with restrictive lung function. By dividing TFQI into tertiles, a higher prevalence of restrictive lung function was observed in groups 2 (OR = 1.48, 95 % CI 1.13–1.94, $P = 0.005$) and 3 (OR = 1.50, 95 % CI 1.15–1.97, $P = 0.003$) compared to the lowest TFQI tertile in the multivariate model. The correlation between TFQI, FT3/FT4 and restrictive lung function was also confirmed by RCS analysis (Fig. 2a and b).

3.5. Subgroup analysis

We conducted a study of the association between TFQI, FT3/FT4, and the risk of obstructive and restrictive lung function in subgroups stratified by age, gender, race, smoking status, BMI, diabetes, hypertension, and cardiovascular disease. Regarding TFQI, while smoking appears to present a higher risk than non-smoking in terms of obstructive and restrictive lung function, this is not statistically significant (P for interaction = 0.070 and 0.075) (Figs. 3 and 4). There was a significant interaction between smoking status and FT3/FT4 in obstructive lung function (**Attachment 1**). No significant interactions were observed in the subgroup analyses of FT3/FT4 and restrictive lung function (**Attachment 1**).

Table 3
Association of thyroid hormone sensitivity-related indices with obstructive lung function.

Thyroid hormone sensitivity-related indices	Non-adjusted model OR 95%CI, P-value	Adjusted model OR 95%CI, P-value
TT4RI	1.02 (1.01, 1.02), <0.001	1.01 (1.00, 1.02), 0.002
TSHI	1.31 (1.15, 1.49), <0.001	1.26 (1.09, 1.44), 0.001
TFQI	1.48 (1.18, 1.84), <0.001	1.34 (1.05, 1.70), 0.017
TFQI-Tertile		
Tertile 1	1.00	1.00
Tertile 2	1.18 (0.98, 1.40), 0.077	1.18 (0.98, 1.43), 0.084
Tertile 3	1.36 (1.14, 1.62), <0.001	1.26 (1.05, 1.52), 0.015
FT3/FT4	0.04 (0.01, 0.14), <0.001	0.05 (0.02, 0.19), <0.001

Adjusted model: Adjusted for age, gender, race, BMI, annual income, diabetes, hypertension, cardiovascular disease, smoking status, respiratory medication.

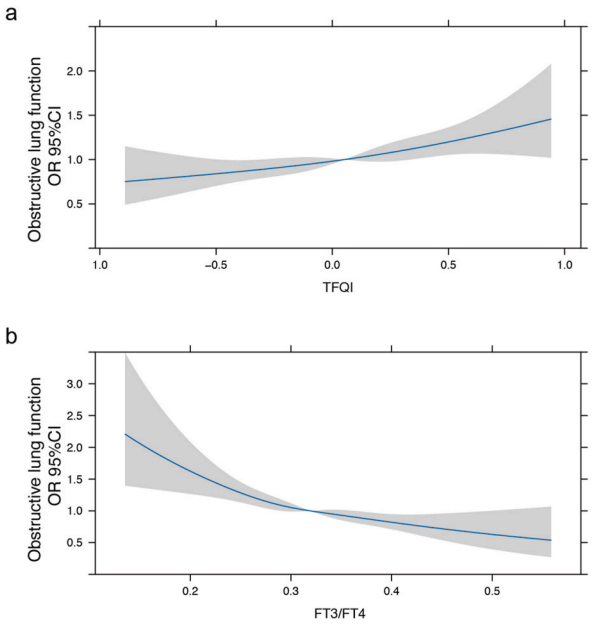

Fig. 1. RCS results between thyroid hormone sensitivity and obstructive lung function (**a** RCS results between TFQI and obstructive lung function; **b** RCS results between FT3/FT4 and obstructive lung function).

Table 4
Association of thyroid hormone sensitivity-related indices with restrictive lung function.

Thyroid hormone sensitivity-related indices	Non-adjusted model OR 95%CI, P-value	Adjusted model OR 95%CI, P-value
TT4RI	1.02 (1.01, 1.03), <0.001	1.01 (1.00, 1.02), 0.036
TSHI	1.51 (1.26, 1.82), <0.001	1.32 (1.08, 1.60), 0.005
TFQI	1.95 (1.42, 2.69), <0.001	1.61 (1.15, 2.25), 0.005
TFQI-Tertile		
Tertile 1	1.00	1.00
Tertile 2	1.60 (1.23, 2.08), <0.001	1.48 (1.13, 1.94), 0.005
Tertile 3	1.75 (1.35, 2.27), <0.001	1.50 (1.15, 1.97), 0.003
FT3/FT4	0.01 (0.00, 0.05), <0.001	0.04 (0.01, 0.23), <0.001

Adjusted model: Adjusted for age, gender, race, BMI, annual income, diabetes, hypertension, cardiovascular disease, smoking status, respiratory medication.

3.6. TFQI and all-cause mortality

A previous study based on the NHANES database showed an association between FT3/FT4 and all-cause mortality [26]. The presence of impaired lung function is also an autonomous risk factor for all-cause mortality within the population of the United States [27–29]. We furthermore explored whether TFQI was also associated with all-cause mortality risk in the United States population. With a median follow-up of 134 months, 570 participants died. Results from the log-rank test demonstrated significant differences in survival rates across the three groups categorized by the TFQI index (Fig. 5) ($\boldsymbol{P} < 0.001$). Specifically, those who were in the highest TFQI groups presented an increased risk of mortality over time. Results from the Cox proportional hazard model revealed TFQI (HR = 1.25, 95 % CI 1.00–1.56, $\boldsymbol{P} = 0.048$) was independent risk factors for all-cause mortality after adjusted for impaired lung function and other risk factors (Table 5).

4. Discussion

Our population-based study explored the relationship between thyroid hormone sensitivity and lung function. The present study found that obstructive lung function was prevalent in approximately 13.8 % of the US population aged 19–79 years, while restrictive lung function was found in 6.2 % of the population, based on measurements of pre-bronchodilator lung volume. This result is broadly consistent with previous estimates of the prevalence of obstructive and restrictive lung function in the US population [30]. In individuals with normal thyroid function, both central and peripheral decreased thyroid hormone sensitivity was independently associated with a greater risk of obstructive and restrictive lung function. In the entire research cohort (2007–2012), TFQI (HR = 1.25, 95 % CI 1.00–1.56, $\boldsymbol{P} = 0.048$) was an independent risk factor for all-cause mortality.

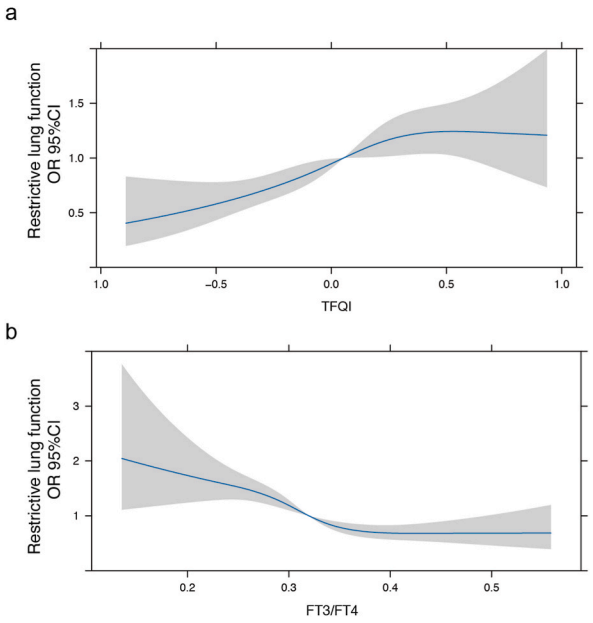

Fig. 2. RCS results between thyroid hormone sensitivity and restrictive lung function (**a** RCS results between TFQI and restrictive lung function; **b** RCS results between FT3/FT4 and restrictive lung function).

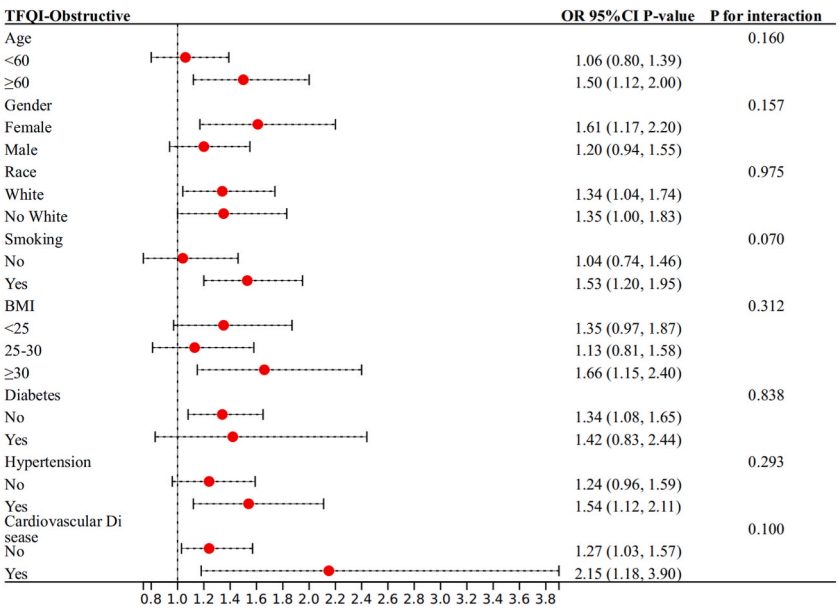

Fig. 3. Subgroup analysis for the association between TFQI and obstructive lung function.

The central sensitivity of the thyroid gland is primarily regulated by TSH, which controls sensitivity to thyroid hormones. Peripheral sensitivity concerns the metabolism and conversion of T4 and T3 in the peripheral tissues. Although the two are different in terms of direction and linkage, our results suggest that impaired lung function is associated with both. Among the metrics that reflect the central sensitivity to thyroid hormones, the TFQI metric shows better performance.

Several studies have attempted to establish a connection between thyroid and lung function within the normal range of thyroid function. Kim et al. found elevated FT4 levels in the obstructive lung pattern group compared to the normal lung function group, whereas no significant difference in TSH levels was observed for either group after adjusting for smoking status [31]. In middle-aged individuals with normal thyroid function, elevated FT4 levels were identified as an autonomous predictor of obstructive pulmonary patterns [31]. Ittertmann et al. integrated data from two population-based studies and their analysis revealed that serum TSH levels, within the standard range, were inversely related to FEV_1/FVC [32]. However, inconsistent results were observed when serum TSH

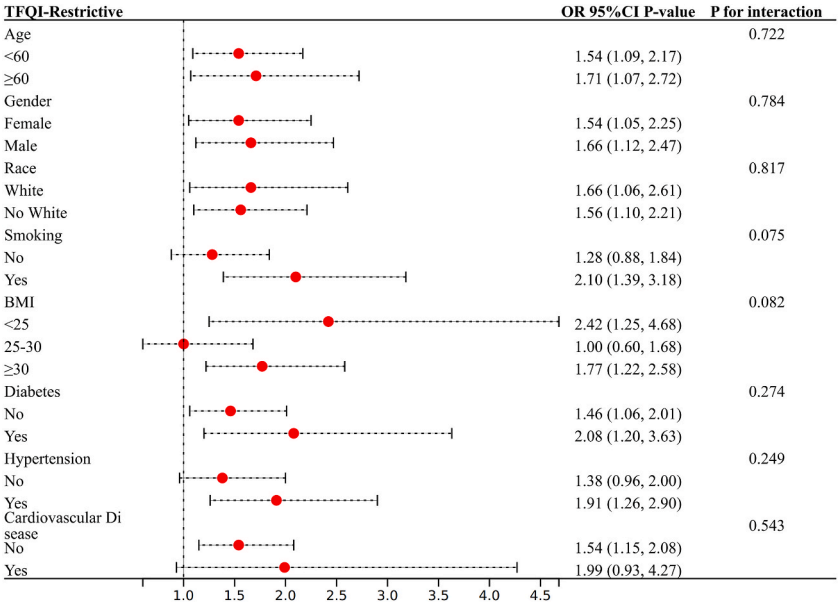

Fig. 4. Subgroup analysis for the association between TFQI and restrictive lung function.

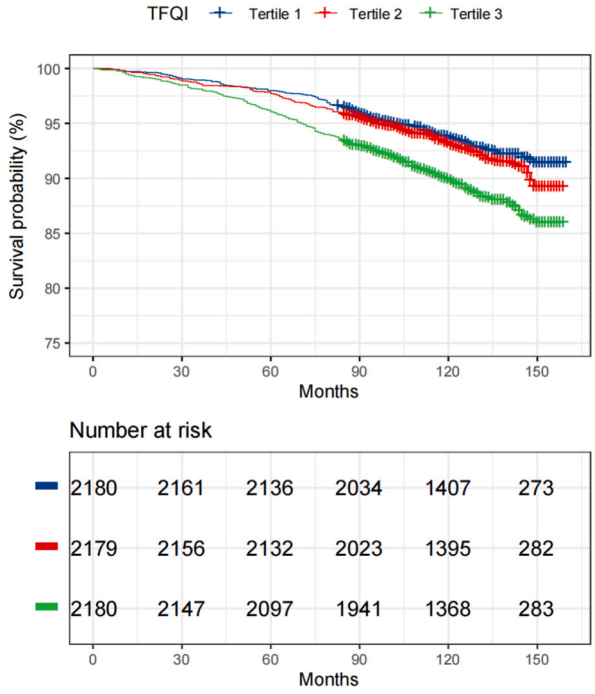

Fig. 5. Kaplan-Meier survival curve based on TFQI tertiles.

levels were classified based on quintiles. Another study conducted by Okutan et al. revealed that the COPD group had significantly lower FT3 levels compared to the control group [33]. Conversely, for FT4 and TSH levels, no significant difference was found between COPD and healthy controls [33]. Based on the fact that thyroid hormone resistance is also present in individuals with normal thyroid function, the evaluation metrics established from a thyroid hormone sensitivity perspective show a stronger correlation with obstructive ventilation patterns than the individual metrics alone. This may help to explain the inconsistencies observed in previous studies and the failure to establish a link between TSH and impaired lung function. In addition, we investigated for the first time the relationship between thyroid function and restrictive lung function in euthyroid individuals. We found that thyroid hormone sensitivity was also impaired in the presence of restrictive lung function.

Table 5
Association of various factors with all-cause mortality.

All-cause mortality	HR	lower	upper	P-value
TFQI	1.25	1.00	1.56	0.048
Mild Obstructive	1.65	1.30	2.12	<0.001
Moderate Obstructive	2.29	1.79	2.92	<0.001
Severe Obstructive	4.30	2.93	6.32	<0.001
Restrictive	1.82	1.38	2.39	<0.001
Age ≥60	5.90	4.58	7.60	<0.001
Male	1.47	1.23	1.75	<0.001
No White	0.74	0.62	0.88	0.001
Under $20,000	1.85	1.55	2.21	<0.001
Smoking	1.34	1.12	1.61	0.002
Diabetes	1.24	1.01	1.51	0.039
Hypertension	1.20	0.99	1.44	0.051
Cardiovascular Disease	1.88	1.53	2.31	<0.001

Thyroid hormones may directly affect lung function by influencing airway smooth muscle tone, airway cell membrane fluidity, and neurotransmitter release. When lung function are impaired, thyroid hormones could participate in the protective and repair processes. This is achieved through several mechanisms, including modulation of water channel expression, enhancement of airway cell proliferation, alteration of cell permeability and induction of cell contraction to regulate lung fluid balance [31,34,35]. There are other factors that mediate the relationship between observed thyroid hormone resistance and lung function, including inflammation, oxidative stress, or metabolic dysfunction [1,36]. Obstructive and restrictive lung function disorders may increase metabolism. To meet the increased energy consumption and metabolic demands caused by higher respiratory effort and oxygen demand, a moderate increase in FT4 levels within the normal upper limit range can be viewed as an adaptive strategy [31]. This occurs to allow the body to adapt and maintain a balance of oxygen consumption and demand.

Previous studies have shown that elevated normal FT4 values are associated with an increased risk of death, but no clear inverse association between TSH and outcome has been found [37–39]. Our findings that central thyroid resistance, represented by TFQI, is associated with an increased risk of death may suggest that the presence of thyroid resistance in the general population masks the association between TSH and outcomes [40]. The presence of obstructive and restrictive lung function was a significant predictor of earlier death during long-term follow-up [29,41]. Although TFQI was associated with impaired lung function, the fitted Cox model showed that TFQI was an independent risk factor for all-cause mortality.

This study used a nationally representative sample that adequately represented the various ethnic groups in the United States and took advantage of the availability of spirometry data. However, some limitations must be considered, including the cross-sectional nature of the study and missing data after bronchodilator use. Given that our study population is derived from the NHANES database, which differs from the GLI-2012 for airway obstruction classification and severity, we adhered to the previous criteria for lung function classification [42]. The adoption of the GOLD criteria might also lead to the misclassification of some patients with normal lung function as having impaired lung function [43]. In addition, potential confounding variables may not have been fully accounted for in the analysis. Future longitudinal studies investigating temporal relationships between TFQI and FT3/FT4 changes, and lung function are also necessary.

5. Conclusion

In representative US population, our study findings suggest that the extent of thyroid resistance is linked to obstructive and restrictive lung function risk. In the evaluation and follow-up of lung function in chronic respiratory diseases, the assessment of thyroid hormone sensitivity might be an important consideration.

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Ethics Statement

This study involving human participants were reviewed and approved by the Research Ethics Review Board of the NCHS. The patients/participants provided their written informed consent to participate in this study.

Data availability

The data used in this study were obtained from publicly available and freely accessible database (NHANES, https://www.cdc.gov/nchs/nhanes/).

CRediT authorship contribution statement

Zhaoxiang Wang: Writing – review & editing, Writing – original draft, Formal analysis, Conceptualization. **Bing Lu:** Writing – review & editing, Methodology, Investigation, Data curation, Conceptualization. **Menghuan Wu:** Writing – review & editing. **Tian Gu:** Investigation, Formal analysis. **Mengjiao Xu:** Software, Methodology, Investigation. **Fengyan Tang:** Visualization, Validation. **Li Zhang:** Visualization, Validation. **Song Bai:** Writing – review & editing. **Shao Zhong:** Visualization, Formal analysis, Data curation. **Qichao Yang:** Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e30309.

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