Original Paper

Association of Thyroid Function With the Estimated Glomerular Filtration Rate in a Large Chinese Euthyroid Population

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Key Words

Thyroid function • Estimated glomerular filtration rate • Chronic kidney disease

Abstract

Background/Aims: We aimed to explore whether thyroid function within a normal range is associated with the estimated glomerular filtration rate (eGFR) and the incidence of chronic kidney disease (CKD) in a large Chinese population. **Methods:** We conducted a cross-sectional study that included 10,859 euthyroid individuals who underwent an annual regular health check-up in Jiangsu Province Official Hospital between August 2012 and August 2013. We measured the thyroid-stimulating hormone (TSH), free triiodothyronine (FT3) and free thyroxine (FT4) levels using a Roche modular analytics E170 and then calculated the eGFR using the Chinese modified Modification of Diet in Renal Disease (CMDRD) equation. **Results:** In multiple linear regression models, TSH was negatively associated with eGFR after adjusting for confounding factors ($\beta = -0.072$, $P = 1.994 \times 10^{-22}$). The significance remained in both males and females. No significant association was observed between FT4 and eGFR. In the logistic regression model, we did not observe significant associations of TSH or FT3 with CKD. Participants in the highest quartile of FT4 versus the lowest quartile (reference) had an increased risk of CKD (OR = 1.763, $P = 0.012$). The risk of CKD was more pronounced in females with the highest quartile of FT4 (OR = 2.424, $P = 0.029$). **Conclusion:** Our findings suggest that TSH is associated with eGFR in euthyroid individuals and that higher FT4 is associated with an increased risk of CKD. More cohort studies are warranted to confirm whether the association is causal.

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Introduction

Chronic kidney disease (CKD) is characterized by a decreased glomerular filtration rate or the presence of albuminuria, and it has an estimated prevalence of 8–16% worldwide [1]. It has been demonstrated that CKD is associated with an increased risk of cardiovascular disease, renal failure, and other complications [2]. Thus, identifying the risk factors for CKD or a decrease in estimated glomerular filtration rate (eGFR), which is a surrogate for the development of CKD, may help in understanding the mechanism of CKD and provide new strategies for preventing CKD.

Thyroid hormones are crucial for renal development and physiology, including the renal blood flow, glomerular filtration rate (GFR) and kidney structure [3, 4]. Several lines of epidemiological evidence and clinical trial data have investigated the effects of thyroid hormones on renal function decline. A growing body of cross-sectional studies suggests that overt and subclinical hypothyroidism is associated with a lower estimated glomerular filtration rate (eGFR) and an increased risk of CKD but that hyperthyroidism is associated with a higher eGFR and a lower risk of CKD [5–10]. Interestingly, the reduction of the eGFR was reversible after thyroid hormone substitution therapy [11, 12]. Shin et al. reported that thyroid hormone replacement therapy attenuated the rate of decline in renal function in CKD patients with subclinical hypothyroidism [7, 11]. However, one recent prospective study reported that an increased risk of CKD and eGFR decline was observed in subjects with lower TSH levels or a hyperthyroid state with a protective effect against hypothyroidism [13]. Another prospective study showed no significant association between thyroid function and renal function change in older adults [14]. Therefore, the effect of thyroid hormone levels on renal function decline is controversial and remains unclear.

Recently, studies have explored the association of thyroid hormones with the eGFR levels or the risk of CKD in euthyroid individuals [15–17]. One population-based study of 29480 individuals in Norway demonstrated that high TSH levels in the reference range were associated with a reduced eGFR and a higher prevalence of CKD [17]. Zhang et al. reported that high-normal levels of TSH and low-normal levels of FT3 were associated with an increased risk of CKD in euthyroid individuals [16]. However, such evidence is sparse in the Chinese population. Therefore, the present study was undertaken to assess the association of thyroid function (FT3, FT4 and TSH) with eGFR levels and incident CKD in health Chinese population with normal thyroid function.

Materials and Methods

Study population

This study was conducted based on a database of 42,269 Chinese Han adults in the health check-up center of Jiangsu Province Official Hospital between August 2012 and August 2013. Overall, 10,859 euthyroid subjects were included in the analysis after excluding those who satisfied one of the following criteria: (1) a history of thyroid disease (including goiter, hypothyroidism, thyroid nodules, and thyroid cancer) or taking medication affecting thyroid function, such as thyroxine, antithyroid drugs, and glucocorticoid, antiepileptic and contraceptive drugs; (2) being pregnant or having malignant tumors, mental disorders, diabetic ketoacidosis, lupus nephritis, heart failure or other severe disorders; and (3) participants missing essential relevant information. This study was approved by the institutional review board of Jiangsu Province Official Hospital. All methods were carried out in accordance with the relevant guidelines and regulations, and informed consent was obtained from all subjects.

Laboratory measurements and definitions

A physician-administered questionnaire was used to collect the individuals' information, including age, gender, previous medical history and related medications. Height, body weight, systolic blood pressure

(SBP) and diastolic blood pressure (DBP) were measured according to the international standards. Body mass index (BMI) was calculated as weight (kg) divided by height (m) squared. Blood samples were collected by venipuncture after an overnight fast. Biochemical parameters, including serum creatinine, fasting blood glucose (FBG), total cholesterol (TC) and total triglycerides (TG), were measured using an automatic biochemical analyzer (Hitachi 7020, Tokyo, Japan). The serum TSH, FT4 and FT3 were assayed using fully automated electrochemiluminescence using a Roche modular analytics E170. The reference intervals provided by the manufacturer were TSH 0.34~5.6 mIU/L, FT3 3.67~10.43 pmol/L and FT4 7.46~21.1 pmol/L. The sensitivities of TSH, FT3 and FT4 were 0.0014 μ U/mL, 1.33 pmol/L and 1.58 pmol/L, respectively. The intra-assay coefficients of variation for TSH, FT3 and FT4 were 3.0%, 2.1% and 2.1%, respectively. The euthyroid subject was defined as an individual with normal TSH, FT3 and FT4 levels and without a history of previous thyroid diseases. Renal function was evaluated based on the eGFR using the Chinese modified Modification of Diet in Renal Disease (CMDRD) equation as follows: $eGFR (mL/min/1.73 m^2) = 175 \times \text{standard creatinine (mg/dL)}^{-1.234} \times \text{age (year)}^{-0.179} \times 0.79$ (if female) [18]. The serum creatinine concentrations were generated from the following calibration equation: Jaffe's kinetic method SCr (mg/dl) = $0.795 \times [\text{enzymatic method SCr (mg/dL)}] + 0.29$ [19]. The moderate chronic kidney disease (CKD) was commonly defined as $eGFR < 60 mL/min/1.73 m^2$ [20].

Statistical analysis

The baseline characteristics are expressed as median (interquartile range) or numbers (%) because the values of BMI, TSH, FT3 and FT4 do not have a normal distribution. The baseline characteristics were compared between male and female groups using a Wilcoxon signed-rank test for continuous variables or a chi-squared test for categorical variables. The eGFR levels were rank-based inverse-normal transformed (INT) to normality for multiple linear regression to assess the association of thyroid function (TSH, FT3 and FT4) with eGFR levels [21]. According to the scatter plots (Fig. 1), the association of TSH or FT4 with eGFR may be linear, but the association between FT3 and eGFR may be not linear. Therefore, we use multiple linear regression to examine the association of TSH or FT3 with eGFR levels. Multivariable logistic regression analysis was performed to evaluate the adjusted odds ratios (ORs) and the 95% confidence intervals (CIs) for incident CKD associated with the thyroid hormone levels. This association was analyzed by categorizing the thyroid hormone levels into quartiles according to their distributions. Furthermore, we plotted the restricted cubic spline curves in the logistic regression model to evaluate the shape of the associations between TSH, FT3 or FT4 and CKD risk. *P* values less than 0.05 were considered statistically significant. All analyses were performed using the R software (version 3.2.5).

Fig. 1. Scatter plots between thyroid hormones (TSH, FT3 and FT4) and inverse-normal transformed eGFR.

Results

Overall, 10,859 euthyroid participants were included in the study. As shown in Table 1, the median age was 55 years old, and 7,254 participants (66.8%) were males. The median (interquartile range, IQR) levels of TSH, FT3, FT4, FBG, TC, TG and eGFR in our study population were 2.26 (1.61-3.09) mIU/L, 4.62 (4.24-5.01) pmol/L, 16.6 (15.25-18.06) pmol/L, 5.37 (5.01-5.80) mmol/L, 4.89 (4.32-5.53) mmol/L, 1.24 (0.88-1.78) mmol/L and 85.24 (77.42-93.20) ml/min/1.73 m², respectively. The FT3 and FT4 levels in males were significantly higher than those in females (all $P < 0.001$), while the TSH and eGFR levels were significantly lower in males than they were in females ($P < 0.001$).

The quartile distributions of TSH, FT3 and FT4 concentrations and clinical characteristics are shown in Table 2. Participants with higher levels of TSH were more likely to be older and female and to have higher TC and TG levels and a lower eGFR (all $P < 0.05$). Participants with higher FT3 or FT4 levels were more likely to be younger and to have a lower TC and higher eGFR (all $P < 0.05$). Further, 117 CKD patients were defined as eGFR < 60 ml/min per 1.73 m², and there were 10682 non-CKD participants. Participants with higher levels of TSH or lower

Table 1. Characteristics of study participants. Values are median (interquartile range) or numbers (%). ^aCKD, Chronic kidney disease; eGFR < 60 ml/min per 1.73 m². BMI, body mass index; TSH, thyroid-stimulating hormone; FT3, free triiodothyronine; FT4, free thyroxine; TC, total cholesterol; TG, total triglycerides; eGFR, estimated glomerular filtration rate

Characteristics	Total (10,859)	Male (7,254)	Female (3,605)	P
Age (years)	55 (44-65)	55 (46-66)	54 (42-64)	<0.001
BMI (kg/m ²)	24.0 (22.03-26.12)	24.73 (22.91-26.64)	22.46 (20.61-24.52)	<0.001
TSH (mIU/L)	2.26 (1.61-3.09)	2.16 (1.56-2.96)	2.49 (1.78-3.39)	<0.001
FT3 (pmol/L)	4.62 (4.24-5.01)	4.78 (4.42-5.15)	4.30 (3.98-4.63)	<0.001
FT4 (pmol/L)	16.60 (15.25-18.06)	16.91 (15.52-18.36)	16.00 (14.84-17.41)	<0.001
FBG (mmol/L)	5.37 (5.01-5.80)	5.42 (5.09-5.90)	5.24 (4.91-5.62)	<0.001
SBP (mmHg)	125 (115-138)	128 (118-140)	120 (109-135)	<0.001
DBP (mmHg)	80 (73-87)	82 (76-89)	74 (68-81)	<0.001
TC (mmol/L)	4.89 (4.32-5.53)	4.85 (4.28-5.44)	5.00 (4.42-5.70)	<0.001
TG (mmol/L)	1.24 (0.88-1.78)	1.33 (0.96-1.88)	1.08 (0.75-1.56)	<0.001
eGFR (ml/min/1.73 m ²)	85.24 (77.42-93.20)	84.68 (77.11-92.38)	86.39 (78.19-94.76)	<0.001
CKD ^a				
No	10682 (98.37)	7136 (98.37)	3546 (98.36)	
Yes	177 (1.63)	118 (1.63)	59 (1.64)	0.969

Table 2. Characteristics of study participants by quantiles of thyroid hormones. BMI, body mass index; FBG, fasting blood glucose; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, total triglycerides; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease. Values are median (interquartile range) or numbers (%). ^aP-values were determined by using the Kruskal-Wallis or χ^2 test

Characteristic	TSH (mIU/L)			FT3 (pmol/L)			FT4 (pmol/L)		
	Quartile 1 (0.35-1.61)	Quartile 4 (3.10-5.60)	P ₂	Quartile 1 (3.67-4.24)	Quartile 4 (5.02-10.26)	P ₂	Quartile 1 (7.56-15.25)	Quartile 4 (18.07-21.10)	P ₂
Participants (n=10859)	2724	2697		2754	2715		2723	2707	
Age (years)	53 (43-63)	58 (48-68)	<0.001	60 (48-72)	50 (40-58)	<0.001	57 (48-68)	52 (41-62)	<0.001
Gender									
Male (n = 7254)	1984 (27.35)	1575 (21.71)		1101 (15.18)	2414 (33.28)		1519 (20.94)	2130 (29.36)	
Female (n = 3605)	740 (20.53)	1122 (31.12)	<0.001	1653 (45.85)	301 (8.35)	<0.001	1204 (33.40)	577 (16.01)	<0.001
BMI (kg/m ²)	24.03 (21.99-26.03)	24.01 (21.94-26.12)	0.770	22.89 (20.90-25.11)	24.84 (23.04-26.82)	<0.001	24.22 (22.06-26.37)	23.94 (21.97-26.03)	0.055
FBG (mmol/L)	5.36 (5.02-5.82)	5.39 (5.03-5.82)	0.166	5.30 (4.99-5.77)	5.39 (5.06-5.81)	<0.001	5.39 (5.02-5.83)	5.35 (5.01-5.82)	0.667
SBP (mmHg)	125 (114-138)	127 (116-140)	<0.001	124 (112-138)	126 (117-138)	<0.001	126.00 (114.00-139.50)	125 (116-138)	0.460
DBP (mmHg)	80 (73-87)	80 (72-87)	0.350	76 (69-83)	82 (76-90)	<0.001	79 (72-86)	81 (74-88)	<0.001
TC (mmol/L)	4.86 (4.29-5.46)	4.94 (4.36-5.59)	0.002	5.01 (4.41-5.72)	4.80 (4.28-5.38)	<0.001	4.94 (4.38-5.58)	4.85 (4.30-5.46)	0.001
TG (mmol/L)	1.19 (0.85-1.71)	1.28 (0.92-1.85)	<0.001	1.13 (0.80-1.61)	1.36 (0.97-1.91)	<0.001	1.29 (0.90-1.87)	1.24 (0.88-1.76)	<0.001
eGFR (ml/min/1.73 m ²)	87.16 (79.30-94.95)	82.48 (75.15-90.89)	<0.001	82.38 (73.82-90.63)	87.94 (80.35-96.12)	<0.001	83.74 (76.62-91.90)	86.23 (78.26-93.96)	<0.001
CKD									
Yes (n = 177)	37 (20.90)	61 (34.46)	0.012	84 (47.46)	20 (11.30)	<0.001	45 (25.42)	44 (24.86)	0.634
No (n = 10682)	2687 (25.15)	2636 (24.38)		2670 (25.00)	2695 (25.23)		2678 (25.07)	2663 (24.93)	

levels of FT3 were more likely to be CKD patients ($P = 0.012$, $P < 0.001$, respectively). Then, we performed multivariate linear regression analysis to assess the association between TSH or FT4 and eGFR (Table 3). In all participants, we observed a significant negative association between TSH within the reference range and eGFR ($\beta = -0.072$, $P = 1.994 \times 10^{-22}$) after adjusting for age, gender, BMI, FBG, SBP, DBP, TC and TG. The effect of TSH on eGFR was significant in both males ($\beta = -0.082$, $P = 2.372 \times 10^{-18}$) and females ($\beta = -0.052$, $P = 1.045 \times 10^{-5}$). Although we observed a significant association between FT4 levels within the reference range and eGFR ($\beta = 0.035$, $P = 1.110 \times 10^{-14}$), the association did not reach statistical significance after adjusting for age, gender, BMI, FBG, SBP, DBP, TC and TG.

The characteristics of CKD patients and non-CKD controls are summarized in Table 4. CKD patients were more likely to be older and to have higher levels of TSH, FBG, SBP and TG and lower levels of FT3 and DBP than were the controls (all $P < 0.05$). The associations between thyroid hormones (TSH, FT3, and FT4) and CKD risk were analyzed by categorizing the thyroid hormone levels into quartiles based on their distributions (Table 5). Quartile 1 was selected as the reference group. After adjusting for age, gender, BMI, FBG, SBP, DBP, TC and TG, we did not find a significant association between TSH or FT3 and the risk of incident CKD. Of note, the risk of incident CKD was significantly higher in the highest quartiles of FT4 than it was in the lowest quartiles of FT4 (OR = 1.763, 95%CI = 1.131-2.749, $P = 0.012$). We further explored the gender effect of thyroid hormones on CKD risk. The significant association between FT4 and CKD remained in females (OR = 2.424, 95%CI = 1.097-5.358, $P = 0.029$). Unfortunately, we did not observe significant heterogeneity (P for heterogeneity = 0.359). In addition, there was a linear relationship between FT4 and CKD in the restricted cubic spline curves after adjusting for age, gender, BMI, FBG, SBP, DBP, TC and TG (Linearity $P_{FT4} = 0.924$, Fig. 2).

Table 3. Association of TSH or FT4 levels with eGFR. Model 1, crude ORs. Model 2, adjustment for age, gender, BMI, FBG, SBP, DBP, TC and TG, and adjustment for age, BMI, FBG, SBP, DBP, TC and TG in male and female subgroup. ^aTest for heterogeneity was based on the model 2

Variables	TSH			FT4		
	β	95%CI	P	β	95%CI	P
Total						
Model 1	-0.118	(-0.135, -0.102)	2.357×10^{-43}	0.035	(0.026, 0.044)	1.110×10^{-14}
Model 2	-0.072	(-0.086, -0.057)	1.994×10^{-22}	0.005	(-0.003, 0.013)	0.189
Male						
Model 1	-0.124	(-0.145, -0.104)	9.041×10^{-32}	0.058	(0.047, 0.069)	1.176×10^{-26}
Model 2	-0.082	(-0.100, -0.063)	2.372×10^{-18}	0.008	(-0.001, 0.018)	0.084
Female						
Model 1	-0.132	(-0.161, -0.104)	2.976×10^{-19}	0.007	(-0.010, 0.024)	0.436
Model 2	-0.052	(-0.075, -0.029)	1.045×10^{-5}	-0.004	(-0.018, 0.009)	0.548
P for heterogeneity ^a		0.050			0.135	

Table 4. Characteristics and thyroid hormones between CKD patients and non-CKD subjects. Values are median (interquartile range). ^aP-values were determined by using the Wilcoxon signed-rank test

Characteristics	CKD (n = 177)	Non-CKD (n = 10682)	P ^a
Age (years)	76 (72-81)	55 (44-65)	<0.001
BMI (kg/m ²)	24.68 (22.49-26.35)	24.03 (22.02-26.12)	0.047
TSH (mIU/L)	2.59 (1.72-3.50)	2.25 (1.61-3.08)	0.006
FT3 (pmol/L)	4.28 (3.85-4.61)	4.63 (4.25-5.02)	<0.001
FT4 (pmol/L)	16.40 (15.25-18.05)	16.61 (15.25-18.06)	0.784
FBG (mmol/L)	5.65 (5.21-6.23)	5.36 (5.01-5.80)	<0.001
SBP (mmHg)	139 (127-152)	125 (115-138)	<0.001
DBP (mmHg)	77 (70-85)	80 (73-87)	0.010
Total cholesterol (mmol/L)	4.90 (4.20-5.56)	4.89 (4.32-5.53)	0.875
Total triglycerides (mmol/L)	1.47 (1.09-2.02)	1.24 (0.88-1.77)	<0.001

Table 5. Odds ratios of CKD, defined as eGFR <60 ml/min per 1.73 m², by categories of thyroid function.
^aAdjustment for age, gender, BMI, FBG, SBP, DBP, TC and TG. ^bAdjustment for age, BMI, FBG, SBP, DBP, TC and TG

Thyroid hormone levels	Number of CKD/total	OR ^a	Total 95%CI ^a	P ^a	OR ^b	Male 95%CI ^b	P ^b	Female OR ^b	Female 95%CI ^b	P ^b	P for heterogeneity
TSH (mIU/l)											
Quartile 1 (0.35-1.61)	37/2724		Ref			Ref			Ref		
Quartile 2 (1.62-2.26)	33/2726	0.818	(0.501, 1.334)	0.420	0.684	(0.375, 1.248)	0.216	1.166	(0.488, 2.784)	0.730	0.323
Quartile 3 (2.27-3.09)	46/2712	1.084	(0.690, 1.705)	0.726	1.046	(0.607, 1.803)	0.872	1.154	(0.504, 2.642)	0.734	0.845
Quartile 4 (3.10-5.60)	61/2697	1.143	(0.743, 1.757)	0.543	1.268	(0.758, 2.12)	0.366	0.961	(0.433, 2.132)	0.922	0.567
FT3 (pmol/l)											
Quartile 1 (3.67-4.24)	84/2754		Ref			Ref			Ref		
Quartile 2 (4.25-4.62)	50/2711	0.865	(0.594, 1.258)	0.447	0.849	(0.532, 1.353)	0.491	0.843	(0.445, 1.597)	0.601	0.987
Quartile 3 (4.63-5.01)	23/2679	0.675	(0.410, 1.111)	0.122	0.729	(0.414, 1.284)	0.274	0.407	(0.12, 1.388)	0.151	0.398
Quartile 4 (5.02-10.26)	20/2715	0.881	(0.515, 1.506)	0.643	0.795	(0.420, 1.504)	0.480	1.312	(0.484, 3.557)	0.594	0.407
FT4 (pmol/l)											
Quartile 1 (7.56-15.25)	45/2723		Ref			Ref			Ref		
Quartile 2 (15.26-16.60)	50/2709	1.402	(0.918, 2.142)	0.118	1.313	(0.778, 2.218)	0.308	1.710	(0.824, 3.548)	0.150	0.565
Quartile 3 (16.61-18.06)	38/2720	1.183	(0.752, 1.86)	0.467	1.053	(0.604, 1.836)	0.854	1.522	(0.691, 3.351)	0.297	0.455
Quartile 4 (18.07-21.10)	44/2707	1.763	(1.131, 2.749)	0.012	1.549	(0.904, 2.653)	0.111	2.424	(1.097, 5.358)	0.029	0.359

Fig. 2. Log odds ratios for incidence of chronic kidney disease (CKD) by TSH, FT3 and FT4 levels. Curves represent adjusted log odds ratios (solid lines) and their 95% confidence intervals (dashed lines) based on restricted cubic splines for thyroid hormone levels. The results were obtained from the logistic regression model and adjusted for age, gender, BMI, FBG, SBP, DBP, TC and TG.

Discussion

In this large population-based study, we first evaluated the relationships between thyroid function within the euthyroid range and eGFR or the risk of CKD in a Chinese population. Our results suggested that serum TSH was negatively associated with eGFR. This relationship was maintained, regardless of gender, but did not persist when evaluating the risk of CKD. Additionally, we observed an increased risk of CKD in the highest quartiles of FT4 compared with the lowest quartiles in all participants and in females.

To date, few studies have explored the association between thyroid hormones and eGFR or the risk of CKD in euthyroid individuals. Most previous studies only evaluated the thyroid hormones by using the TSH levels. In accordance with our results, Asvold et al. conducted a large population-based study in 29,480 Norwegians without previously known thyroid disease and found an inverse association between TSH within the reference range (0.50-3.5 mU/L) and eGFR [17]. Importantly, the research findings from 8,418 euthyroid participants in Taiwan demonstrated that TSH was inversely correlated with e-GFR in both genders [15]. In the present study, we did not find a significant association of TSH with the risk of CKD in the euthyroid Chinese population. Two recent prospective studies supported our findings. One study showed no association between TSH and CKD in 555 old participants [14]. The second study found no association of TSH with CKD in 4,488 euthyroid participants in Rotterdam

[13]. Interestingly, a recent longitudinal study including 17,067 Korean adults demonstrated that the risk of CKD was associated not with the baseline TSH levels but with the rate of TSH change per year [22]. To date, only one study, the prospective Kangbuk Samsung Health (KSH) Study, has evaluated the effect of TSH, FT3 and FT4 on the risk of incident CKD, doing so in 104,633 Korean euthyroid participants with a mean age of 38.0 years [16]. Our results partially conflicted with the findings from the KSH study, which showed that high-normal levels of TSH and low-normal FT3 levels, but not the FT4 levels, had an increased risk of incident CKD [16]. This difference might be attributed to the older subjects, different study design and different eGFR equation included in our study. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation in the KSH study was developed based on Whites and Blacks, and it was later shown to introduce inaccuracies when estimating GFR in Asians [23-25]. In our study, we used the CMDRD equation to estimate GFR, which improved the accuracy and performance of GFR estimation in a Chinese population [26].

The mechanisms underlying the association between the serum levels of TSH and FT3 and eGFR in euthyroid individuals remain unclear. It has been suggested that the TSH receptor is expressed not only on the thyroid follicular cell surface but also in a variety of extra-thyroidal tissues, including the kidney [27]. Previous research has suggested that thyroid hormones may affect renal function via some pre-renal and direct renal effects [10]. The pre-renal effects may be mediated by the influence of thyroid hormones on the cardiovascular system and the renal blood flow (RBF), while the direct renal effects may be mediated by the effect of thyroid hormones on the glomerular filtration rate, tubular secretory and re-absorptive processes and by the hormonal influences on renal tubular physiology. Furthermore, investigations in neonatal rats have proved the accelerating effect of thyroid hormones on renal development [28]. Unfortunately, we did not observe a significant association of the levels of TSH and FT3 with the risk of CKD. Therefore, the relationship between thyroid hormones and kidney function in euthyroid individuals is complex, and future studies are needed to determine the clinically relevant interactions between thyroid hormones and kidney function.

The strength of our study includes the large euthyroid Chinese population, the higher accuracy of the newly modified CKD-EPI equation for Chinese, the detailed characterization of the thyroid hormones, including TSH, FT3 and FT4, and the inclusion of more adjusted confounding factors. However, several limitations should be acknowledged. First, it is unclear whether thyroid hormone alterations are the cause or consequence of CKD. Due to the cross-sectional design, we could not determine the causality between thyroid hormones and the incidence of CKD. Hence, further prospective and longitudinal studies should be conducted to confirm our findings. Second, despite controlling for several confounders in our analysis, we did not have information on urine albuminuria or proteinuria [29], diet [30-32], or physical activity [33]; thus, these possible unmeasured confounders may have influenced our findings.

Conclusion

Our findings suggest that there is a significant association between TSH levels within the normal range and renal function in the euthyroid Chinese population. We propose that monitoring the FT4 levels within the normal range may determine some early alterations in the future development of CKD.

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W.T. and Z.S. conceived and designed the study. K.W. and K.X. wrote the main manuscript text. L.G. and B.X. prepared tables. J. C., Q. L., Y. Y., S. S. and D. W. collected the data. K.W., K.X., L. D. and C. H. revised the manuscript.

Availability of raw data: These are available from the corresponding author on reasonable request.

Disclosure Statement

We have no conflicts of interest.

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