

The Relationship Between Metabolic Parameters, Age, and Thyroid Status: A Cross-Sectional Study-Based National Survey of Iodine Nutrition, Thyroid Disease

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Aim: The relationship between thyroid status and metabolic factors was investigated as well as iodine nutrition in the general population and among the elderly population.

Methods: We performed a cross-sectional survey of 2483 subjects to assess the status of national iodine nutrition and incidence of thyroid disease. The general and elderly populations were divided into normal thyroid function (NTF) and subclinical hypothyroidism (SCH) groups. The anthropometric parameters and biochemical indicators were then analyzed.

Results: Overall, 327 participants were diagnosed with thyroid diseases, 73 (22.32%) of whom were 65 years or older. For the general population, compared with the NTF group, individuals in the SCH group were older, presented with higher systolic blood pressure, fasting blood glucose, serum cholesterol, and urinary iodine concentration (all $p < 0.05$) but lower blood uric acid (UA) ($p < 0.05$). Linear regression analysis further revealed that age and triglyceride (TG) serum levels positively correlated with serum thyroid-stimulating hormone (TSH) levels. Multiple regression analyses revealed that age, TG, waist circumference (WC), and body mass index were independent predictors for abnormal TSH serum levels. For the elderly population, compared with NTF group, individuals in the SCH group were substantially older ($p < 0.05$) but presented with lower UA ($p < 0.05$). Pearson linear regression analysis revealed a positive correlation between age ($p = 0.003$) as well as TG levels ($p < 0.001$) and serum TSH levels. In contrast, WC ($p = 0.003$) was negatively related to TSH serum levels. Further multiple regression analysis revealed that age, TG, WC and heart rate were independent predictors of blood TSH.

Conclusion: The large-scale national study of iodine nutrition, thyroid disease has shown a vital relationship between metabolic indicators and serum TSH levels. Age and metabolic diseases increase the likelihood of developing thyroid diseases, both the general population and among the elderly.

Keywords: thyroid function, metabolic status, aging

Introduction

Thyroid disease is a common disease affecting people of all ages around the world.¹ Subclinical hypothyroidism (SCH), characterized by high levels of serum thyroid stimulating hormone (TSH) but normal serum-free thyroxine levels, is very common in the general population. Even though the global incidence of SCH is estimated to be between 5% and 10%, the disease is more prevalent in the elderly

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and among women.² In the past decade, the prevalence of SCH has increased from 3.22% to 16.7%, as same as the proportion of people with positive thyroid peroxidase antibodies from 9.81% to 11.5%.³ SCH can be divided into two categories based on the TSH level: Mild SCH is characterized by less than 10 mIU of TSH per liter of blood, whereas severe SCH is characterized by more than 10 mIU of TSH per liter of blood.⁴ Mild SCH accounts for 90% of the SCH cases.⁵ In euthyroid subjects with a TSH in the upper normal range (2.5–4.5 mIU/L) were more obese, had higher triglycerides, and had an increased likeliness for the metabolic syndrome.⁶ Patients with SCH are at a higher risk of developing coronary heart disease, particularly when TSH concentrations is above 10 mIU/L. TSH levels higher than 7 mIU/L further increase the risk of death from cardiovascular complications.⁷ Also, higher levels of TSH in SCH patients increase the risk of heart failure.⁸ Meanwhile, hypothyroidism is associated with reversible dementia,⁹ whereas SCH adversely affects lipid metabolism.¹⁰ Also, hypothyroidism increases the death risk of patients on dialysis.¹¹ The prevalence of cerebrovascular diseases in type 2 diabetic patients is higher in hypothyroidism than hyperthyroidism patients even after adjustment for age and sex. In a related study, the prevalence of hypothyroidism in diabetics was found to be 6.8%, with the majority of them presenting with underlying SCH.¹²

Several studies have demonstrated the high serum TSH in elderly population. We hypothesize that all or some of the SCH-related diseases are also closely associated with age-related metabolic imbalance^{12,13}. However, reports on the association between SCH and metabolic disease are not entirely consistent.^{14–16} This may be attributed to differences in the race, sampling and sample sizes as well as the non-community crowd. Therefore, we conducted a population-based cross-sectional survey to explore the relationship between serum TSH levels and blood glucose, blood lipids, blood pressure, UIC, circulating thyroid antibodies and other metabolic parameters.

Subjects and Methods

Study Population

A total of 2663 individuals attending the National Survey of Thyroid Diseases and Diabetes in Chongqing of China between 2014 and 2017 were enrolled for this study. We remained with 2483 participants after excluding 180 individuals with incomplete data. Of the 2483 people, 336

(1.53%) of them were aged 65 or older (73 ± 7.8 years old). To be included in the study, one must have fulfilled the following: (1) be 18 years or older; (2) of Han race; (3) have lived in respective a random community or village for more than 5 years; (4) not have undergone tests utilizing iodine as contrast agent or had taken amiodarone within the last three months; (5) details for treatment of underlying complication are availed and (6) not pregnant. The protocol for this study was approved by the Ethics Committee of Chongqing University Central Hospital. All procedures in the study were performed in accordance with the ethical standards of the 1964 Declaration of Helsinki. All participants were informed about the purpose of the study. The written informed consents were obtained from all individual participants included in the study.

Anthropometric Parameters

The major anthropometric parameters measured were blood pressure, height, weight, and waist circumference (WC). For height, the patients removed their shoes, stood upright with back against the weighing scale column, the heels close to each other and looked straight ahead. The head plate was then gently pulled down till it just touched the tip of the head, before the measurements were read. The accuracy of our height measurement scale was 0.1 cm. Before weight measurement, the participants fasted for xyz hours. Just before the weight was measured, the patients micturited, took off the shoes and hat and stood at the center of the weighing scale. The weight was read after the pointer stabilized. The accuracy of the weighing machine used was 0.1 kg. The waist circumference was measured using a tape measure with an accuracy of 0.1 cm. The measurement was based on the distance between the mid-point of the horizontal line of the anterior superior iliac crest and the lower edge line of the 12th rib. Participants rested for 10 minutes before systolic and diastolic blood pressures were measured (Omron HEM7430, Omron Corporation).

Biochemical Indicators

Whole blood samples were drawn after overnight fasting. The urinary iodine concentration (UIC) was measured using inductively coupled plasma mass spectrometry (Agilent 7700×, Agilent Technologies, USA). The fasting blood glucose (FBG) level was measured using glucose-oxidase assay method. The glycosylated hemoglobin (HbA1c) levels were measured using high-performance liquid chromatography (BioRad VARIANT II

Haemoglobin Analyzer). The cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglyceride (TG), and blood uric acid (UA) levels were measured using enzyme-based assays (Mindray BS-180 Analyzer). The anti-thyroglobulin antibodies (TgAb), TSH concentration, and thyroid peroxidase antibodies (TPOAbs) were detected and measured using immunochemiluminescence assays (Cobas 601 analyzer, Roche Diagnostics).

Assessment of Normal Functioning of Thyroid Glands and Thyroid Antibodies

The elderly participants were divided into NTF group and SCH group based on the level of several serum hormones: free thyroxine (FT4) (9–22 mmol/L), TSH (0.3–4.2 mmol/L), TPOAb (0–34 mmol/L), and TgAb (0–115 mmol/L). The thyroid gland is considered functioning normally if the FT4 and TSH levels are within the normal range. SCH is based on TSH higher than 4.2 mmol/L, even if FT4 is within the normal range.

Statistical Analysis

Continuous variables were expressed as mean \pm standard deviation. Differences between NTF and SCH groups were assessed using Student's *t*-test (SPSS statistical software, version 22.0). The data were subjected to normal distribution analysis using the Kolmogorov–Smirnov test before statistical analysis. The correlation between different variables was assessed using Pearson correlation analysis whereas the association between TSH levels and likely influencing factors was assessed using multiple regression analysis and multiple stepwise regression analysis. $P < 0.05$ was considered statistically significant for all of the analyses.

Results

Overall, 327 individuals were diagnosed with thyroid diseases. Eleven (0.44%), 17 (0.68%), 13 (11.5%), and 286 (11.5%) were diagnosed with hyperthyroidism, subclinical hyperthyroidism, hypothyroidism and SCH, respectively. In addition, 9% and 10.6% of the individuals presented with higher TgAb and TPOAb, respectively. Also, 336 of the study participants were 65 years or older. Of the elderly participants, 261 (77%) of them had NTF, whereas the rest, and 66 (20%) were diagnosed with SCH.

Table 1 shows the levels of anthropometric parameters and biochemical indicators of all the study participants. Compared with individuals in the NTF group, those in the

Table 1 The Anthropometric Parameters and Biochemical Indicators in the General Population

	NTF (n=2156)	SCH (n=286)	t	P
Age	42.53 \pm 17.3	50.01 \pm 19.33	6.224	0.000
BMI	23.36 \pm 3.60	23.68 \pm 4.33	1.224	0.222
WC	80.40 \pm 9.85	79.59 \pm 10.1	1.313	0.189
HR	76.84 \pm 10.86	76.15 \pm 10.44	1.025	0.306
SBP	122.47 \pm 17.72	124.96 \pm 19.43	2.060	0.040
DBP	78.31 \pm 11.31	77.47 \pm 11.06	1.187	0.235
FBG	5.49 \pm 1.52	5.71 \pm 1.38	2.396	0.017
TG	1.56 \pm 1.42	1.70 \pm 1.73	1.586	0.113
TC	4.54 \pm 0.95	4.71 \pm 1.00	2.774	0.006
LDL-C	2.58 \pm 0.71	2.63 \pm 0.73	1.177	0.239
HDL-C	1.30 \pm 0.46	1.31 \pm 0.43	0.011	0.991
UA	352.11 \pm 106.07	337.95 \pm 105.28	2.122	0.034
HbA1c	5.38 \pm 0.98	5.48 \pm 0.89	1.590	0.112
TSH	2.24 \pm 0.85	6.84 \pm 5.48	14.187	0.000
TPOAb	33.45 \pm 84.50	37.30 \pm 92.06	0.716	0.474
TgAb	69.76 \pm 22.01	82.46 \pm 32.58	0.617	0.537
UIC	245.21 \pm 247.61	310.46 \pm 448.63	2.412	0.016

Abbreviations: NTF, normal thyroid function group; SCH, subclinical hypothyroidism group; BMI, body mass index; WC, waist circumference; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; TG, triglyceride; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; UA, uric acid; HbA1c, glycosylated hemoglobin; TSH, thyroid stimulating hormone; TPOAb, thyroid peroxidase antibody; TgAb, anti-thyroglobulin antibodies; UIC, urinary iodine.

SCH group were older and presented with higher SBP, FBG, TC and UIC (all $p < 0.05$) but lower UA ($p < 0.05$). There was no significant difference in the levels of the parameters between the two groups.

Overall, as shown in Table 2, TSH levels positively correlated with age ($r = 0.106$; $p = 0.000$), SBP ($r = 0.085$; $p = 0.000$), FBG ($r = 0.044$; $p = 0.031$), TG ($r = 0.063$; $p = 0.062$), and TC ($r = 0.045$; $p = 0.027$). However, there was no association between serum TSH levels and BMI, WC, HR, DBP, LDL-C, HDL-C, UA, HbA1c, TPOAb, TgAb or UIC. Multiple linear regression analysis revealed age ($p = 0.000$) and TG levels ($p = 0.009$) positively correlated with TSH serum levels (Table 3). Multivariate stepwise regression analysis revealed that Age, TG, WC, and BMI were independent predictors of serum TSH levels (Table 4).

Table 2 Pearson's Correlation Analysis for TSH in the General Population

	TSH	
	r	P
Age	0.106	0.000
BMI	0.021	0.297
WC	-0.029	0.157
HR	-0.020	0.329
SBP	0.085	0.000
DBP	0.031	0.131
FBG	0.044	0.031
TG	0.063	0.002
TC	0.045	0.027
LDL-C	0.020	0.315
HDL-C	-0.030	0.141
UA	-0.036	0.079
HbA1c	0.022	0.285
TPOAb	-0.015	0.455
TgAb	-0.019	0.353
UIC	0.036	0.076

Abbreviations: BMI, body mass index; WC, waist circumference; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; TG, triglyceride; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; UA, uric acid; HbA1c, glycosylated hemoglobin; TPOAb, thyroid peroxidase antibody; TgAb, anti-thyroglobulin antibodies; UIC, urinary iodine.

As shown in Figure 1, elderly SCH patients were significantly older ($p=0.003$) and displayed lower heart rate ($p=0.04$) than their NTF counterparts. There was no significant difference in the rest of the parameters between elderly NTF and SCH patients. There was also a strong correlation between TSH levels and age ($r=0.193$; $p<0.001$), SBP ($r=0.134$;

Table 3 Multiple Linear Regression Analysis for TSH in the General Population

	Non-Standardized Coefficient		Standardized Coefficient	t	P
	B	Standard Error	β		
Age	0.013	0.004	0.094	3.808	0.000
SBP	0.005	0.003	0.033	1.399	0.162
FBG	-0.016	0.037	-0.010	-0.430	0.667
TG	0.100	0.038	0.058	2.605	0.009
TC	-0.025	0.059	-0.009	-0.415	0.678

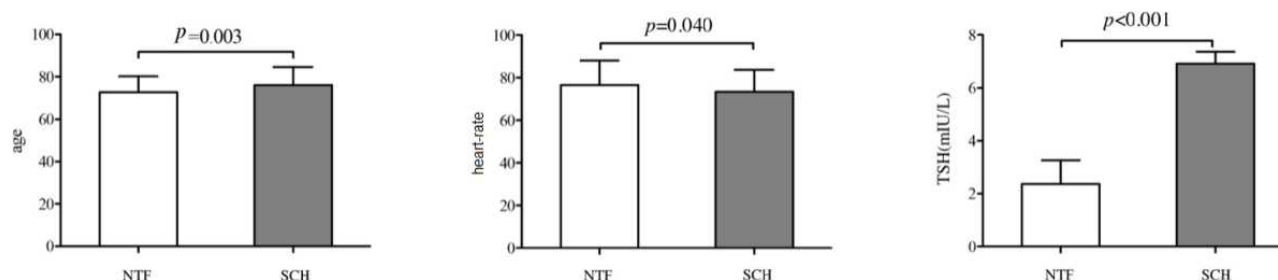
Abbreviations: SBP, systolic blood pressure; FBG, fasting blood glucose; TG, triglyceride; TC, total cholesterol.

Table 4 Multiple Stepwise Regression Analysis of Metabolic Parameters and TSH in the General Population

	Nonstandardized Coefficient		Standardized Coefficient	t	P
	B	Standard Error	β		
Age	0.015	0.005	0.06	2.957	0.003
TG	0.19	0.066	0.061	2.866	0.004
WC	-0.058	0.014	-0.127	-4.22	0.000
BMI	0.124	0.036	0.102	3.44	0.001

Abbreviations: BMI, body mass index; WC, waist circumference; TG, triglyceride.

$p=0.015$), waistline ($r=-0.163$; $p=0.003$), TG ($r=0.160$; $p=0.004$), and HbA1c ($r=-0.011$; $p=0.044$) (Figure 2). Multiple linear regression analysis revealed age ($p=0.003$) and TG ($p<0.001$) positively related with TSH levels, contrary to WC ($p=0.003$), which negatively correlated with TSH levels (Table 5). Age, TG, WC and heart rate were independent predictors of TSH levels (Table 6).

**Figure 1** The anthropometric parameters and biochemical indicators in the elderly.

Abbreviations: NTF, normal thyroid function group; SCH, subclinical hypothyroidism group; TSH, thyroid stimulating hormone.

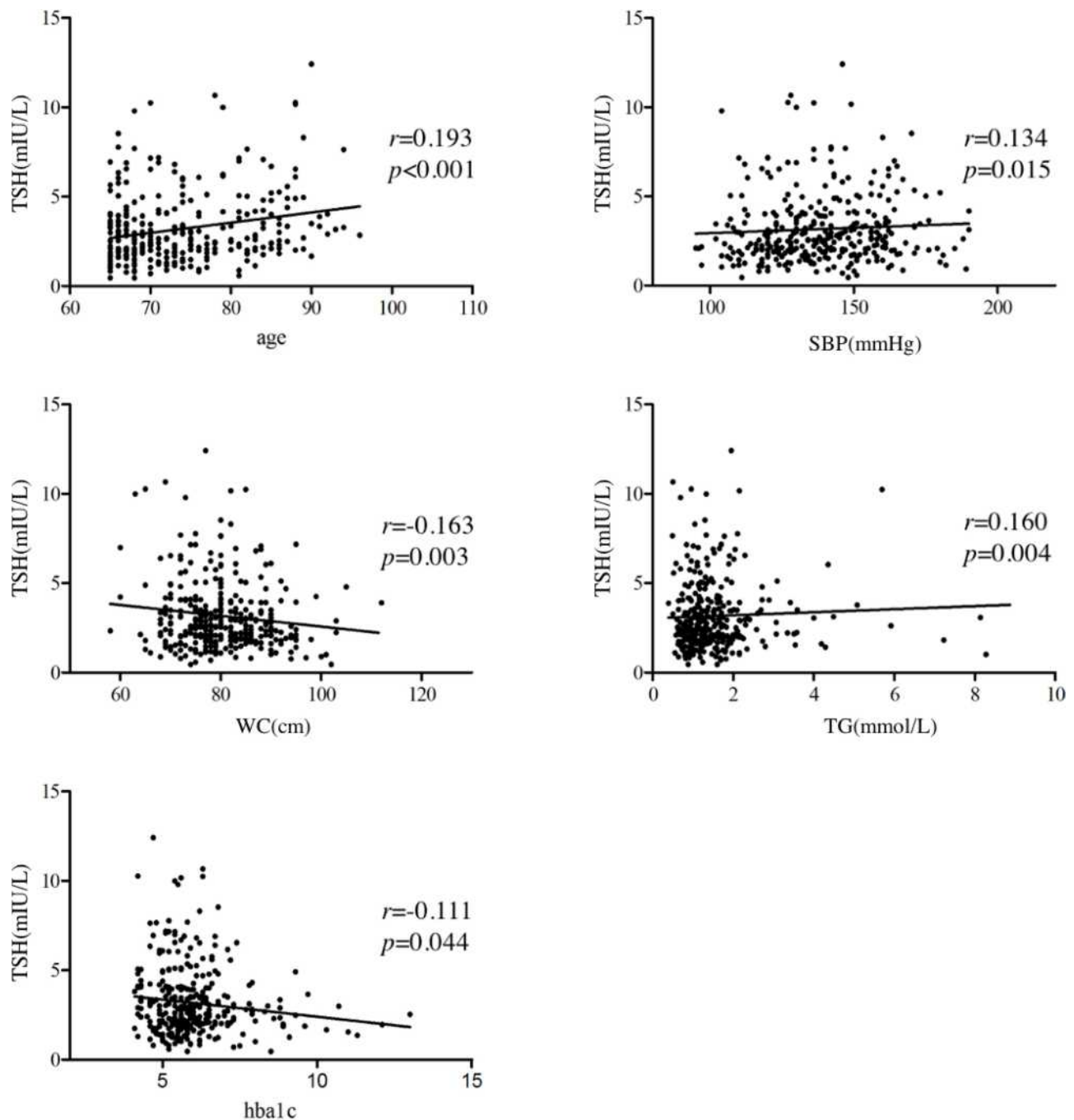


Figure 2 Pearson's correlation analysis for TSH in the elderly population.

Abbreviations: WC, waist circumference; SBP, systolic blood pressure; TG, triglyceride.

Discussion

Higher TSH levels are closely associated with multiple metabolic disorders and cardiovascular diseases. In addition, older age increases the likelihood of developing thyroid dysfunctions. In Europe and US, the incidence of higher TSH level (>5.1 mIU/L) in individuals between 20 and 29 years was estimated to be approximately 9.5%.¹⁷ In this research, the

incidence of higher TSH levels (>2.5 mIU/L) in the general population was 10.6%, compared with 40% for those 80 years or older. In one study, 14.5% of sampled individuals presented with TSH level of higher than 4.5 mIU/L.¹⁸ In this study, 295 (11.88%) of the sampled individuals had high serum TSH (TSH >4.2 mmol/L). Comparatively, 67 (20%) of the older population (≥ 65 years) presented with high TSH. The variation

Table 5 Multiple Linear Regression Analysis in the Elderly Population

	Non-Standardized Coefficient		Standardized Coefficient	t	P
	B	Standard Error	β		
Age	0.055	0.018	0.168	3.020	0.003
SBP	0.012	0.007	0.089	1.656	0.099
WC	-0.051	0.017	-0.164	-2.983	0.003
TG	0.443	0.106	0.227	4.170	0.000
HbA1c	-0.179	0.105	-0.091	-1.709	0.088

Abbreviations: WC, waist circumference; SBP, systolic blood pressure; TG, triglyceride; HbA1c, glycosylated hemoglobin.

Table 6 Multiple Stepwise Regression Analysis of Metabolic Parameters and TSH Level in the Elderly Population

	Nonstandardized Coefficient		Standardized Coefficient	t	P
	B	Standard Error	β		
Age	0.064	0.018	0.192	3.588	0.000
TG	0.489	0.107	0.247	4.559	0.000
WC	-0.053	0.017	-0.169	-3.119	0.002
Heart rate	-0.024	0.012	-0.106	-2.013	0.045

Abbreviations: WC, waist circumference; TG, triglyceride.

in the proportion level may be attributed to racial differences and indicator parameters used. However, the findings underline the burden of abnormal TSH production in elderly population.

Herein, both the whole and older population, we found age was an independent predictor of TSH levels, consistent with previous findings.^{12,13} The likelihood of developing thyroid disease also increases with age. This is in part attributed to the high likelihood of autoimmune diseases in older patients. Also, physiological changes and intake of drugs for chronic disease drug, which are likely to occur with age, disrupt hypothalamus-pituitary-thyroid axis.¹⁹

Similar to age, TG level was also an independent predictor of TSH levels both in the general and elderly populations, consistent with previous findings.^{14,16} Researches show that lipotoxicity targets thyroid gland.²⁰

Also, lipid metabolism disorders are often accompanied with cardiovascular diseases. For instance, higher serum TSH increases the risk of developing coronary heart disease and atherosclerosis.²¹ Converging evidence has demonstrated that lipid metabolism changes with age. In this study, we found no association between serum TSH and LDL-C, HDL-C and metabolism. However, separate studies have demonstrated the correlation between HDL, LDL as well as TC metabolism and serum TSH levels.^{10,15,16,22} Further research are needed to discern these disparities.

Except for age and TG, WC and BMI were independent predictors of serum TSH across the entire population. Research shows that SCH is associated with metabolic syndrome and related complications, particularly high BMI and obesity, though the relationship is weak.²³ In a related study, Pesic et al found that SCH is associated with high BMI,¹⁶ consistent with our findings. In addition to age and TG, we found WC and heart rate were also independent predictors of TSH levels in the elderly. Meanwhile, Sakurai et al found no association between serum TSH level and waist circumference,²⁵ contrary to our findings. Overall, our findings suggest that abnormal serum TSH level is a risk factor for developing metabolic syndrome.

Regarding limitations, first, being a cross-sectional not a follow-up study. Second, we did not adjust for several factors such as smoking and alcohol intake. Third, underlying comorbidities and use of certain drugs such as aspirin, non-steroidal anti-inflammatory drugs, glucocorticoids, etc., may affect production of thyroid hormones in the elderly.^{19,25} However, the large sample size and stratification of study participants based on age enhanced the credibility of our findings.

Abbreviations

NTF, normal thyroid function; SCH, subclinical hypothyroidism; SBP, systolic blood pressure; WC, waist circumference; DBP, diastolic blood pressure; TgAb, anti-thyroglobulin antibodies; TSH, thyroid stimulating hormone; TPOAb, thyroid peroxidase antibody; LDL-C, low-density lipoprotein cholesterol; UA, uric acid; TG, triglyceride; FBG, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; HbA1c, glycosylated hemoglobin; UIC, urinary iodine concentration; FT4, free thyroxine.

Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and

interpretation of data; BD, YY, MZ, RR, WD and XD took part in drafting the article and revising it critically for important intellectual content; All authors agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no conflicts of interest in this work.

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