Thyroid Research

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The association of thyroid hormone levels and incidence of chronic kidney disease: the Tehran thyroid study (TTS)

Atoosa Motaghedi Larijani[1], Safdar Masoumi[1], Hengameh Abdi[1], Atieh Amouzegar[1*] and Fereidoun Azizi[1]

Abstract

Background Evidence regarding the relationship between thyroid hormone levels within the normal range and the incidence of chronic kidney disease (CKD) in adults is scarce. This study aimed to identify the association between thyrotropin (TSH) and free thyroxine (FT4) levels with the incidence of CKD in a large cohort study over long-term follow-up.

Methods This prospective cohort study, with an 18-year follow-up, included 4118 adults without CKD from the Tehran thyroid Study (TTS). Participants were categorized by tertiles of normal TSH levels (low-normal, middle-normal, and high-normal) and abnormal TSH. The study outcome was incident CKD, defined as an estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73m^2. Multivariable Cox proportional hazard models were used to estimate hazard ratios (HRs) for CKD incidence based on thyroid hormone levels.

Results The HR for CKD development was 1.08 (95%CI: 1.01–1.15) per 1 SD increase in the TSH levels. Compared with participants with low-normal TSH levels, those with high-normal (HR:1.37; 95%CI: 1.03–1.84) and abnormal TSH (HR:1.24; 95%CI: 1.05–1.46) had a significantly higher risk of developing CKD. In subgroup analyses, the association between TSH level and CKD was significant in participants younger than 60 years, females, non-obese, non-smokers, and those without diabetes and hypertension. No association was observed between FT4 levels and incident CKD (HR: 0.92; 95%CI: 0.79–1.09). However, a significant association was observed between FT4 levels within the normal range and CKD development in those younger than 60 years old (HR: 0.77; 95% CI: 0.61–0.98).

Conclusion Increased TSH levels, even within the normal range, linearly increased the risk of CKD even after adjustment for important risk factors. As a result, TSH may potentially be an independent risk factor for incident CKD.

Keywords Thyroid hormones, Chronic kidney disease, Kidney function, Glomerular filtration rate

*Correspondence:
Atieh Amouzegar
amouzegar@endocrine.ac.ir
[1]Endocrine Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Introduction

Chronic kidney disease (CKD) is a major health issue affecting approximately 10% of the global population [1]. In addition to its high and increasing prevalence, CKD-associated morbidity and mortality ranked 18th in 2019 and is predicted to be among the top five leading causes of death by 2040 [2]. Notably, the burden of CKD is growing at a faster pace in low- and middle-income countries. While diabetes, hypertension, insulin resistance, and family history of CKD are established risk factors for CKD [3, 4], identifying other important risk factors may help in understanding the pathogenesis of CKD [5]. Expanding knowledge about potential CKD risk factors could lead to the development of effective prevention strategies and interventions, ultimately reducing the global burden of this debilitating disease.

The thyroid gland is involved in regulating most physiological actions in the body. Thyroid dysfunction can affect the production of thyroid hormone levels and activity, subsequently reducing cardiac output and increasing systemic vascular resistance, leading to a decrease in renal blood flow and a reduction in GFR [6–8]. Evidence from cross-sectional studies has shown that overt and subclinical hypothyroidism are associated with an increased prevalence of CKD [9–14], and some studies have reported improved kidney function after treating thyroid dysfunction [15–17]. Few studies have explored the link between thyroid-stimulating hormone (TSH) levels and CKD in people with normal thyroid function, with most being cross-sectional and lacking long-term evaluation [13, 18–22]. Only a handful of prospective studies have examined the relationship over time [19, 23]. Some have shown that increased TSH levels are associated with an increased risk of CKD [19, 24], while others have demonstrated a non-significant association [13, 21, 25]. Furthermore, these findings are inconsistent across different population subgroups.

This study aimed to evaluate the prospective association of TSH and free thyroxine (FT4) levels with the incidence of CKD among a large cohort of adult participants over 18 years of follow-up. Furthermore, the association was examined in the different subgroups of the population.

Materials and methods

Study population

The Tehran Lipid and Glucose Study (TLGS) is a long-term community-based cohort study of Iranian men and women aged three years or older, designed in 1997 to identify risk factors of non-communicable diseases in Iran. The Tehran Thyroid Study (TTS) was conducted within the TLGS study framework to investigate the prevalence, incidence, and natural history of thyroid diseases and their long-term outcomes. A detailed description of the project has been published elsewhere [26].

The present study included all participants older than 20 years who were initially recruited in phase I (1999–2001) or phase II (2002–2005) with at least one follow-up visit between January 1, 2002, and February 28, 2018 (Fig. 1). We excluded participants who had the following conditions at baseline: Participants without data on serum thyroid hormone levels ($n = 17$), TSH < 0.3 mIU/L or FT4 levels outside the reference range ($n = 801$), CKD at baseline ($n = 355$), use of thyroid medication or history of thyroid surgery or radioactive iodine treatment ($n = 69$), pregnancy ($n = 11$), history of cancer ($n = 67$) and those with missing data on covariates at baseline and missing follow-up ($n = 335$). Finally, 4118 participants over 20 years old without CKD were included in the main analysis.

Data collection

In the TTS cohort, demographic data, medical history, and medical examinations were collected and performed by trained health professionals. The information obtained from participants in each examination visit included age, sex, education level, history of smoking, medical history and medications, blood pressure, and anthropometric data such as height, weight, and waist circumference. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Obesity was defined as BMI ≥ 30 kg/m^2. Blood samples were taken after 10 to 12 h of fasting, and laboratory measurements, including blood lipid markers, fasting blood sugar, urea, and serum creatinine, were measured. Smoking status was classified into two groups: smokers and never-smokers. A smoker was defined as someone who smoked 100 cigarettes in their lifetime and smokes regularly or irregularly. A never-smoker was defined as someone who has never smoked or smoked less than 100 cigarettes in their lifetime. Data on physical activity was collected with the lipid research clinic (LRC) and modifiable activity questionnaires (MAQ) and rescored in the metabolic equivalent of the task (MET) scale. The physical activity levels were defined as low (MET < 600 min/week) and moderate/high (MET ≥ 600 METs/week) physical activity.

In this study, we used the creatinine-based CKD-EPI 2021 formula to calculate the estimated glomerular filtration rate (eGFR) [27]. Based on the Kidney Disease Outcome Quality Initiative (KDOQI) guideline, patients with eGFR < 60 mL/min/1.73m^2 are considered to have CKD [27]. Diabetes was defined based on high fasting blood glucose (FBS ≥ 126 mg/dl) or use of glucose-lowering medication, and hypertension, based on high systolic blood pressure (SBP ≥ 140 mmHg), diastolic blood pressure (DBP ≥ 90 mmHg) or use of antihypertensive drugs.

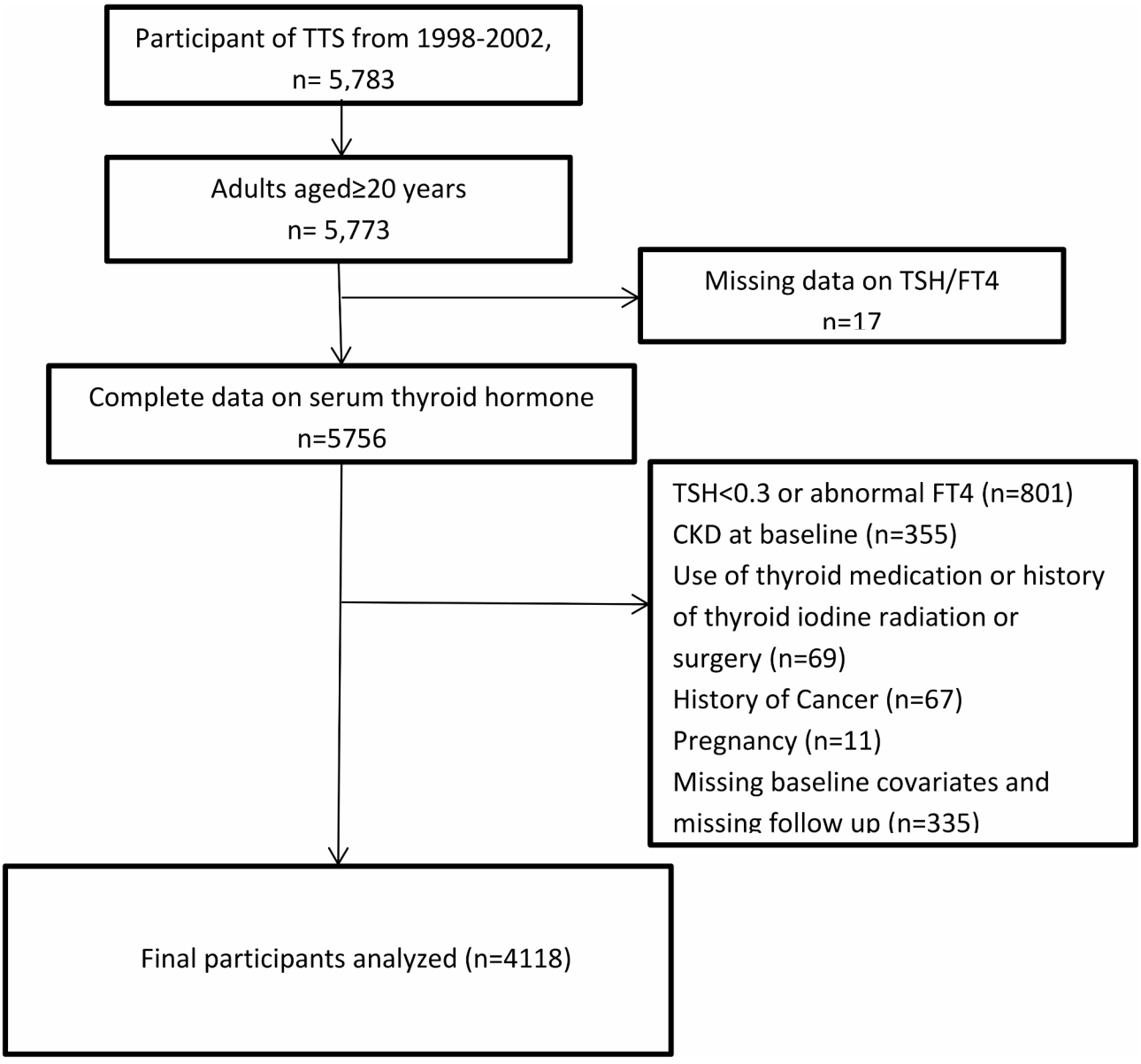

Fig. 1 Flowchart showing the selection of eligible participants

Serum TSH, FT4, and thyroid peroxidase antibody (TPOAb) were assessed at three-year intervals. FT4 and TSH were determined on -70ºC stored serum samples by the electrochemiluminescence immunoassay (ECLIA) method, using Roche Diagnostics kits & Roche/Hitachi Cobas e- 411 analyzers (GmbH, Mannheim, Germany). Lyophilized quality control material (Lyphochek Immunoassay plus Control, Bio-Rad Laboratories) was utilized to monitor assay accuracy; intra- and inter-assay CVs were 1.3% and 3.7% for FT4 and 1.5% and 4.5% for TSH determinations, respectively. TPOAb was measured by an immune enzymometric assay (IEMA) using related kits (Monobind, Costa Mesa, CA, USA) and the Sunrise ELISA reader (Tecan Co., Salzburg, Austria); intra- and inter-assay CVs were 3.9% and 4.7%, respectively. Serum creatinine level was measured using the kinetic colorimetric Jaffe method. Biochemical blood tests were performed on the day of sampling using commercial kits (Pars Azmon Inc., Iran) by the Selectra 2 auto-analyzer (Vital Scientific, Spankeren, The Netherlands).

Statistical analysis

The primary outcome of this study was incident CKD. Participants were followed from the baseline visit to the CKD diagnosis, the last available visit, or the end of the study. Since the exact time of incident CKD occurrence was between the visit where CKD was detected and the previous visit, we estimated the onset at the midpoint

between the two visits. The association of baseline TSH level with incident CKD was analyzed using continuous and categorical approaches with proportional hazard regression models. In the categorical approach, participants were divided into four groups based on their TSH levels. Participants with TSH levels within the normal range (0.3–5.06 mIU/L) were categorized into tertiles: low-normal (0.30–1.20 mIU/L), middle-normal (1.21–2.05 mIU/L), and high-normal (2.06–5.06 mIU/L). Additionally, participants with TSH levels outside this range were classified as having abnormal TSH levels. Participants were also categorized by tertiles of FT4 levels as follows: low-normal (0.91–1.12 ng/dL), middle-normal (1.12–1.27 ng/dL), and high-normal (1.27–1.55 ng/dL).

To adjust for confounding variables, we used five models with increasing degrees of adjustment. The first model was adjusted for age (continuous) and sex. The second model was further adjusted for education (less than six years, 6–12 years, and more than 12 years of education), smoking (smoker vs. never-smoker), physical activity (low vs. moderate/high physical activity), and BMI (continuous). The third model further included serum FT4 level (continuous) and TPOAb (Positive/negative). The fourth model also included anti-hypertensive drug use (yes/no), glucose-lowering drug use (yes/no), and lipid-lowering drug use(yes/no). The fifth model was further adjusted for systolic blood pressure (continuous) and serum levels of triglycerides(continuous), HDL cholesterol (continuous), fasting blood sugar (continuous), and eGFR at baseline.

Finally, we performed subgroup analyses in pre-specified subgroups defined by age (< 60, 60 years), sex (male, female), body mass index (BMI < 30, BMI ≥ 30 kg/m2), hypertension (yes, no), diabetes (yes, no), and smoking status (never-smoker, smoker). All analyses were performed using STATA version 14 (StataCorp LP, College Station, TX, USA). A two-sided *P*-value < 0.05 was considered statistically significant.

Results

Baseline characteristics

The current study enrolled 4118 adults (42.6% male) without CKD with a mean age of 39.5 years. During a median follow-up of 14.8 years, 967 new CKD cases occurred. The baseline characteristics of the study participants are presented according to the TSH levels in Table 1. Participants with low-normal TSH tended to be older, male, smokers, less physically active, and TPOAb negative. They also had lower mean BMI, higher mean fasting plasma glucose, and higher prevalence of dyslipidemia.

The relationship between serum TSH levels and the incidence of CKD is shown in Fig. 2; Table 2. We identified a linear association between TSH levels and incident

Table 1 Baseline characteristics of participants in the Tehran thyroid study

Characteristics	Overall	Serum TSH levels (mIU/L) quartiles				Pvalue
		Low-normal TSH (0.30, 1.2)	Middle-normal TSH (1.21, 2.05)	High-normal TSH (2.06, 5.06)	Abnormal TSH (5.07, 20)	
Number of participants	4,118	1,301	1,291	1,287	239	
Age years, mean ± SD	39.47 ± 12.95	41.36 ± 12.78	39.14 ± 12.95	38.11 ± 12.87	38.36 ± 13.25	< 0.001
Male, n (%)	1753(42.57)	670(51.50)	604(46.79)	426(33.10)	53(22.18)	< 0.001
Body mass index (kg/m2), mean ± SD	26.72 ± 4.37	26.49 ± 4.35	26.86 ± 4.30	26.78 ± 4.45	26.84 ± 4.40	< 0.001
Waist circumference (cm), mean ± SD	87.62 ± 11.90	87.85 ± 11.82	88.04 ± 11.54	87.19 ± 12.14	86.47 ± 12.80	< 0.001
Education, n (%)						0.056
Illiterate/primary school (< 6 yrs.)	1463(35.53)	477(36.66)	434(33.62)	470(36.52)	82(34.31)	
High school (6–12 years)	2045(49.66)	630(48.42)	657(50.89)	640(49.73)	118(49.37)	
Higher education (> 12 years)	610(14.81)	194(14.91)	200(15.49)	177(13.75)	39(16.32)	
Current Smoking, n (%)	497(12.07)	231(17.76)	153(11.85)	101(7.85)	12(5.02)	< 0.001
Low physical activity, n (%)	1941 (47.13)	552 (42.43)	620 (48.02)	634 (49.26)	135 (56.49)	< 0.001
Hypertension, n (%)	733(17.80)	247(18.99)	235(18.20)	203(15.77)	48(20.08)	< 0.001
Dyslipidemia, n (%)	1827(44.37)	599(46.04)	570(44.15)	561(43.59)	97(40.59)	< 0.001
Diabetes, n (%)	273 (6.63)	100 (7.69)	92 (7.13)	62 (4.82)	19 (7.95)	0.079
SBP (mmHg), mean ± SD	116.39 ± 16.98	117.49 ± 17.10	116.27 ± 16.87	115.26 ± 16.85	117.11 ± 17.27	< 0.001
DBP (mmHg), mean ± SD	76.31 ± 10.42	77.03 ± 10.65	76.10 ± 10.46	75.88 ± 10.15	75.79 ± 10.27	< 0.001
FBS (mg/dL), mean ± SD	95.48 ± 28.58	97.64 ± 32.20	95.30 ± 27.42	93.34 ± 24.28	96.15 ± 33.99	< 0.001
Triglyceride (mg/dL), mean ± SD	162.26 ± 108.3	163.97 ± 103.87	162.86 ± 110.47	160.63 ± 110.17	158.46 ± 111.53	< 0.001
Cholesterol(mg/dL), mean ± SD	206.05 ± 43.76	208.34 ± 45.15	203.96 ± 42.51	205.05 ± 43.63	209.35 ± 41.99	< 0.001
HDL-C (mg/dL), mean ± SD	41.63 ± 11.00	41.52 ± 11.09	41.03 ± 10.44	42.13 ± 11.22	42.74 ± 12.16	< 0.001
Positive TP-Ab, IU/mL	519 (12.61)	62 (4.77)	110 (8.52)	220 (17.12)	127 (53.14)	< 0.001

Abbreviations: SD, standard deviation; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBS, fasting blood sugar, HDL-C, high-density lipoprotein cholesterol

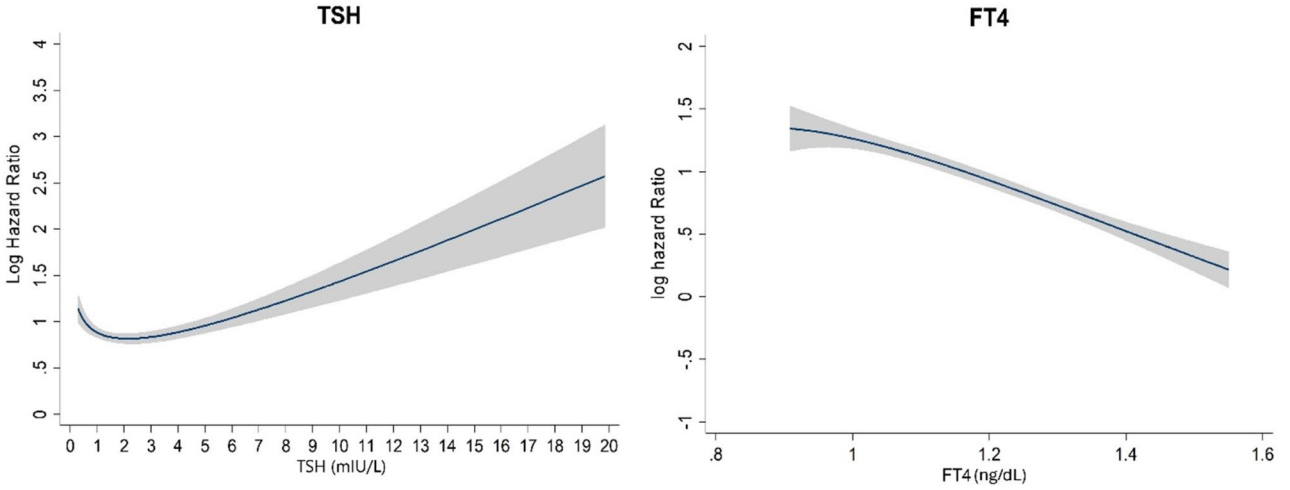

Fig. 2 Associations between TSH levels and FT4 levels and incidence of chronic kidney disease during 18 years follow up. Associations were investigated by multivariable Cox regression models based on restricted cubic splines. Solid lines represent hazard ratios, whereas shaded sections represent 95% CIs. Risk estimate adjusted for age and sex

Table 2 Associations between TSH and FT4 levels and incidence of chronic kidney disease: 18 years follow up-Tehran thyroid study

	Events	IR (95% CI) *	Model 1	Model 2	Model 3	Model 4	Model 5
			HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
TSH levels (1 SD)	976	17.4 (16.3–18.5)	1.12 (1.05–1.18)	1.11 (1.04–1.18)	1.13 (1.05–1.20)	1.13 (1.06–1.21)	1.08 (1.01–1.15)
Serum TSH levels quartiles							
Low-normal TSH ($n=1,301$)	304	16.8 (15.0-18.8)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
Middle-normal TSH ($n=1,291$)	303	17.3 (15.5–19.4)	1.21 (1.04–1.42)	1.18 (1.00-1.38)	1.18 (1.00-1.38)	1.18 (1.01–1.38)	1.16 (0.99–1.36)
High-normal TSH ($n=1,287$)	303	17.4 (15.6–19.5)	1.29 (1.10–1.52)	1.26 (1.07–1.47)	1.29 (1.10–1.51)	1.26 (1.07–1.49)	1.24 (1.05–1.46)
Abnormal TSH ($n=239$)	66	21.4 (16.8–27.2)	1.43 (1.09–1.88)	1.37 (1.04–1.80)	1.43 (1.10–1.91)	1.41 (1.05–1.88)	1.37 (1.03–1.84)
Ft4 levels (1 SD)	976	17.4 (16.4–18.5)	0.99 (0.92–1.06)	0.99 (0.93–1.06)	1.02 (0.95–1.09)	1.00 (0.94–1.08)	0.98 (0.92–1.06)
Serum FT4 Tertiles							
Low-normal FT4 ($n=1,381$)	405	21.5 (19.5–23.7)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
Middle-normal FT4 ($n=1,372$)	322	17.3 (15.5–19.3)	0.95 (0.82–1.10)	0.95 (0.82–1.11)	0.99 (0.85–1.14)	0.98 (0.84–1.14)	0.96 (0.83–1.12)
High-normal FT4 ($n=1,365$)	249	13.4 (11.8–15.1)	0.92 (0.79–1.09)	0.94 (0.80–1.10)	0.98 (0.83–1.15)	0.94 (0.80–1.11)	0.89 (0.75–1.05)

Abbreviations: HR hazard ratio; CI confidence interval; RE reference.

*IR: Incidence rate per 1,000 person-years.

Model 1: Adjusted for age and sex

Model 2: Adjusted for age, sex, education, smoking status, physical activity, and body mass index

Model 3: Adjusted for age, sex, education, smoking status, physical activity, and body mass index, FT4, TPO-Ab

Model 4: Adjusted for age, sex, education, smoking status, physical activity, body mass index, FT4, TPO-Ab, anti-hypertensive drug use, glucose-lowering drug use, lipid-lowering drug use

Model 5: Adjusted for age, sex, education, smoking status, physical activity, body mass index, FT4, TPO-Ab, anti-hypertensive drug use, glucose-lowering drug use, lipid-lowering drug use, systolic blood pressure, triglycerides, HDL cholesterol and fasting blood sugar and baseline eGFR

CKD ($P>0.05$ for nonlinearity, Fig. 2). After adjustment of age and sex, the HR of CKD incidence was 1.12 (95%CI: 1.05–1.18) per 1 SD increase in the TSH levels. In the fully adjusted model, the HR per 1 SD increase in TSH level was 1.08 (95%CI: 1.01–1.15). In the categorical approach, considering the low-normal TSH as the reference group, both high-normal and abnormal TSH levels were significantly associated with an increased risk of CKD (Table 2). The multivariate-adjusted HR for CKD incidence was 1.16 (95%CI: 0.99–1.36) in the middle-normal TSH group, 1.24 (1.05–1.46) in the high-normal TSH group, and 1.37 (1.03–1.84) in the abnormal TSH group. Kaplan–Meier survival curves stratified by TSH level categories showed that participants with high-normal and abnormal TSH levels had the highest cumulative incidence of CKD (Fig. 3).

Regarding the association between FT4 levels and the incidence of CKD, after multivariate adjustment, there was no significant association between FT4 levels within the normal range and incident CKD (Table 2; Fig. 3).

Stratified and sensitivity analyses

In the stratified analyses, no significant interaction was observed among the population subgroups based on

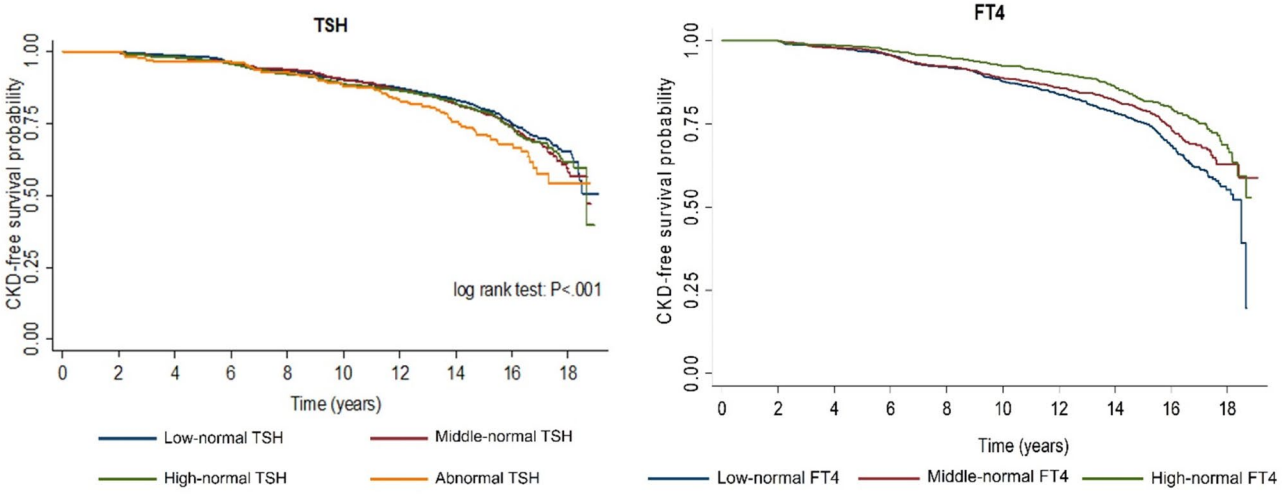

Fig. 3 (**A**) Kaplan-Meier survival curves for the incidence of chronic kidney disease events by TSH level tertiles at the baseline measurements during 18 years follow up (Low-normal TSH group [Tertile 1]: (0. 3, 1.2), middle-normal TSH group [Tertile 2]: (1.21, 2.05), high-normal TSH group [Tertile 3]: (2.06, 5.06), and abnormal TSH group (5.07–20) (**B**) Kaplan-Meier survival curves for the incidence of chronic kidney disease events by FT4 level tertiles at the baseline measurements during 18 years follow up (low-normal FT4 group [Tertile 1]: (0.30, 1.2), middle-normal FT4 group [Tertile 2]: (1.21, 2.05) and high-normal FT4 group [Tertile 3]: (2.06,0.06)

Table 3 Stratified analyses of the associations between TSH levels and incidence of chronic kidney disease: 18 years follow up-Tehran thyroid study

	TSH levels (1 SD)	Low-normal TSH	Middle-normal TSH	High-normal TSH	Abnormal TSH	*P* interaction
Age						
< 60 years	1.11 (1.04–1.19)	1.00 (Reference)	1.19 (0.99–1.44)	1.34 (1.11–1.633)	1.56 (1.12–2.17)	0.12
≥ 60 years	1.02 (0.90–1.15)	1.00 (Reference)	1.12(0.81–1.55)	1.06(0.75–1.50)	1.04(0.55–1.96)	
Sex						
Male	1.02 (0.90–1.16)	1.00 (Reference)	1.14(0.89–1.45)	1.05(0.79–1.40)	1.95(1.06–3.60)	0.75
Female	1.11 (1.03–1.18)	1.00 (Reference)	1.18(0.96–1.47)	1.39(1.13–1.70)	1.38(1.00-1.92)	
Diabetes						
No	1.07 (1.01–1.15)	1.00 (Reference)	1.20(1.00-1.43)	1.35(1.13–1.61)	1.40(1.01–1.94)	0.90
Yes	1.06(0.92–1.21)	1.00 (Reference)	0.94(0.62–1.43)	0.74(0.45–1.23)	0.99(0.50–1.94)	
Hypertension						
No	1.08 (1.0 -1.17)	1.00 (Reference)	1.22(0.99–1.51)	1.43(1.16–1.77)	1.39(0.91–2.10)	0.84
Yes	1.06 (0.97–1.17)	1.00 (Reference)	1.11(0.86–1.43)	1.11(0.85–1.45)	1.16(0.76–1.78)	
Bmi						
< 30 kg/m^2	1.14 (1.06–1.23)	1.00 (Reference)	1.34(1.09–1.65)	1.27(1.03–1.57)	2.03(1.41–2.91)	0.61
≥ 30 kg/m^2	1.0 (0.90–1.11)	1.00 (Reference)	0.92(0.70–1.21)	1.19(0.90–1.57)	0.72(0.41–1.27)	
Smoking						
Never	1.11 (1.05–1.18)	1.00 (Reference)	1.16(0.98–1.38)	1.28(1.08–1.52)	1.30(0.96–1.76)	0.62
Current	0.87 (0.61–1.22)	1.00 (Reference)	1.09(0.65–1.84)	1.11(0.57–2.18)	0.88(0.15–5.22)	

Data are presented as HR (95% CI). Adjusted for age, sex, education, smoking status, physical activity, body mass index, FT4, TPO-Ab, anti-hypertensive drug use, glucose-lowering drug use, lipid-lowering drug use, systolic blood pressure, triglycerides, HDL cholesterol and fasting blood sugar and baseline eGFR

baseline variables, including age, sex, diabetes, hypertension, BMI, eGFR, and smoking status ($P > 0.05$ for the interaction) (Table 3). There was a significant association between each SD increase in TSH levels and CKD in participants aged < 60 years (HR: 1.56; 95%CI: 1.04–1.19), women (HR: 1.11; 95%CI: 1.03–1.18), non-obese (HR: 1.14; 95%CI: 1.06–1.23), never-smokers (HR: 1.11; 95%CI: 1.05–1.18), and those without baseline diabetes (HR: 1.07; 95%CI: 1.01–1.15), and hypertension (HR: 1.08; 95%CI: 1.00-1.17). In addition, in the categorical approach, the participants with middle-normal, high-normal, and abnormal TSH levels were significantly at a higher risk of future CKD compared to the low-normal TSH group in non-diabetic and non-obese subgroups (P value < 0.05). Moreover, men with abnormal TSH levels had an increased risk of CKD (HR:1.96; 95%CI: 1.06–3.60). The association between FT4 levels and CKD incidence was only observed in the participants aged < 60

Table 4 Stratified analyses of the associations between FT4 levels and incidence of chronic kidney disease: 18 years follow up-Tehran thyroid study

	FT4 levels (1 SD)	Low-normal FT4 (0.91–1.12 ng/dL)	Middle-normal FT4 (1.12–1.27 ng/dL)	High-normal FT4 (1.27–1.55 ng/dL)	*P* interaction
Age					
< 60 years	0.92(0.85–0.99)	1.00 (Reference)	0.93(0.78–1.11)	1.07(0.89–1.30)	0.81
≥ 60 years	0.93(0.81–1.07)	1.00 (Reference)	1.11(0.82–1.50)	0.71(0.50–1.01)	
Sex					
Male	0.95(0.85–1.06)	1.00 (Reference)	0.83(0.64–1.08)	0.86(0.66–1.11)	0.001
Female	1.06(0.97–1.16)	1.00 (Reference)	1.06(0.89–1.28)	1.01(0.81–1.25)	
Diabetes					
Yes	0.99(0.92–1.07)	1.00 (Reference)	0.95(0.81–1.11)	0.91(0.76–1.09)	0.28
No	1.10(0.93–1.32)	1.00 (Reference)	1.21(0.79–1.85)	1.23(0.80–1.88)	
Hypertension					
Yes	1.04(0.95–1.14)	1.00 (Reference)	0.90(0.74–1.10)	1.04(0.84–1.29)	0.78
No	0.96(0.86–1.07)	1.00 (Reference)	1.11(0.88–1.40)	0.80(0.61–1.05)	
BMI					
< 30 kg/m^2	1.02(0.93–1.12)	1.00 (Reference)	1.07(0.88–1.31)	0.97(0.79–1.21)	0.02
≥ 30 kg/m^2	0.99(0.88–1.11)	1.00 (Reference)	0.91(0.71–1.17)	0.91(0.68–1.21)	
Smoking					
Never	1.00(0.93–1.08)	1.00 (Reference)	1.01(0.86–1.18)	0.92(0.77–1.09)	0.47
Current	0.97(0.76–1.26)	1.00 (Reference)	0.64(0.35–1.17)	1.02(0.57–1.80)	

Data are presented as HR (95% CI). Adjusted for age, sex, education, smoking status, physical activity, body mass index, FT4, TPO-Ab, anti-hypertensive drug use, glucose-lowering drug use, lipid-lowering drug use, systolic blood pressure, triglycerides, HDL cholesterol and fasting blood sugar and baseline eGFR

years (HR: 0.92; 95%CI: 0.85–0.99 per 1-SD increase in FT4 levels) (Table 4).

Discussion

In this large-scale prospective study with nearly 18-year follow-up, we found that an increase in serum TSH levels, even within the normal range, was associated with a higher risk of future CKD. Our findings suggest an almost linear relationship between TSH levels and the risk of CKD, independent of important confounding risk factors, such as age and sex, education, smoking, physical activity, body mass index, medication, blood pressure, lipid profile, fasting blood sugar, and baseline eGFR. In addition, stratified analyses showed that TSH levels significantly increased the risk of CKD in women, young and middle-aged adults, never-smokers, non-obese, and those without baseline diabetes or hypertension. No association was observed between FT4 levels within the normal range and the risk of CKD. However, we observed that in young and middle-aged adults, higher FT4 levels had a protective effect on incident CKD.

In the current study, baseline serum TSH levels were significantly associated with incident CKD over 18 years of follow-up. Individuals with high-normal (TSH > 2 mIU/L) and abnormal (TSH > 5 mIU/L) TSH levels had 24% and 37% increased risk compared to individuals with low-normal TSH levels. The relationship between thyroid dysfunction and incident CKD has remained controversial. Most studies in the literature are cross-sectional, and only a few studies have prospectively evaluated this association, particularly in the euthyroid and subclinical hypothyroid populations. Consistent with our findings, a study on 104,633 participants in South Korea demonstrated that the individuals in the highest TSH quantile (2.85-5.00 mIU/L) had a 26% increased risk for CKD over 3.5 years of follow-up. In the Atherosclerosis Risk in Communities (ARIC) study, which included 12,785 individuals in the United States, the cross-sectional investigation showed that TSH and FT4 were associated with reduced kidney function at baseline. However, none of these markers nor their corresponding clinical classifications were associated with CKD incidence during 19.6 years of follow-up [13]. In a recent study by You et al. in the United States, TSH levels higher than 3.0 mIU/L were linked to CKD incidence/progression during 11 years of follow-up [24]. Potential explanations for the discrepancies in these studies may lie in the age of the study participants, ethnicity, adjustments, or follow-up duration.

Thyroid hormones have an intricate relationship with kidney function, and the exact mechanisms of their contribution to the development or progression of CKD are not fully understood. However, there are a few potential pathways through which thyroid hormones may have an impact on kidney function. In animal studies, hypothyroidism has been linked to a smaller kidney size relative to body weight [28], reduced tubular mass [29], and alterations in the glomerular basement membrane structure [30, 31]. Hypothyroidism may induce kidney dysfunction through various pathways. These include diminished cardiac output, decreased contractility, and heart

rate [32]. Also, vasoconstriction within the kidneys may occur due to lowered synthesis and activity of vasodilators like nitric oxide and adrenomedullin [33]. Reduced production and activity of the renin-angiotensin-aldosterone system can also hinder the autoregulation of kidney perfusion [34]. Recent research in the literature suggests that slightly reduced thyroid function, marked by high-normal TSH levels (approximately 2.5-3.0 mIU/L), is associated with endothelial dysfunction [35] and poorer survival outcomes in patients with advanced CKD or end-stage kidney disease (ESKD) [36, 37]. More research is needed to determine the precise TSH levels that ensure optimal health for the CKD population.

In the current study, we found an association between TSH and incident CKD in adults under 60 years of age but not in older adults at baseline. Notably, we did not find an association between serum FT4 levels and CKD, except that higher FT4 levels are protective for CKD incidence in those aged < 60 years old. The ARIC study, which involved middle-aged and older adult populations (mean age 57 years), found no prospective association between thyroid parameters and CKD. This aligns with our findings in the subgroup of adults aged > 60 years, where no significant association was observed. A study in Taiwan involving 41,454 elderly (aged > 65 years) showed that thyroid dysfunction (subclinical and overt hypothyroidism) was linked to future CKD in women and participants without diabetes. However, they did not investigate the relationship between TSH and FT4 levels within the normal range and CKD [14]. Similarly, although You et al. found that those with high-normal TSH have an increased risk of future CKD in the general population, they did not investigate this association in their subgroup analysis of the population.

We took a step further in our analysis and, for the first time, found that TSH levels within the normal range can significantly be an independent risk factor for CKD in young and middle-aged adults. In the general population, the distribution of serum TSH gradually shifts towards higher concentrations with increasing age [38], indicating that higher TSH levels in older adults may be a physiological change. Recently, age- and sex-specific TSH reference ranges based on median distribution of TSH values in the age and sex subgroups have been proposed [39]. Notably, in the American Thyroid Association guideline, the optimum dose of levothyroxine for managing hypothyroidism is considered when the TSH is in the range of 0.5-2.0 mIU/L in non-elderlies, higher TSH levels are considered optimal in the elderlies [40]. The difference in this association between non-elderly and elderly adults may be attributed to different responses to the hypothalamic-pituitary feedback system or stimulation adrenergic signaling, both of which are weakened in the elderly [41]. The current study emphasizes the importance of TSH levels, even in the normal range with CKD incidence, and the need for further investigation and monitoring in this seemingly healthy group.

The subgroup analyses in the current study did not show significant interactions between the subgroups based on sex, baseline eGFR, BMI, smoking status, diabetes, or hypertension. However, the association between TSH level and CKD was significant in women, non-obese, never-smokers, and those without diabetes or hypertension. Regarding sex difference, our finding may be due to the higher prevalence of elevated TSH levels within the normal range in women, which tends to increase with advancing age. As in the most recent study by Yamada et al. on 14,860 euthyroid individuals, the reference range based on the central 95% TSH values of women was 0.5–4.6 mIU/L in their 30s and 0.7–7.8 mIU/L in their 60s, while in men, the reference ranges were narrower, at 1.0-1.7 mIU/L in their 30s and 1.0-1.6 mIU/L in their 60s [39]. Some previous studies have also reported a more pronounced risk of adverse health outcomes for higher TSH within normal ranges in women [42, 43]. This may be due to the effect of menopause on the HPA axis and, subsequently, on metabolic and renal factors [44].

The reason for the significant association of TSH with CKD in those without comorbidities is that these subgroups are less likely to have confounding factors that could obscure the relationship between TSH and CKD. Individuals with hypertension, obesity, and diabetes have a 1.5-2.0 fold [45], 1.5-2.0 fold [46], and 2.8–3.3 fold [47] increased risk for CKD incidence, respectively. Additionally, the duration of these diseases and the types of medications used for their control are important confounding factors [48, 49], which are not possible to adjust for in a single study. This observation is consistent with findings from other studies that have reported a more pronounced effect of TSH in healthy populations [24]. The current study demonstrated that higher serum TSH values may be an additional risk factor for CKD in seemingly healthy individuals, suggesting that high-normal TSH levels could play an important role in the development of CKD in women and those without obvious health issues.

The current study is the longest population-based study to date, with 18 years of follow-up, to evaluate the relationship between thyroid hormones and kidney function. Most previous studies have focused on patients with overt or subclinical hypothyroidism. This study is the first to investigate the risk of CKD in individuals with baseline euthyroid status across different subpopulations. Additionally, we measured TPOAb and FT4, allowing for a more accurate characterization of participants' thyroid status beyond TSH measurement. We used high-quality laboratory methods with extensive quality control. Finally, we measured a broad panel of health-related variables, allowing for fine-tuning of potential confounders.

However, there are some limitations in the current study that must be considered when interpreting our results. Our study population consisted of Iranian adults, and therefore, the results may not be generalizable to other races/ethnicities. Another limitation is that we confirmed CKD diagnosis based on one creatinine measurement. However, it is common in cohort studies with long follow-ups to use this approach due to the challenges of frequent examination visits and laboratory measurements at short intervals. We were not able to utilize data on proteinuria/albuminuria to detect earlier stages of CKD (mild CKD). Additionally, the association between T3 and CKD was not measured due to a lack of data on T3.

Conclusion

In this large-scale prospective study with nearly 18 years of follow-up, we discovered that increased serum TSH levels, even within the normal range, are independently associated with a higher risk of future CKD. We found that having high-normal TSH increases the risk of CKD, especially in women, the non-elderly, and those without comorbidities. In addition, we observed that higher levels of FT4 within the normal range were protective against future CKD in young and middle-aged adults. These findings underscore the importance of monitoring thyroid function as a potential risk factor for CKD in the seemingly healthy population.

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None.

Author contributions
All authors contributed to writing the manuscript. AML conducted of the current analysis and drafted the initial manuscript. HA contributed to the interpretation of results and revision of the manuscript. SM performed statistical analysis and AA and FA conceptualized and designed the study, assisted in manuscript preparation and interpretation of results, reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Data availability
Datasets generated during and analyzed during the current study are not publicly available due to institutional policies but are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This study was performed according to the ethical principles of the Helsinki Declaration and approved by the National Research Council of the Islamic Republic of Iran (IR.SBMU.ENDOCRINE.REC.1401.107), the Human Research Review Committee of the Endocrine Research Center, Shahid Beheshti University, Tehran, Iran. Written informed consent was obtained from all subjects.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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