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Impaired sensitivity to thyroid hormones is associated with albuminuria in the euthyroid population: results from NHANES

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Abstract

Purpose The relationship between thyroid hormone sensitivity and albuminuria remains unclear. We aimed to investigate the association between thyroid hormone sensitivity and the risk of albuminuria in a euthyroid population.

Methods This cross-sectional study included 7634 euthyroid adults collected from the National Health and Nutrition Examination Survey (NHANES) between 2007 and 2012. Central sensitivity to thyroid hormones was evaluated using the thyroid-stimulating hormone index (TSHI), the thyrotrophic thyroxine resistance index (TT4RI), and the thyroid feedback quantile-based index (TFQI). Peripheral sensitivity to thyroid hormones was measured using the free triiodothyronine/free thyroxine (FT3/FT4) ratio. Furthermore, the independent relationship between sensitivity to thyroid hormones and albuminuria was assessed.

Results The proportion of albuminuria increased with a higher interquartile range of TFQI levels (7.31% vs. 7.89% vs. 7.95% vs. 9.89%, $P = 0.024$). Furthermore, TFQI was found to be independently associated with the risk of albuminuria after adjusting for confounding factors (OR = 1.28, 95% CI 1.01–1.60, $P = 0.037$). Subgroup analysis revealed a significant relationship between TFQI and albuminuria, especially among individuals over 60.

Conclusions In euthyroid subjects, impaired central sensitivity to thyroid hormones is associated with albuminuria. TFQI holds significant potential as an epidemiological tool for quantifying the impact of impaired central sensitivity on the risk of albuminuria.

Keywords NHANES · Albuminuria · Sensitivity to thyroid hormones · Thyroid feedback quantile-based index · Population-based study

Introduction

Chronic kidney disease (CKD) is a progressive condition that has emerged as a significant cause of mortality and morbidity in the twenty-first century, impacting over 10% of the global population [1]. Albuminuria, which refers to the excessive presence of albumin in the urine, is a crucial marker for glomerular injury and renal dysfunction [2]. It is frequently linked to kidney diseases, including diabetic nephropathy and hypertensive nephropathy [3, 4]. Under normal physiological conditions, the glomerulus filters only a minimal amount of albumin, while the renal tubules reabsorb the majority. However, in the presence of renal dysfunction or impairment, the permeability of the glomerular filtration barrier becomes compromised, resulting in the leakage of albumin into the urine. Moreover, it is strongly associated with an increased risk of progressive decline in renal function, metabolic disease, cardiovascular events, and all-cause mortality [5–8]. Non-invasive methods, like urine testing, are commonly used to diagnose albuminuria. This type of testing involves measuring the urinary albumin/creatinine ratio (UACR) or the amount of albumin eliminated over a specific period.

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Previous studies have indicated an intricate relationship between thyroid hormones and albuminuria [9–13]. Thyroid hormones impact several aspects of kidney function, including kidney structure, hemodynamics, glomerular filtration rate (GFR), and sodium and water homeostasis [14, 15]. Imbalances in the levels of thyroid hormones, specifically hypothyroidism, have been linked to an elevated risk of developing albuminuria [16–18]. However, a recent study has suggested a mild form of thyroid hormone resistance in the general population [19]. Thus, a novel metric, TFQI, has been proposed to assess deviations from the average suppression of thyroid hormone in the pituitary gland. However, its clinical relevance remains largely unclear [19].

To our knowledge, no studies have previously examined the connection between sensitivity to thyroid hormones and the likelihood of albuminuria. Therefore, we undertook a study to explore the association between central and peripheral sensitivity to thyroid hormones, primarily measured through TFQI and FT3/FT4, with albuminuria risk among euthyroid individuals from the NHANES database.

Materials and methods

Data source

This population-based study was conducted by sourcing data from the NHANES, conducted by the National Center for Health Statistics of the Centers for Disease Control and Prevention [20]. NHANES conducted a randomized, stratified, multi-stage survey with a nationwide representation; participants underwent physical examinations, questionnaires about their health and nutrition, and laboratory assessments. The research adhered to the guidelines provided by the Ethics Review Board of the National Center for Health Statistics, and written informed consent was obtained from all participants.

Our analysis finally comprised 7634 eligible participants, obtained by merging data from the following NHANES cycles: 2007–2008, 2009–2010, and 2011–2012 (30,442 participants). All included participants were aged between 19 and 79 years, had no records of pregnancy, exhibited complete indicators of thyroid function, and provided complete data on the UACR and estimated glomerular filtration rate (eGFR). In line with the medical guidelines for clinical practice by the American Association of Clinical Endocrinologists, serum TSH levels between 0.4 and 4.5 mIU/L were considered normal [21]. We excluded subjects with TSH levels < 0.4 mIU/L or > 4.5 mIU/L, as well as individuals with abnormal reference ranges for both FT3 and FT4. Additionally, participants undergoing thyroid hormone replacement therapy (levothyroxine, liothyronine, thyroid desiccated, or other) were excluded, along with those who had a previous history of thyroid disease (Fig. 1).

Fig. 1 Flowchart of the sample selection from NHANES 2007–2011
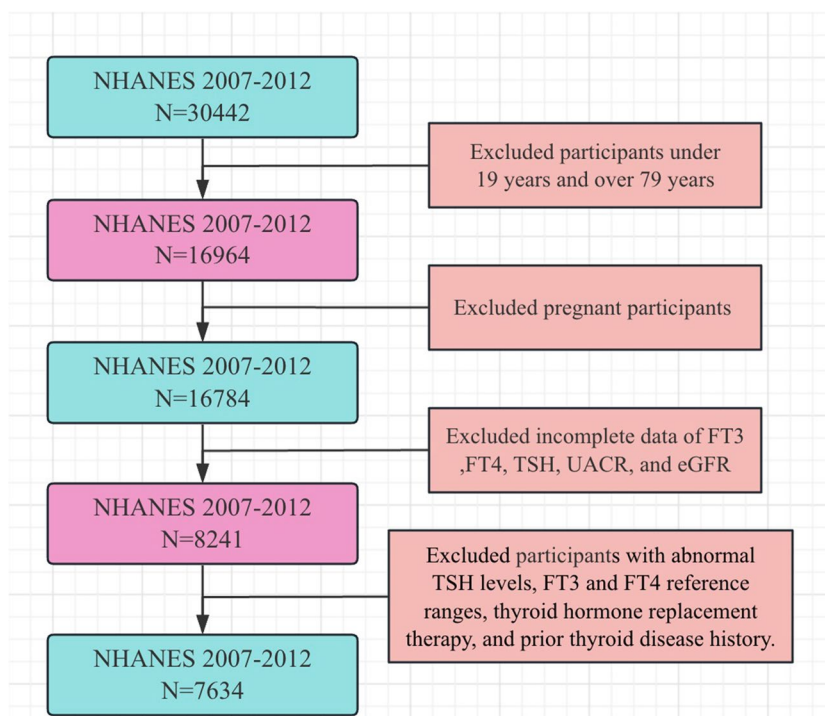
Outcome definitions

UACR was calculated as the ratio of urinary concentration of albumin (measured in mg/dL) to creatinine (measured in mg/L). UACR values of 30–300 mg/g and ≥ 300 mg/g indicate the presence of microalbuminuria and macroalbuminuria, respectively. The occurrence of albuminuria (UACR ≥ 30 mg/g) served as the outcome variable for our study [22].

Exposure definitions

Three indices were used to evaluate central sensitivity to thyroid hormones, as follows: TSHI, TT4RI, and TFQI. TSHI was calculated as ln TSH (mIU/L) + 0.1345 · FT4 (pmol/L). TT4RI was measured by multiplying the values for FT4 (pmol/L) by TSH (mIU/L). The formula for calculating TFQI was cumulative distribution function (cdfFT4) − (1 − cdfTSH). The values for TFQI range from − 1 to 1, where negative values indicate greater sensitivity of the hypothalamic-pituitary-thyroid axis to thyroid hormone fluctuations, and positive values denote lesser sensitivity [19]. Furthermore, the ratio of FT3 to FT4 measured peripheral sensitivity to thyroid hormones[23].

Covariate definitions

The study collected demographic data, including age, gender, and race. It also included several potential covariates, such as annual income, education level, physical activity, smoking status, hypertension, diabetes, cardiovascular disease, body mass index (BMI, kg/m^2), alanine transaminase (ALT, U/L), aspartate transaminase (AST, U/L), gamma-glutamyl transferase (GGT, U/L), triglycerides (TG, mmol/L), total cholesterol (TC, mmol/L), high-density lipoprotein cholesterol (HDL-c, mmol/L), low-density lipoprotein cholesterol (LDL-c, mmol/L), blood urea nitrogen (BUN, mg/dL), serum creatinine (Scr, mg/dL), serum uric acid (SUA, μmol/L), and eGFR. eGFR was calculated using the CKD-EPI creatinine equation, considering factors such as age, gender, race, and Scr [23]. 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. The presence of cardiovascular disease was determined based on self-reported history of heart attack, stroke, congestive heart failure, coronary artery disease, or angina. Detailed measurement procedures for all variables in this study were publicly available in the NHANES database (https://www.cdc.gov/nchs/nhanes/).

Statistical analysis

Population-weighted descriptive statistics were calculated and are presented in this study. Continuous variables are reported as mean with standard error (SE) and categorical variables as percentages. The weighted Student's t-test and chi-squared test were used to compare continuous and categorical variables in multiple groups. Weighted Pearson correlation analysis was used to assess the association of TFQI with other covariates. A logistic regression model was employed to investigate the associations between thyroid hormone levels and sensitivity-related indicators (FT3, FT4, TSH, FT3/FT4, TSHI, TT4RI, and TFQI) with the risk of albuminuria. Three models were used, as follows: model 1 without covariates; model 2 with adjustments for age, gender, and race; and model 3 with adjustments for age, gender, race, annual income, education level, smoking status, physical activity, diabetes, hypertension, cardiovascular disease, BMI, ALT, AST, GGT, TG, TC, HDL, LDL, BUN, SUA, Scr, and eGFR. Smooth curve fitting analysis was conducted using a generalized additive model for albuminuria, UACR, BUN, Scr, and eGFR, with the TFQI index as the independent variable, after adjusting for age, gender, and race. Receiver operating characteristic (ROC) analysis was also employed to evaluate the impact of thyroid hormone sensitivity–related indices on albuminuria. Subgroup analyses were performed stratified by age ($< 60/ \geq 60$ years), gender (female/male), BMI ($< 25/25$–$30/ \geq 30$ kg/m^2), diabetes (yes/no), hypertension (yes/no), cardiovascular disease (yes/no), and eGFR ($< 60/60$–$90/ \geq 90$ mL/min/1.73 m^2). All statistical analyses followed the guidelines provided by the Centers for Disease Control and Prevention, considering the complex multi-stage cluster survey design and incorporating weights from three cycles. The data analyses used were Empower (http://www.empowerstats.com) and R software (http://www.r-project.org). Statistical significance was determined as a two-sided P value < 0.05.

Results

Baseline characteristics of the study population

The study included 7634 subjects who met the inclusion criteria, with an average age of 44.91 ± 0.40 years and a male composition of 50.27%. We analyzed and compared the general information and clinical indicators between the groups categorized as non-albuminuria and albuminuria (Table 1). The results demonstrated that the albuminuria group exhibited significantly higher values in regard to age, annual income below $20,000, smoking, diabetes, hypertension, cardiovascular disease, BMI, ALT, AST, GGT, TG, BUN, SUA, Scr, FT4 levels, TSH levels, TSHI levels, TT4RI

Table 1 Baseline characteristics of study population according to non-albuminuria/albuminuria, weighted

	Overall	Non-albuminuria ($N=6765$)	Albuminuria ($N=869$)	P value
Age (years)	44.91 ± 0.40	44.36 ± 0.40	50.98 ± 0.75	<0.001
Male gender, % (SE)	50.27 (0.54)	50.55 (0.53)	47.20 (2.72)	0.107
Race, % (SE)				<0.001
Mexican American	8.50 (0.99)	8.31 (0.98)	10.53 (1.45)	
Other Hispanic	5.59 (0.83)	5.52 (0.80)	6.31 (1.32)	
Non-Hispanic White	68.18 (2.32)	68.79 (2.28)	61.35 (3.45)	
Non-Hispanic Black	10.87 (1.21)	10.38 (1.20)	16.24 (1.81)	
Other Races	6.87 (0.68)	6.99 (0.67)	5.56 (1.23)	
Annual income (below $20,000), % (SE)	14.05 (0.89)	13.16 (0.91)	23.83 (1.47)	<0.001
Education level (above high school), % (SE)	56.91 (1.64)	58.00 (1.62)	44.81 (2.92)	<0.001
Moderate physical activity, % (SE)	41.59 (0.89)	42.04 (0.96)	36.55 (2.25)	0.007
Smoking status, % (SE)				0.004
Never	54.30 (1.20)	54.87 (1.22)	47.99 (2.55)	
Former	23.59 (0.63)	23.30 (0.66)	26.70 (1.61)	
Current	22.11 (0.92)	21.82 (0.92)	25.31 (2.12)	
Diabetes, % (SE)	8.21 (0.47)	6.43 (0.39)	27.89 (2.52)	<0.001
Hypertension, % (SE)	28.15 (0.80)	26.34 (0.79)	48.21 (2.48)	<0.001
Cardiovascular disease, % (SE)	6.44 (0.42)	5.50 (0.38)	16.86 (1.57)	<0.001
BMI (kg/m^2)	28.53 ± 0.12	28.38 ± 0.12	30.22 ± 0.35	<0.001
ALT (U/L)	26.21 ± 0.26	26.04 ± 0.27	28.15 ± 1.14	0.013
AST (U/L)	26.05 ± 0.25	25.77 ± 0.24	29.12 ± 1.29	<0.001
GGT (U/L)	29.20 ± 0.70	27.68 ± 0.48	46.11 ± 6.85	<0.001
TG (mmol/L)	1.50 ± 0.03	1.46 ± 0.03	1.89 ± 0.10	<0.001
TC (mmol/L)	5.07 ± 0.02	5.07 ± 0.02	5.01 ± 0.06	0.166
HDL-c (mmol/L)	1.35 ± 0.01	1.35 ± 0.01	1.27 ± 0.02	<0.001
LDL-c (mmol/L)	3.00 ± 0.02	3.02 ± 0.02	2.79 ± 0.06	<0.001
BUN (mmol/L)	4.52 ± 0.04	4.46 ± 0.04	5.15 ± 0.15	<0.001
SUA (µmol/L)	324.02 ± 1.64	322.61 ± 1.75	339.75 ± 4.30	<0.001
Scr (mg/dL)	76.53 ± 0.48	75.59 ± 0.40	86.97 ± 2.15	<0.001
eGFR (mL/min/1.73 m^2)	98.35 ± 0.69	99.03 ± 0.70	90.82 ± 1.11	<0.001
FT3 (pg/mL)	3.19 ± 0.01	3.20 ± 0.01	3.12 ± 0.01	<0.001
FT4 (pmol/L)	10.25 ± 0.07	10.22 ± 0.07	10.44 ± 0.12	0.001
TSH (mIU/L)	1.70 ± 0.02	1.69 ± 0.02	1.80 ± 0.05	0.005
FT3/FT4	0.32 ± 0.00	0.32 ± 0.00	0.31 ± 0.00	<0.001
TSHI	1.78 ± 0.01	1.77 ± 0.01	1.86 ± 0.03	<0.001
TT4RI	17.35 ± 0.15	17.18 ± 0.15	18.64 ± 0.56	<0.001
TFQI	-0.01 ± 0.01	-0.01 ± 0.01	0.04 ± 0.03	<0.001
Urinary albumin (mg/L)	31.70 ± 3.27	8.82 ± 0.20	285.58 ± 42.65	<0.001
Urinary creatinine (mg/dL)	120.97 ± 1.66	121.19 ± 1.74	118.47 ± 3.34	0.396

Values for categorical variables are given as weighted percentage (standard error) and for continuous variables as weighted mean ± standard error. Weighted Student's t-test and chi-squared test were used

BMI body mass index, *ALT* alanine transaminase, *AST* aspartate transaminase, *GGT* gamma-glutamyl transferase, *TG* triglyceride, *TC* total cholesterol, *HDL-c* high-density lipoprotein cholesterol, *LDL-c* low-density lipoprotein cholesterol, *BUN* blood urea nitrogen, *SUA* serum uric acid, *Scr* serum creatinine, *eGFR* estimated glomerular filtration rate, *FT3* free triiodothyronine, *FT4* free thyroxine, *TSH* thyroid-stimulating hormone, *TSHI* thyroid-stimulating hormone index, *TT4RI* thyrotrophic thyroxine resistance index, *TFQI* thyroid feedback quantile-based index, *FT3/FT4* free triiodothyronine/free thyroxine

levels, and urinary albumin in comparison to the non-albuminuria group ($P < 0.05$). However, the albuminuria group exhibited significant decreases in education level above high school, moderate physical activity, HDL-c, LDL, eGFR, FT3 levels, and FT3/FT4 levels ($P < 0.05$). Furthermore, significant differences in race distribution were observed between the groups ($P < 0.001$). Notably, the albuminuria group exhibited higher TFQI levels than the non-albuminuria group ($P < 0.001$).

Clinical features of the participants according to the quartiles of TFQI

The study participants were categorized into four groups based on their levels of TFQI, as follows: quartile I, quartile II, quartile III, and quartile IV, as shown in Table 2. In comparison to the quartile I-TFQI group, the quartile II-TFQI, quartile III-TFQI, and quartile IV-TFQI groups showed significant increases in age, education level above high school, prevalence of diabetes, hypertension, cardiovascular disease, BMI, ALT, AST, GGT, BUN, SUA, Scr, and levels of FT4, TSH, TSHI, and TT4RI ($P < 0.05$). Additionally, moderate physical activity, HDL-c, eGFR, FT3/FT4 levels, and urinary creatinine significantly decreased ($P < 0.001$). There were also significant differences in the distribution of race and smoking status among the various quartile groups ($P < 0.001$). Furthermore, no differences in gender, annual income, TG, TC, LDL-c, FT3 levels, and urinary albumin were observed between groups. Importantly, as the TFQI levels increased progressively, both the UACR (22.75 ± 3.46 vs. 24.82 ± 4.05 vs. 34.57 ± 6.77 vs. 42.45 ± 8.59, $P = 0.026$) and the prevalence of albuminuria (7.31% vs. 7.89% vs. 7.95% vs. 9.89%, $P = 0.024$) also showed a gradual increase.

Correlation of TFQI with clinical parameters

From the weighted Pearson correlation analysis, TFQI exhibited significant associations with multiple variables (Table 3). Specifically, TFQI positively correlated with age, education level above high school, diabetes, hypertension, cardiovascular disease, BMI, BUN, Scr, SUA, UACR, and albuminuria ($P < 0.01$). In contrast, TFQI negatively correlated with moderate physical activity, smoking status, TC, HDL-c, LDL-c, eGFR, and urinary creatinine ($P < 0.05$).

Associations between sensitivity to thyroid hormones and albuminuria

Table 4 presents the association between thyroid hormone sensitivity and albuminuria. The unadjusted models revealed positive associations between FT4, TSH, TSHI, TT4RI, and TFQI and an increased risk of albuminuria ($P < 0.001$). In contrast, FT3 and FT3/FT4 showed a negative association

with the prevalence of albuminuria ($P < 0.001$). Except for FT3, these associations remained statistically significant after adjusting for age, gender, and race ($P < 0.05$). Following additional adjustment for multiple covariates, only TT4RI and TFQI were related to albuminuria risk. The results indicated a 28% increased risk of albuminuria per unit increase in TFQI (OR = 1.28, 95% CI 1.01–1.60, $P = 0.037$). Classifying TFQI into quartiles demonstrated that higher TFQI quartiles were associated with a higher prevalence of albuminuria than the lowest quartiles in the fully adjusted model (P for trend = 0.035). Finally, the smooth curve fitting analysis results confirmed a positive correlation between TFQI and albuminuria, UACR, BUN, and Scr while also showing a negative correlation with eGFR (Fig. 2). No significant threshold effect was found.

ROC analysis results of thyroid hormone sensitivity on albuminuria

Figure 3 illustrates the evaluation of thyroid hormone sensitivity–related indices, including FT3/FT4, TSHI, TT4RI, and TFQI, in terms of their predictive power for albuminuria risk using ROC analysis. The corresponding area under the curve (AUC) for each index is as follows: FT3/FT4 (57.79%), TSHI (54.12%), TT4RI (53.71%), and TFQI (60.64%).

Subgroup analysis

We carried out additional investigations of TFQI and the risk of albuminuria in subgroups stratified by various factors, including age ($< 60/ \geq 60$ years), gender (female/male), BMI ($< 25/25$–$30/ \geq 30$ kg/m^2), diabetes (yes/no), hypertension (yes/no), cardiovascular disease (yes/no), and eGFR ($< 60/60$–$90/ \geq 90$ mL/min/1.73 m^2) (Fig. 4). Our findings revealed a significant interaction between age and TFQI in relation to albuminuria (P for interaction = 0.020). Specifically, TFQI exhibited a stronger association with the risk of albuminuria in the elderly population (OR = 1.65, 95% CI 1.20–2.26, $P = 0.002$) compared to individuals under 60 years old (OR = 1.02, 95% CI 0.78–1.33, $P = 0.903$). Furthermore, no other significant interactions were observed in the subgroup analyses of TFQI and the risk of albuminuria (P for interaction > 0.05).

Discussion

This is, to our knowledge, the first population-based study investigating the relationship between thyroid hormone sensitivity and albuminuria risk in euthyroid subjects. Our study demonstrated that impaired central sensitivity to thyroid hormones is associated with albuminuria, which is more

Table 2 Clinical and laboratory characteristics based on TFQI quartiles, weighted

	Quartile I	Quartile II	Quartile III	Quartile IV	P value
Age (years)	42.51 ± 0.42	43.75 ± 0.55	45.54 ± 0.61	47.78 ± 0.53	< 0.001
Male gender, % (SE)	49.85 (1.70)	48.09 (1.31)	51.32 (1.72)	51.86 (1.25)	0.084
Race, % (SE)					< 0.001
Mexican American	8.52 (1.07)	8.47 (1.09)	8.27 (1.02)	8.72 (1.23)	
Other Hispanic	6.27 (1.15)	6.03 (0.82)	4.63 (0.77)	5.45 (0.77)	
Non-Hispanic White	62.24 (2.76)	69.19 (2.60)	70.27 (2.38)	70.72 (2.50)	
Non-Hispanic Black	17.01 (1.62)	10.50 (1.35)	9.02 (1.17)	7.20 (1.09)	
Other Races	5.95 (0.69)	5.81 (0.89)	7.81 (1.17)	7.90 (1.11)	
Annual income (below $20,000), % (SE)	14.33 (1.28)	14.34 (1.28)	13.63 (0.97)	13.89 (1.33)	0.904
Education level (above high school), % (SE)	53.51 (1.93)	56.03 (2.01)	58.93 (1.85)	59.05 (2.37)	0.001
Moderate physical activity, % (SE)	42.00 (1.66)	43.89 (1.48)	43.36 (1.76)	37.02 (1.29)	< 0.001
Smoking status, % (SE)					< 0.001
Never	50.99 (2.13)	54.40 (1.56)	56.40 (1.45)	55.27 (1.97)	
Former	21.03 (1.32)	23.45 (1.16)	23.82 (1.24)	25.96 (1.49)	
Current	27.99 (1.73)	22.15 (1.26)	19.79 (1.38)	18.77 (1.50)	
Diabetes, % (SE)	6.04 (0.64)	6.97 (0.70)	8.73 (0.86)	11.04 (1.01)	< 0.001
Hypertension, % (SE)	24.75 (1.28)	25.63 (1.32)	29.60 (1.63)	32.60 (1.54)	< 0.001
Cardiovascular disease, % (SE)	5.07 (0.58)	5.12 (0.39)	6.28 (0.64)	9.27 (0.90)	< 0.001
BMI (kg/m^2)	28.12 ± 0.19	28.20 ± 0.22	28.79 ± 0.22	28.99 ± 0.23	< 0.001
ALT (U/L)	25.94 ± 0.51	25.59 ± 0.51	25.98 ± 0.36	27.35 ± 0.70	0.040
AST (U/L)	25.89 ± 0.34	25.62 ± 0.51	25.70 ± 0.23	26.99 ± 0.62	0.033
GGT (U/L)	31.36 ± 1.04	27.55 ± 0.88	27.40 ± 0.76	30.65 ± 2.28	0.004
TG (mmol/L)	1.44 ± 0.05	1.46 ± 0.04	1.52 ± 0.05	1.55 ± 0.07	0.134
TC (mmol/L)	5.10 ± 0.03	5.09 ± 0.03	5.05 ± 0.03	5.03 ± 0.04	0.181
HDL-c (mmol/L)	1.38 ± 0.02	1.35 ± 0.02	1.33 ± 0.01	1.32 ± 0.01	< 0.001
LDL-c (mmol/L)	3.01 ± 0.04	3.04 ± 0.04	2.97 ± 0.04	2.97 ± 0.04	0.295
BUN (mmol/L)	4.30 ± 0.05	4.44 ± 0.07	4.55 ± 0.04	4.78 ± 0.06	< 0.001
SUA (μmol/L)	317.74 ± 2.61	319.14 ± 2.62	327.22 ± 3.30	331.86 ± 2.65	< 0.001
Scr (mg/dl)	74.85 ± 0.55	75.61 ± 0.66	76.73 ± 0.85	78.88 ± 0.69	< 0.001
eGFR (mL/min/1.73 m^2)	102.36 ± 0.63	99.49 ± 0.82	97.55 ± 0.99	94.13 ± 0.83	< 0.001
FT3 (pg/mL)	3.19 ± 0.02	3.18 ± 0.01	3.20 ± 0.01	3.21 ± 0.01	0.392
FT4 (pmol/L)	8.88 ± 0.05	9.93 ± 0.06	10.60 ± 0.08	11.58 ± 0.06	< 0.001
TSH (mIU/L)	1.03 ± 0.01	1.46 ± 0.03	1.86 ± 0.04	2.47 ± 0.03	< 0.001
FT3/FT4	0.36 ± 0.00	0.33 ± 0.00	0.31 ± 0.00	0.28 ± 0.00	< 0.001
TSHI	1.15 ± 0.01	1.61 ± 0.01	1.96 ± 0.01	2.42 ± 0.01	< 0.001
TT4RI	8.90 ± 0.07	13.57 ± 0.17	18.68 ± 0.30	28.22 ± 0.27	< 0.001
Urinary albumin (mg/L)	27.30 ± 3.65	25.64 ± 3.73	37.95 ± 9.09	35.86 ± 7.60	0.583
Urinary creatinine (mg/dL)	127.66 ± 2.40	123.35 ± 3.34	120.12 ± 2.29	112.91 ± 2.08	< 0.001
UACR (mg/g)	22.75 ± 3.46	24.82 ± 4.05	34.57 ± 6.77	42.45 ± 8.59	0.026
Albuminuria, % (SE)	7.31 (0.69)	7.89 (0.75)	7.95 (0.56)	9.89 (0.95)	0.024

Values for categorical variables are given as weighted percentage (standard error) and for continuous variables as weighted mean ± standard error. Weighted Student's *t*-test and chi-squared test were used

pronounced in the elderly. Compared with other thyroid hormone sensitivity–related indices, TFQI is an excellent potential epidemiological tool to quantify the role of central thyroid hormone resistance in the risk of albuminuria.

Thyroid hormone sensitivity can be categorized into two distinct types, namely, central sensitivity and peripheral sensitivity [19]. Impaired central sensitivity disrupts the feedback loop within the central nervous system, thereby bringing about modifications in the set point for regulating thyroid hormone levels. In contrast, impaired peripheral sensitivity hampers the signaling and action of thyroid hormones at the cellular level, ultimately diminishing their

Table 3 Pearson correlation analysis results of TFQI with other parameters in the whole study population, weighted

	Correlation	95%CI lower	95%CI upper	*P* value
Age (years)	0.133	0.111	0.155	<0.001
Gender	0.017	−0.005	0.040	0.132
Race	−0.019	−0.041	0.004	0.104
Annual income (below $20,000)	−0.006	−0.028	0.017	0.611
Education level (above high school)	0.046	0.023	0.068	<0.001
Moderate physical activity	−0.037	−0.059	−0.014	0.001
Smoking status	−0.061	−0.083	−0.038	<0.001
Diabetes	0.072	0.049	0.094	<0.001
Hypertension	0.061	0.038	0.083	<0.001
Cardiovascular disease	0.071	0.049	0.094	<0.001
BMI (kg/m^2)	0.048	0.026	0.071	<0.001
ALT (U/L)	0.021	−0.002	0.043	0.069
AST (U/L)	0.021	−0.001	0.044	0.062
GGT (U/L)	−0.009	−0.032	0.013	0.430
TG (mmol/L)	0.024	−0.009	0.056	0.152
TC (mmol/L)	−0.033	−0.055	−0.011	0.004
HDL-c (mmol/L)	−0.043	−0.066	−0.021	<0.001
LDL-c (mmol/L)	−0.036	−0.069	−0.004	0.029
BUN (mmol/L)	0.107	0.085	0.129	<0.001
Scr (mg/dl)	0.069	0.046	0.091	<0.001
SUA (μmol/L)	0.066	0.044	0.089	<0.001
eGFR (mL/min/1.73 m^2)	−0.157	−0.179	−0.134	<0.001
Urinary albumin (mg/L)	0.016	−0.007	0.038	0.164
Urinary creatinine (mg/dl)	−0.079	−0.102	−0.057	<0.001
UACR (mg/g)	0.034	0.011	0.056	0.003
Albuminuria	0.033	0.010	0.055	0.004

Table 4 Logistic regression analysis results of thyroid hormone sensitivity–related indices and albuminuria

Albuminuria	OR (95%CI) *P* value		
Continuous	Non-adjusted model 1	Adjusted model 2	Adjusted model 3
FT3	0.54 (0.44, 0.66) <0.001	0.91 (0.73, 1.13) 0.375	1.03 (0.87, 1.22) 0.704
FT4	1.07 (1.03, 1.11) <0.001	1.05 (1.02, 1.09) 0.006	1.02 (0.98, 1.07) 0.260
TSH	1.15 (1.06, 1.24) <0.001	1.09 (1.00, 1.18) 0.046	1.08 (0.99, 1.17) 0.103
FT3/FT4	0.03 (0.01, 0.10) <0.001	0.20 (0.06, 0.69) 0.011	0.63 (0.17, 2.29) 0.487
TSHI	1.32 (1.16, 1.50) <0.001	1.21 (1.06, 1.38) 0.006	1.14 (0.99, 1.31) 0.076
TT4RI	1.02 (1.01, 1.02) <0.001	1.01 (1.00, 1.02) 0.004	1.01 (1.00, 1.02) 0.040
TFQI	1.55 (1.26, 1.91) <0.001	1.40 (1.13, 1.73) 0.002	1.28 (1.01, 1.60) 0.037
Categories			
Quartile I	1.00	1.00	1.00
Quartile II	1.08 (0.87, 1.33) 0.501	1.07 (0.86, 1.33) 0.545	1.03 (0.82, 1.29) 0.826
Quartile III	1.23 (1.00, 1.51) 0.047	1.19 (0.96, 1.47) 0.114	1.15 (0.92, 1.43) 0.228
Quartile IV	1.49 (1.22, 1.81) <0.001	1.36 (1.10, 1.67) 0.004	1.24 (0.99, 1.54) 0.061
P for trend	<0.001	0.002	0.035

Adjusted model 2: age, gender, and race were adjusted. Adjusted model 3: additionally adjusted for annual income, education level, smoking status, physical activity, diabetes, hypertension, cardiovascular disease, BMI, ALT, AST, GGT, TG, TC, HDL, LDL, BUN, SUA, Scr, and eGFR

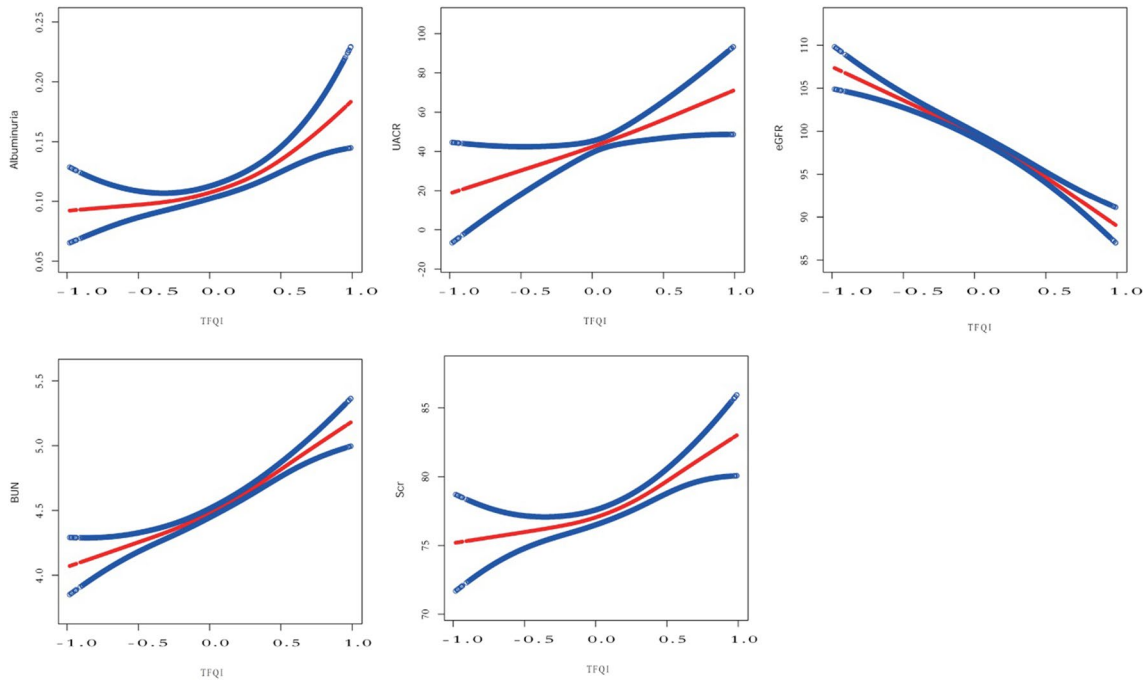*OR* odds ratio, *95% CI* 95% confidence interval

Fig. 2 Smooth curve fitting results of TFQI and albuminuria, UACR, BUN, Scr, and eGFR
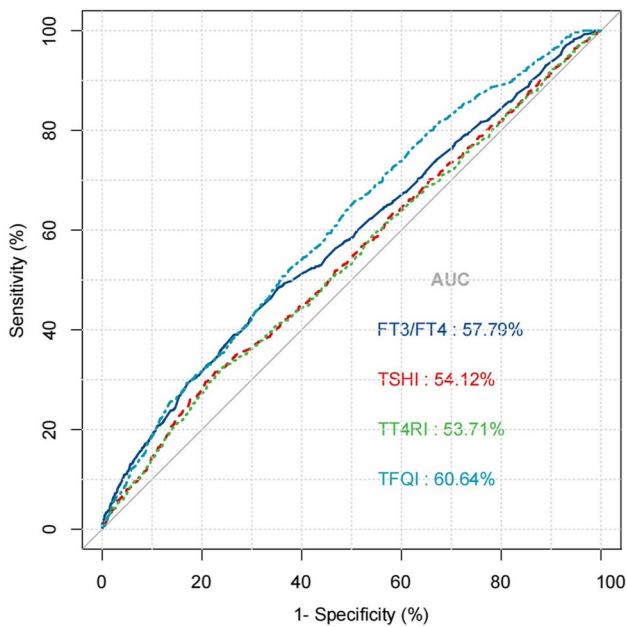

Fig. 3 ROC curve analysis of FT3/FT4, TSHI, TT4RI, and TFQI in assessing albuminuria risk

metabolic effects. Several studies have investigated the relationship between thyroid function and albuminuria/CKD. Yang et al. observed higher TSH levels and lower levels of FT4 in individuals with type 2 diabetes who had diabetic kidney disease (DKD) as compared to those without DKD. Moreover, the FT4 level shows a negative correlation with UACR and eGFR. In turn, TSH exhibits a positive correlation with UACR and eGFR [11]. However, Reinhardt et al. suggest that TSH or FT4 does not significantly correlate with UACR and albuminuria severity in CKD patients [9]. A separate study demonstrated that elevated levels of TT4 and FT4 in individuals with CKD are associated with an elevated risk and severity of albuminuria [10]. Nonetheless, these findings are primarily limited to a specific population and do not account for thyroid hormone resistance, indicating that relying solely on TSH or thyroid hormone levels may not adequately explain the connection between the thyroid system and albuminuria. Moreover, the results demonstrate certain inconsistencies. In the context of thyroid hormone resistance in euthyroid individuals, assessment measures based on thyroid hormone sensitivity have shown stronger correlations with albuminuria compared to those measures alone. This finding could potentially explain the inconsistencies observed in previous studies while also aiding in establishing a link between thyroid function and albuminuria in euthyroid individuals. Among the three indices that assess central thyroid hormone sensitivity, TFQI exhibited a stronger correlation with albuminuria. Moreover, TFQI demonstrated superior stability compared to both TT4RI and TSHI in assessing the abnormal range of thyroid response to TSH, particularly when the deviation is near normal [19]. Notably, this suggests that TFQI may provide a more accurate assessment of thyroid function in individuals with borderline or subclinical thyroid abnormalities, this being consistent with our findings.

Fig. 4 Subgroup analysis results based on age, gender, BMI, diabetes, hypertension, cardiovascular disease, and eGFR
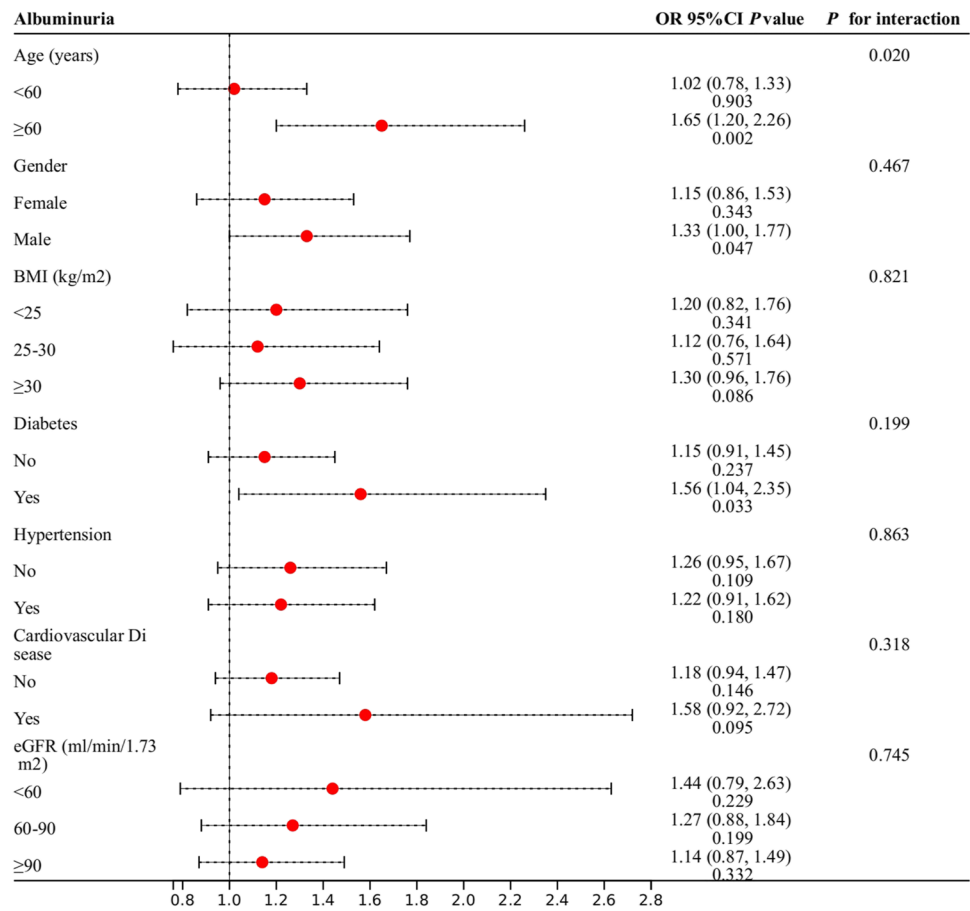
In comparison, the FT3/FT4 ratio is a valuable indicator of the T4-T3 conversion rate, reflecting the sensitivity of peripheral tissues to thyroid hormones. Previous studies have demonstrated strong associations between FT3/FT4 levels and microangiopathy, metabolic disease, cardiovascular disease, and other disorders [24–28]. In addition, FT3/FT4 is recognized as an autonomous prognostic of all-cause and cardiovascular mortality [28]. After controlling for age, gender, and race, a higher FT3/FT4 ratio was linked to a reduced risk of albuminuria. However, this association lost significance after additional adjustment for multiple confounding factors. Unlike central sensitivity, which can be measured by observing thyroid hormone and TSH concentrations or their derived indicators, assessing thyroid hormone peripheral sensitivity is challenging and susceptible to multiple factors [19, 29]. A previous study in type 2 diabetics also showed no significant association with the risk of albuminuria, although there was an inverse association between FT3/FT4 and UACR [30]. Hence, further investigation is required to explore the connection between thyroid hormone peripheral sensitivity and albuminuria.

Several potential mechanisms may explain the correlation between central thyroid hormone sensitivity and albuminuria. Thyroid hormones can be directly involved in vascular and endothelial dysfunction and the formation of albuminuria [14]. Moreover, interactions between other metabolic hormones and albuminuria may influence thyroid resistance [31]. For instance, thyroid resistance is associated with metabolic processes involving blood glucose and insulin [19, 31–33]. Furthermore, thyroid resistance can also potentially induce alterations in the immune microenvironment of kidney disease, thereby augmenting the immune inflammatory response and ultimately causing kidney injury and albuminuria [34].

To summarize, our study sheds light on a potential link between impaired central sensitivity to thyroid hormones and albuminuria in individuals with normal thyroid function. The findings suggest that even in the absence of overt thyroid dysfunction, thyroid hormone resistance may play a role in the development or progression of albuminuria. Moreover, thyroid hormone resistance is associated with an increased risk of kidney disease, cardiovascular events, and mortality. It may also have implications for risk assessment, early detection, and management of kidney disease in individuals with normal thyroid function. Our study has also shown the potential of TFQI as a valuable tool for assessing the impact of impaired central sensitivity on the risk of albuminuria. However, further investigation is needed in

the future to determine its clinical applications for targeting euthyroid patients.

It is necessary to acknowledge the limitations of our study. Firstly, the cross-sectional design does not establish a cause-and-effect relationship between sensitivity to thyroid hormones and albuminuria. Cohort studies and intervention trials are needed to determine whether there is a cause-and-effect relationship. Secondly, the study did not include thyroid-related antibodies, which could also potentially be a confounding factor. Thirdly, this study did not specifically exclude subjects with chronic kidney disease (defined as eGFR < 60 mL/min/1.73 m^2) or proteinuria. Additional analyses based on eGFR are provided in Attachment 1. Finally, since our study was conducted using a sample from the US population, the generalizability of our findings necessitates further validation.

Conclusion

In a nationally representative study of adults aged 19–79 with normal thyroid function, an association was observed between impaired central thyroid sensitivity and an increased risk of albuminuria.

Declarations

Ethical approval The Research Ethics Review Board of the NCHS reviewed and approved this study involving human participants.

Informed consent The patients/participants provided written informed consent for participation in this study.

Conflict of interest The authors declare no competing interests.

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