

# Epidemiology of metabolic syndrome and its components in Chinese patients with a range of thyroid-stimulating hormone concentrations

Journal of International Medical Research

48(11) 1–14

© The Author(s) 2020


Article reuse guidelines:

[sagepub.com/journals-permissions](https://sagepub.com/journals-permissions)

DOI: 10.1177/0300060520966878

[journals.sagepub.com/home/imr](https://journals.sagepub.com/home/imr)



Kun Tang<sup>1,2</sup>, Qiao Zhang<sup>2</sup>, Nian-chun Peng<sup>2</sup>,  
Miao Zhang<sup>2</sup>, Shu-jing Xu<sup>2</sup>, Hong Li<sup>2</sup>,  
Ying Hu<sup>2</sup>, Chun-ju Xue<sup>3</sup>, Li-xin Shi<sup>2</sup>  and  
the REACTION Study Group

## Abstract

**Objective:** To investigate the relationship between thyroid stimulating hormone (TSH) concentration and the risks of developing metabolic syndrome and its components.

**Methods:** A total of 10,140 residents of the Yunyan district of Guiyang (Guizhou, China) who were  $\geq 40$  years old were selected by cluster random sampling between May and August 2011, of whom 5692 were eligible. TSH concentration and indices of metabolic syndrome were documented at baseline and 3 years later. Participants were allocated to a euthyroid (TSH 0.55–4.78 mIU/L) or high TSH concentration (TSH  $>4.78$  mIU/L) group. Patients with overt hypothyroidism or were undergoing treatment for hypothyroidism were excluded.

**Results:** The crude and adjusted prevalences of metabolic syndrome were 39.9% and 33.9% in the euthyroid group and 44.3% and 37.5% in the high TSH group, respectively. Binary logistic regression analysis revealed a positive correlation between a high TSH concentration at baseline and the cumulative incidence of metabolic syndrome during follow up.

**Conclusions:** High TSH is associated with a higher risk of developing metabolic syndrome or one of its components; therefore, people with a high TSH concentration should be screened regularly to permit the early identification of metabolic syndrome and followed up thoroughly.

<sup>3</sup>Guizhou Medical University, Guiyang, Guizhou, China

## Corresponding author:

Li-xin Shi, Department of Endocrinology, Affiliated Hospital of Guizhou Medical University, Guiyang, Guizhou 550004, China.

Email: [slx1962@medmail.com.cn](mailto:slx1962@medmail.com.cn)

<sup>1</sup>Department of Endocrinology, The Second Affiliated Hospital of Soochow University, Suzhou, Jiangsu, China

<sup>2</sup>Department of Endocrinology, Affiliated Hospital of Guizhou Medical University, Guiyang, Guizhou, China



## Keywords

Thyroid stimulating hormone, metabolic syndrome, prevalence, cumulative incidence, central obesity, triglyceride, high-density lipoprotein cholesterol

Date received: 22 April 2020; accepted: 25 September 2020

## Introduction

Metabolic syndrome consists of a combination of central obesity, hyperglycemia (diabetes and/or impaired glucose tolerance), hypertension, high serum triglyceride concentration, and low serum high-density lipoprotein (HDL) concentration, which are associated with higher risks of heart disease, stroke, and type 2 diabetes mellitus. It has also been shown that metabolic syndrome is a risk factor for aberrant cardiovascular metabolism and early arteriosclerosis.<sup>1-8</sup> Thus, metabolic syndrome represents a major emerging public health challenge globally.<sup>9,10</sup> The easy availability of energy-dense foods, coupled with a sedentary lifestyle, has significantly increased the prevalence of this condition.<sup>11-13</sup> According to data published by the International Diabetes Federation, about one-quarter of the world's population has metabolic syndrome.<sup>14</sup> In addition, numerous clinical studies have demonstrated that the presence of metabolic syndrome is associated with three-fold higher incidence of cardiovascular disease and a three-fold higher mortality rate from this disease.<sup>14-17</sup> Furthermore, metabolic syndrome has recently been recognized as a diabetogenic state;<sup>18</sup> the incidence of type 2 diabetes mellitus has been found to be five times higher in patients with metabolic syndrome.<sup>14</sup> Therefore, both clinicians and the wider public have stakes in establishing deeper understanding of the pathophysiology and improving the treatment of metabolic syndrome.

Thyroid disorders are some of the most common endocrine diseases in the world, with more than 300 million people experiencing thyroid dysfunction.<sup>19</sup> Forty-two million people are estimated to have thyroid disorders in India, and the prevalence of thyroid disorders in the Korean population has also significantly increased, according to a national population-based study.<sup>20,21</sup> In addition, some previous studies have suggested that thyroid disorders are positively related to atherosclerotic heart disease, because these disorders can lead to alterations in cardiovascular hemodynamics.<sup>22,23</sup> Thyroid stimulating hormone (TSH) has become a subject of much attention because it is a critical endocrine regulator of thyroid function, and a reduction in thyroid function can directly increase the risk of cardiac dysfunction and atherosclerosis.<sup>24-26</sup>

Recent studies have suggested a significant overlap between thyroid disorders and metabolic syndrome.<sup>27-29</sup> It has been reported that high TSH is associated with a higher prevalence of metabolic syndrome, not only in patients with subclinical hypothyroidism, but also in euthyroid individuals with TSH concentrations within the normal range.<sup>30,31</sup> A cross-sectional study of participants with normal thyroid function indicated that high serum TSH is associated with high serum triglyceride concentrations in people with metabolic syndrome in a specific sex and age range.<sup>32</sup> Therefore, it is crucial to elucidate the relationship between thyroid function,

TSH, and metabolic syndrome. A high TSH concentration may induce changes in the hypothalamus–pituitary–leptin axis, which would cause resistance to thyroid hormones. This would lead to increases in body weight, waist circumference, and body mass index, resulting in central obesity.<sup>33</sup> To investigate this possibility, we recruited patients with a range of TSH concentrations to investigate the relationships between TSH and the prevalence and cumulative incidence of metabolic syndrome and its components (including central obesity, low HDL cholesterol, and hypertriglyceridemia) over a 3-year period. The findings of this study should provide useful information regarding the prevention and treatment of metabolic syndrome.

## Materials and methods

### Research participants

**Recruitment.** Residents of the Yunyan district of Guiyang (Guizhou, China) were selected by cluster random sampling between May and August 2011. The present study was part of the baseline survey for the Risk Evaluation of cAncers in Chinese diabeTic Individuals: a lONgitudinal (REACTION) study, which was conducted in 259,657 adults aged  $\geq 40$  years in 25 communities across mainland China from 2011 to 2012.<sup>34–37</sup> The history, anthropometric parameters, and biochemical test results were recorded for each participant. The study protocol was approved by the ethics committee of Guizhou Medical University Affiliated Hospital (2011 (51)) and each participant provided their written informed consent prior to the start of the study.

**Follow-up protocol.** After evaluation, participants with metabolic syndrome at baseline were excluded from the follow-up component of the study. After the study period ( $38.55 \pm 1.59$  months from May to August

of 2011 to July to December of 2014), all the anthropometric and biochemical parameters that were evaluated at baseline were re-evaluated.

**Classification of the participants.** According to the reference range for TSH at Guizhou Medical University Affiliated Hospital, all the eligible participants were allocated to one of two groups: a euthyroid group with TSH concentrations within the normal range for the laboratory (0.55–4.78 mIU/L), and a high TSH group with concentrations  $>4.78$  mIU/L.

**Definitions used.** Metabolic syndrome was defined as per the International Diabetes Federation criteria that were published in 2005.<sup>9</sup> The definition of metabolic syndrome was as follows: 1. Central obesity (required condition), waist circumference: Chinese: male  $\geq 90$  cm, female  $\geq 80$  cm; European descent: male  $\geq 94$  cm, female  $\geq 80$  cm; South Asian: male  $\geq 90$  cm, female  $\geq 80$  cm; 2. Two or more of the following components: (1) TG  $\geq 1.7$  mmol/L, or treatment for hypertriglyceridemia; (2) Low HDL-C: male  $<1.04$  mmol/L, female  $<1.3$  mmol/L, or treatment for dyslipidemia; (3) blood pressure  $\geq 130/85$  mmHg, or a diagnosis of hypertension and antihypertensive treatment; and (4) fasting plasma glucose (FPG)  $\geq 5.6$  mmol/L or type 2 diabetes. A history of smoking was defined as the smoking of at least one cigarette per day for at least 6 months,<sup>38</sup> and a history of excess alcohol intake was defined as the drinking of at least 30 g of ethanol weekly for at least a 1-year period. An exercise status of “active” was defined as the participation in exercise for at least 30 minutes on at least 3 days a week.<sup>39</sup>

**Exclusion criteria.** Individuals with TSH concentrations below the normal range; patients with thyroid disease who were already under treatment; people who were

taking medications that could affect thyroid function; patients with malignant tumors, critical illnesses, extreme exhaustion, cachexia, or liver/renal insufficiency; women who were pregnant or within 1 year of childbirth; individuals with psychiatric illness; and people unwilling to complete the questionnaire, or undergo physical examination or blood tests, were excluded from the study.

### *Investigation methods*

**General information.** A questionnaire was administered to all the participants by professionally trained endocrinologists during a face-to-face interview. The basic information collected in the questionnaire included the participant's name, sex, age, smoking history, history of alcohol intake, and exercise status. In addition, their past medical history, including of hypertension, diabetes, thyroid disorders, and dyslipidemia, was collected through the questionnaire during the interview.

**Physical examination.** All the participants were examined by endocrinologists and their height, body mass, waist circumference, and blood pressure were recorded. During the blood pressure measurement, the participants were asked to sit in a quiet room for 5 minutes, then the mean of three readings obtained using an electronic blood pressure monitor (Omron Model HEM-725FUZZY, Omron Company, Dalian, China) was recorded. The cuff was placed around an upper arm and there were 3-minute intervals between each measurement. For the measurement of waist circumference, the participants were required to stand upright with their feet 30 to 40 cm apart, while wearing underwear and with an unfastened belt, and breathing normally. A measuring tape was used to measure the circumference at the midpoint between the line connecting the anterior

superior iliac crest and the inferior edge of the twelfth rib. The measuring tape was held against the skin, but without pressure being applied, and the measurements were made to the nearest 0.1 cm. Body mass index (BMI) was calculated using the equation:  $BMI = \text{body mass (kg)}/\text{height (cm)}^2$ .

**Biochemical tests.** Serum lipid profile analysis was performed on venous samples that were collected from each participant after fasting for  $\geq 10$  hours using an Abbott automatic biochemical immunoassay analyzer (Architect-ci16200; Abbott Laboratories, Abbott Park, IL, USA). Oral glucose tolerance testing (OGTT) was performed on all the participants with no history of diabetes. Plasma glucose concentrations were measured using the hexokinase method. For participants with a history of diabetes, the FPG and 2-hour post-meal glucose concentrations were determined after the consumption an 80-g instant noodle cake. TSH concentrations were measured using an Advia Centaur XP automated immunoassay analyzer (Siemens Healthineers Global, Malvern, PA, USA). This assay had an intra-assay coefficient of variation of 1.70% to 4.69% and an inter-assay coefficient of variation of 0.88% to 4.20%.

**Statistical analysis.** All the data were double-entry verified using EpiData software ([www.epidata.dk](http://www.epidata.dk)). Normally distributed continuous data are expressed as means  $\pm$  standard deviations, and categorical data are expressed as frequencies and percentages. Comparisons of the differences in rates and proportions between the high TSH and euthyroid groups were performed using the chi-square test, and Student's *t* test or analysis of variance (ANOVA) were used to identify significant differences in mean values between two or among multiple groups, respectively (SPSS Statistics for Windows, Version 17.0, SPSS Inc., Chicago, IL, USA). The prevalences and

cumulative incidences of metabolic syndrome were normalized by age and sex using the 2010 National Census data for China and the risk factors for metabolic syndrome were identified using binary logistic regression analysis. Differences were considered statistically significant when  $P < 0.05$ .

## Results

### Participants

A total of 10,140 residents were selected, of whom 9618 qualified for the present study. After evaluation, 3926 participants with metabolic syndrome at baseline were excluded from the follow-up component of the study. Therefore, 5692 participants were followed up for 3 years. A total of 4292 participants completed the full 3-year period of the study, which yielded a completion rate of 75.40%.

### Comparison of the baseline characteristics of the euthyroid and high TSH groups

Table 1 shows a comparison of the baseline characteristics of the two groups. The serum triglyceride, low-density lipoprotein (LDL) cholesterol, and HDL cholesterol concentrations were all significantly higher in the high TSH group than in the euthyroid group. The high TSH group contained a relatively larger number of women. The 2-hour post-meal plasma glucose concentration of the high TSH concentration group was lower than that of the euthyroid group. In addition, the high TSH group contained significantly fewer participants with histories of excess alcohol consumption and/or smoking. However, there were no significant differences in the waist circumference, BMI, systolic blood pressure, diastolic blood pressure, FPG, homeostatic model assessment of insulin resistance, or exercise history between the two groups at baseline. Finally, individuals

**Table 1.** Comparison of the characteristics of participants in the euthyroid and high TSH groups at baseline.

Variable	Euthyroid Group (n = 7706)	High TSH Group (n = 1912)	P-value
Thyroid stimulating hormone concentration (mIU/L)/Range (mIU/L)	2.47 (1.75–3.34)	6.22 (5.41–8.11)	<0.001
Age (years)	58.30 ± 8.14	58.37 ± 8.30	0.71
Sex (female/male)	5437/2269	1565/347	<0.001
Waist circumference (cm)	84.30 ± 8.88	84.26 ± 8.51	0.864
Body mass index (kg/m <sup>2</sup> )	24.03 ± 3.22	24.09 ± 3.22	0.502
Systolic blood pressure (mmHg)	122.33 ± 18.92	122.24 ± 18.96	0.848
Diastolic blood pressure (mmHg)	77.24 ± 11.01	77.09 ± 11.08	0.573
Fasting plasma glucose (mmol/L)	6.21 ± 1.62	6.15 ± 1.62	0.117
2-hour post-meal blood glucose (mmol/L)	8.78 ± 3.65	8.56 ± 3.59	0.021
Triglycerides (mmol/L)	1.73 ± 1.34	1.90 ± 1.41	<0.001
Low-density lipoprotein cholesterol (mmol/L)	2.62 ± 0.88	2.73 ± 0.92	<0.001
High-density lipoprotein cholesterol (mmol/L)	1.23 ± 0.37	1.25 ± 0.38	0.049
Homeostatic model assessment of insulin resistance	2.44 ± 2.29	2.47 ± 2.67	0.597
History of smoking, n (%)	1636/21.23%	244 (12.76%)	<0.001
History of excessive alcohol consumption, n (%)	822/10.67%	134 (7.01%)	<0.001
History of exercise, n (%)	1649/21.40%	405 (21.18%)	0.836

Data are mean ± SD or n (%). Student's *t* test. TSH, thyroid stimulating hormone.

>65 years old accounted for 20.7% of the enrolled participants.

### Relationships between indices related to metabolic syndrome and its components and serum TSH concentration

Of the total of 9618 randomly selected participants, 3926 were found to have metabolic syndrome. The total crude and standardized prevalences of metabolic syndrome were 40.8% and 34.5%, respectively, in the complete sample at baseline (Table 2). The crude prevalences of metabolic syndrome, central obesity, low HDL cholesterol concentration, and high triglyceride concentration were higher in the high TSH group than in the euthyroid group at baseline, before the exclusion of the individuals who had metabolic syndrome ( $P < 0.05$ ). The crude prevalences of hypertension and high FPG were similar in the two groups. However, the standardized prevalence of metabolic syndrome ( $P < 0.01$ ) and its components (central obesity,  $P < 0.01$ ; low HDL cholesterol concentration,  $P = 0.045$ ; high triglyceride concentration,  $P < 0.01$ ) tended to be higher in the high TSH group.

### Relationship between the cumulative incidence of metabolic syndrome and its components and serum TSH concentration

Over the course of the 3-year follow-up period, 966 participants out of the 4292 who completed the study were diagnosed with metabolic syndrome, which yielded cumulative crude and standardized 3-year incidences of metabolic syndrome of 22.5% and 20.6%, respectively (Table 3). The cumulative crude incidence of low HDL cholesterol was significantly higher in the high TSH group than in the euthyroid group ( $P = 0.014$ ), whereas those of the other metabolic syndrome components were similar in the two groups. The incidence of metabolic syndrome was also found to increase with increasing serum TSH concentration when the participants were placed into four groups according to their TSH values (0 to 2.49, 2.5 to 4.99, 5.0 to 7.49, and 7.5 to 10.0 mIU/L) (Figure 1).

To identify factors that influence the cumulative incidence of metabolic syndrome in the high TSH group, binary

**Table 2.** Comparison of the crude and standard prevalences of metabolic syndrome and its components in the euthyroid and high TSH groups at baseline.

Parameter	Euthyroid group (n=7,706)			High TSH group (n=1,912)			P-value
	Number of affected individuals	Crude prevalence (%)	Standardized prevalence (%)	Number of affected individuals	Crude prevalence (%)	Standardized prevalence (%)	
Metabolic syndrome	3079	39.96	33.90	847	44.30	37.56	<0.01
Central obesity	4393	57.01	49.28	1193	62.40	52.53	<0.01
Low high-density lipoprotein cholesterol	2447	31.75	26.84	653	34.15	27.75	0.045
High triglycerides	1831	23.76	20.93	598	31.28	27.31	<0.01
Hypertension	2118	27.49	23.20	545	28.50	24.02	0.373
High fasting plasma glucose	2981	38.68	32.37	771	40.32	34.36	0.188

Chi-square test.

TSH, thyroid stimulating hormone.

logistic regression analysis was performed, with metabolic syndrome incidence as the dependent variable and all the other characteristics as covariates (Table 4). We found a significant positive correlation between the cumulative incidence of metabolic syndrome and TSH concentration.

## Discussion

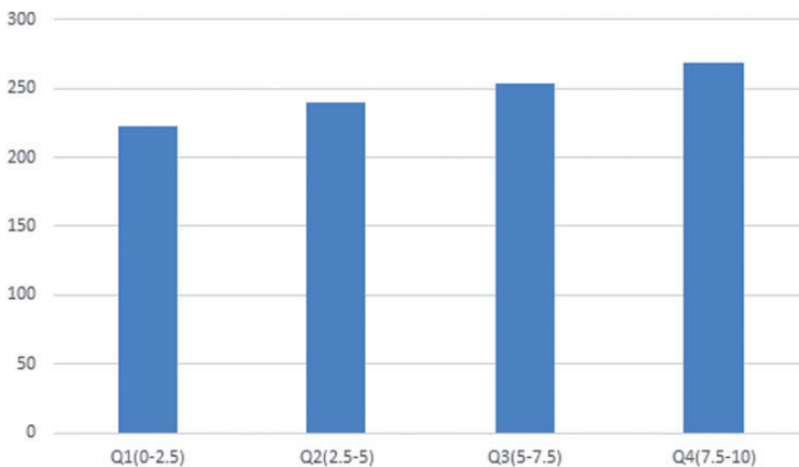
### *Relationships between the prevalence of metabolic syndrome and its components and TSH*

A study performed in the United States between 2003 and 2012 showed the total

**Table 3.** Comparison of the crude and standard cumulative incidences of metabolic syndrome and its components in the euthyroid and high TSH groups.

Parameter	Euthyroid group (n = 7,706)			High TSH group (n = 1,912)			P-value
	Number of affected individuals	Crude incidence (%)	Standardized incidence (%)	Number of affected individuals	Crude incidence (%)	Standardized incidence (%)	
Metabolic syndrome	768	22.01	20.22	198	24.69	23.20	0.101
Central obesity	986	28.25	25.11	252	31.42	26.50	0.074
Low high-density lipoprotein cholesterol	562	16.10	15.86	158	19.70	27.91	0.014
High triglycerides	1042	29.86	33.05	253	31.55	30.31	0.347
Hypertension	1313	37.62	37.56	291	36.28	38.24	0.480
High fasting plasma glucose	1177	33.72	35.25	248	30.92	35.28	0.129

P values refer to comparisons of the crude incidence rates between the groups. Chi-square test. TSH, thyroid stimulating hormone.



**Figure 1.** Incidence of metabolic syndrome increases alongside increases in serum TSH concentration. TSH, thyroid stimulating hormone.

**Table 4.** Identification of risk factors for metabolic syndrome using binary logistic regression analysis.

Parameter	$\beta$ coefficient	Standard deviation	Wald chi-square statistic	Odds ratio	95% confidence interval	P-value
Female sex	3.135	0.416	56.714	22.997	10.169–52.007	<0.001
Age (years)	0.013	0.016	0.630	1.013	0.982–1.045	0.427
TSH (mIU/L)	0.047	0.023	4.222	1.048	1.002–1.097	0.04
Body mass index (kg/m <sup>2</sup> )	0.082	0.060	1.846	1.098	0.976–1.234	0.174
Waist circumference (cm)	0.101	0.022	20.484	1.106	1.059–1.156	<0.001
Fasting plasma glucose (mmol/L)	0.088	0.137	0.412	1.092	0.835–1.429	0.521
2-hour post-meal blood glucose (mmol/L)	0.081	0.053	2.297	1.084	0.977–1.203	0.13
Systolic blood pressure (mmHg)	0.029	0.009	10.367	1.030	1.012–1.049	0.001
Diastolic blood pressure (mmHg)	0.020	0.015	1.715	1.020	0.990–1.052	0.19
High-density lipoprotein cholesterol (mmol/L)	−3.646	0.554	43.368	0.026	0.009–0.077	<0.001
Triglycerides (mmol/L)	0.415	0.114	13.341	1.514	1.212–1.892	<0.001
Low-density lipoprotein cholesterol (mmol/L)	0.300	0.141	4.525	1.350	1.024–1.781	0.033
Homeostatic model assessment of insulin resistance	0.207	0.079	6.913	1.230	1.054–1.436	0.009
History of smoking	−0.129	0.376	0.118	0.879	0.421–1.837	0.731
History of excessive alcohol consumption	1.221	0.512	5.688	3.391	1.243–9.250	0.017
History of exercise	0.044	0.235	0.035	1.045	0.659–1.657	0.851

standardized prevalence of metabolic syndrome to be 33%, having increasing from 32.9% (95% confidence interval: 31.6, 34.2) in 2003 to 2004 to 34.7% (95% confidence interval: 33.5, 36.0) in 2011 to 2012.<sup>40</sup> In the present study, the total crude and standardized prevalences of metabolic syndrome at baseline were 40.8% and 34.5%, respectively, which were similar to the prevalence estimates in the United States.

The results of a long-term, large-scale follow-up study conducted in Taiwan suggested that the prevalence of metabolic syndrome is positively related to serum TSH concentration: a significant difference in the prevalence of metabolic syndrome was found in participants with TSH concentrations in the highest quartile, compared with

those with concentrations in the lowest quartile.<sup>41</sup> In addition, a retrospective study conducted in the United States found that patients with hypothyroidism had a 2.6-fold higher prevalence of metabolic syndrome than euthyroid individuals.<sup>42</sup> Similarly, a study of the relationship of metabolic syndrome and its components with thyroid dysfunction in Algerian patients found that high TSH was associated with a higher incidence of metabolic syndrome, and that TSH concentration positively correlated with the prevalence of metabolic syndrome.<sup>43</sup> Furthermore, a study of 949 euthyroid postmenopausal women found that the prevalence of metabolic syndrome in women in the highest TSH concentration quintile was about



1.95 times higher than that for women in the lowest quintile.<sup>44</sup> A Korean study also showed a significant increase in the prevalence of metabolic syndrome alongside an increase in TSH concentration.<sup>45</sup> Another study of 2760 young euthyroid women with normal TSH concentrations suggested that women with TSH concentrations at the higher end of the normal range had a two-fold higher risk of metabolic syndrome than those with values at the lower end, even after adjustment for age and BMI.<sup>46</sup> Finally, a 3-year follow-up study of 5998 Korean people >18 years of age concluded that a high TSH concentration could be considered a predictor of the future development of metabolic syndrome.<sup>47</sup> Thus, a high TSH concentration, even when within the normal range, may represent a risk factor for metabolic syndrome.

In the present study, the high TSH group had a higher crude prevalence of metabolic syndrome, central obesity, low HDL cholesterol, and high triglycerides than the euthyroid group ( $P < 0.05$ ). This implies that people with TSH concentrations above the normal range may be at a higher risk of developing metabolic syndrome and its components. Thyroid hormones are significant regulators of lipid biosynthesis and metabolism, and thyroid dysfunction can therefore result in lipid abnormalities.<sup>48</sup> Previous studies have shown that a high circulating TSH concentration can cause alterations to the hypothalamic–pituitary–leptin axis, and such alterations, along with the partial inactivation of TSH proteins, could further cause resistance to thyroid hormones. Resistance to thyroid hormone action would likely retard nutrient metabolism, leading to increases in body weight, waist circumference, and BMI, and ultimately central obesity.<sup>33</sup> In addition, it has been reported that TSH concentration is positively correlated with plasma cholesterol ester transfer protein concentrations. High TSH might

increase the accumulation of cholesterol ester transfer protein, which could in turn accelerate the inter-conversion of HDL cholesterol, LDL cholesterol, and extremely low LDL cholesterol. This might result in greater transport of cholesterol from peripheral tissues to hepatocytes in HDL cholesterol, which would reduce the HDL cholesterol concentration.<sup>49</sup> In addition, TSH could increase triglyceride accumulation in hepatocytes by activating the TSH receptor/peroxisome proliferator-activated receptor/adenylate-activated protein kinase/sterol regulatory element-binding protein 1c signaling pathway.<sup>50</sup> Previous studies have shown a positive correlation between TSH and vascular resistance in the small renal arteries and a negative correlation with renal blood flow and glomerular filtration rate. Therefore, a high TSH concentration might induce pathophysiological changes in the renal circulation, and thereby increase the risk of high blood pressure.<sup>51</sup> Furthermore, a high TSH concentration might have an impact on glucose metabolism by affecting insulin sensitivity, or by altering the release of thyroxine (T4), which has an important influence on glucose and energy homeostasis.<sup>52</sup>

### *Relationships between the incidence of metabolic syndrome and its components and TSH*

In the present study, the cumulative crude and standardized incidences of metabolic syndrome in all the participants, over a 3-year period, were 22.5% and 20.6%, respectively. The cumulative crude and standardized incidences of the euthyroid group were 22.0% and 20.2%, respectively, but they were 24.7% and 23.2% in the high TSH group. The cumulative crude incidence of low HDL cholesterol was significantly higher in the high TSH group than in the euthyroid group (27.9% vs. 15.9%,  $P = 0.014$ ). However, both groups exhibited

similar crude incidences of metabolic syndrome, central obesity, high triglyceride concentration, hypertension, and high FPG. Because there were more women than men in the high TSH group, the crude incidence was corrected for the participants' sex and age. After this adjustment, the standardized incidences of metabolic syndrome and its components were higher in the high TSH group, with the exception of the serum triglyceride concentration, which did not differ between the groups.

A 6-year prospective cohort study<sup>27</sup> of an elderly population, with a mean age of 73.6 years, showed an independent positive correlation between TSH and triglyceride, and a negative correlation with HDL cholesterol. These relationships were similar to those found in the present study. However, the same study did not show relationships between TSH and metabolic syndrome and its components (including central obesity, hypertension, and high FPG). This might have been because of the small sample size or the advanced age of the participants, because many previous studies of elderly populations have shown that older people have higher circulating TSH concentrations<sup>53</sup>.

A 3-year population-based cohort study showed that both overt and subclinical hypothyroidism, especially in older people, are associated with metabolic syndrome.<sup>54</sup> This finding was mirrored by that of a hospital-based cross-sectional study conducted in Nepal,<sup>55</sup> and another cross-sectional study conducted in India showed that overt hypothyroidism is associated with a higher risk of metabolic syndrome.<sup>56</sup> Finally, a population-based survey conducted in Italy showed a positive correlation between circulating TSH and triglyceride concentrations, and positive relationships between free thyroxine (FT4) and the components of metabolic syndrome.<sup>57</sup>

Binary logistic regression analysis showed that the odds ratio (OR) of developing metabolic syndrome over a 3-year period in the high TSH group was 1.047 ( $P=0.043$ , 95% confidence interval: 1.001, 1.095). Insulin resistance is considered to be a primary underlying cause of metabolic syndrome. To eliminate confounding of the results by the presence of insulin resistance, logistic regression analysis was performed using homeostasis model assessment of insulin resistance as a covariate, but there was a similar OR for metabolic syndrome in the high TSH group (OR = 1.048,  $P=0.040$ , 95% confidence interval 1.002, 1.097), which indicates that the TSH concentration is associated with metabolic syndrome independently of insulin resistance. There were significantly larger numbers of men than women in the high TSH group, and because most of the female participants were not smokers or drinkers, the incidences of metabolic syndrome in participants with a history of smoking and excessive alcohol intake were below the expected levels, given that most of the smokers and drinkers were in the euthyroid group. However, because the comparison of the incidences between the two groups was normalized using the sex of the participants, these variations did not affect the overall results of this study.

The study had a few limitations. First, we did not have the serum total T3 and T4 concentrations of the participants. Second, we did not study the relationships of markers of thyroid immunity, such as anti-thyroid peroxidase antibody titer, with the incidences of metabolic syndrome and its components. Third, there were significantly fewer male than female participants, which could also have had a bearing on the results. Finally, further studies are needed to establish whether high TSH is a cause or a consequence of metabolic syndrome and the associated inflammatory milieu.

## Conclusions

A 3-year prospective cohort study of 5692 participants, with a completion rate of 75.40%, revealed a higher crude prevalence of metabolic syndrome in participants with high serum TSH concentrations than those who were euthyroid. Similarly, participants with high TSH concentrations had a higher cumulative standardized incidence of metabolic syndrome than euthyroid participants. Furthermore, binary logistic regression analysis showed that TSH concentration was positively related to the incidences of metabolic syndrome and its components. Our findings indicate that there is an association between high TSH and the development of metabolic syndrome. However, further studies are required to determine whether treatment of high TSH concentration is capable of preventing the development or reducing the severity of incident metabolic syndrome and its components.

## Author contributions

K.T. acquired the data and wrote the manuscript. C.X. analyzed the data. N.P., Y.H., H. L., and S.X. designed the questionnaire and performed the study. M.Z., and Q.Z. expedited the ethical approval process. L.S. is the guarantor of this work and, as such, had full access to all the data for the study and takes responsibility for the integrity of the data, as well as the accuracy of the data analysis.

## Availability of data and materials

The datasets generated and analyzed during the present study are available from the corresponding author on reasonable request.

## Declaration of conflicting interest


The authors declare that there is no conflict of interest.

## Funding

This work was supported by grants from the National Clinical Research Centre for

Metabolic Diseases (2013BAI09B13), the National Key New Drug Creation and Manufacturing Program of Ministry of Science and Technology (2012ZX09303006-001), the Government Foundation of Guizhou Province of China, the National Key R&D Program of China (2016YFC0901203, 2017YFC1310700, and 2017YFC1310701), the National Health and Family Planning Commission of PRC (201502007), and the key clinical specialty cultivation project of Guizhou province (2016).

## ORCID iD

Li-xin Shi  <https://orcid.org/0000-0002-0389-2732>

## References

1. Eckel RH, Grundy SM and Zimmet PZ. The metabolic syndrome: The Lancet. *Lancet* 2010; 375: 181–183.
2. Alberti K, Eckel RH, Grundy SM, et al. Harmonizing the metabolic syndrome: a joint interim statement of the international diabetes federation task force on epidemiology and prevention; national heart, lung, and blood institute; American heart association; world heart federation; international atherosclerosis society; and international association for the study of obesity. *Circulation* 2009; 120: 1640–1645.
3. Jabbar A, Pingitore A, Pearce SHS, et al. Thyroid hormones and cardiovascular disease. *Nat Rev Cardiol* 2017; 14: 39–55.
4. Lakka HM, Laaksonen DE, Lakka TA, et al. The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. *JAMA* 2002; 288: 2709–2716.
5. Grundy SM. Obesity, Metabolic Syndrome, and Cardiovascular Disease. *J Clin Endocrinol Metab* 2004; 89: 2595–2600. DOI: 10.1210/jc.2004-0372.
6. Isomaa B, Almgren P, Tuomi T, et al. Cardiovascular morbidity and mortality associated with the metabolic syndrome. *Diabetes Care* 2001; 24: 683–689.
7. Pascual A, Guerriero S, Rams N, et al. Clinical and ultrasound features of benign, borderline, and malignant invasive

- mucinous ovarian tumors. *Eur J Gynaecol Oncol* 2017; 38: 382–386.
8. Li X, Li X, Lin H, et al. Metabolic syndrome and stroke: A meta-analysis of prospective cohort studies. *J Clin Neurosci* 2017; 40: 34–38.
  9. Zimmet P, Alberti KGM and Serrano Ríos M. A new international diabetes federation worldwide definition of the metabolic syndrome: the rationale and the results. *Rev Esp Cardiol* 2005; 58: 1371–1375.
  10. Zimmet P, Magliano D, Matsuzawa Y, et al. The metabolic syndrome: a global public health problem and a new definition. *J Atheroscler Thromb* 2005; 12: 295–300.
  11. Nestel P, Lyu R, Low LP, et al. Metabolic syndrome: recent prevalence in East and Southeast Asian populations. *Asia Pac J Clin Nutr* 2007; 16: 362–367.
  12. Tsou MT, Chang BCC, Huang WH, et al. Prevalence of metabolic syndrome and risk factor analysis among urban elderly in one medical center in northern Taiwan. *Int J Gerontol* 2014; 8: 127–132.
  13. Hwang LC, Bai CH, Sun CA, et al. Prevalence of metabolically healthy obesity and its impacts on incidences of hypertension, diabetes and the metabolic syndrome in Taiwan. *Asia Pac J Clin Nutr* 2012; 21: 227–233.
  14. O'Neill S and O'Driscoll L. Metabolic syndrome: a closer look at the growing epidemic and its associated pathologies. *Obes Rev* 2015; 16: 1–12.
  15. DeBoer MD, Gurka MJ, Morrison JA, et al. Inter-relationships between the severity of metabolic syndrome, insulin and adiponectin and their relationship to future type 2 diabetes and cardiovascular disease. *Int J Obes* 2016; 40: 1353.
  16. Lim S, Min SH, Lee JH, et al. Components of Metabolic Syndrome in Korean Adults: A Hospital-Based Cohort at Seoul National University Bundang Hospital. *J Obes Metab Syndr* 2019; 28: 118–128. DOI: 10.7570/jomes.2019.28.2.118.
  17. Ansari-Moghaddam A, Adineh HA, Zareban I, et al. Prevalence of metabolic syndrome and population attributable risk for cardiovascular, stroke, and coronary heart diseases as well as myocardial infarction and all-cause mortality in middle-east: Systematic review & meta-analysis. *Obes Med* 2019; 14: 100086. DOI: <https://doi.org/10.1016/j.obmed.2019.100086>.
  18. Klein BE, Klein R and Lee KE. Components of the metabolic syndrome and risk of cardiovascular disease and diabetes in Beaver Dam. *Diabetes Care* 2002; 25: 1790–1794.
  19. Saluja M, Pyarsabadi P, Jelja S, et al. Study of thyroid dysfunction in metabolic syndrome and association with its components. *Current Medicine Research and Practice* 2018; 8: 3–7.
  20. Unnikrishnan AG and Menon UV. Thyroid disorders in India: An epidemiological perspective. *Indian J Endocrinol Metab* 2011; 15: S78.
  21. Kwon H, Jung JH, Han KD, et al. Prevalence and Annual Incidence of Thyroid Disease in Korea from 2006 to 2015: A Nationwide Population-Based Cohort Study. *Endocrinol Metab (Seoul)* 2018; 33: 260–267.
  22. Lekakis J, Papamichael C, Alevizaki M, et al. Flow-mediated, endothelium-dependent vasodilatation is impaired in subjects with hypothyroidism, borderline hypothyroidism, and high-normal serum thyrotropin (TSH) values. *Thyroid* 1997; 7: 411–414.
  23. Hak L, Pols H, Visser T, et al. Subclinical hypothyroidism is an independent risk factor for atherosclerosis and myocardial infarction in elderly women: the Rotterdam Study. *Ann Intern Med* 2000; 132: 270–278.
  24. Ning Y, Cheng YJ, Liu LJ, et al. What is the association of hypothyroidism with risks of cardiovascular events and mortality? A meta-analysis of 55 cohort studies involving 1,898,314 participants. *BMC Med* 2017; 15: 21.
  25. Moon S, Kim MJ, Yu JM, et al. Subclinical hypothyroidism and the risk of cardiovascular disease and all-cause mortality: a meta-analysis of prospective cohort studies. *Thyroid* 2018; 28: 1101–1110.
  26. Rodondi N, Den Elzen WP, Bauer DC, et al. Subclinical hypothyroidism and the risk of

- coronary heart disease and mortality. *JAMA* 2010; 304: 1365–1374.
27. Waring AC, Rodondi N, Harrison S, et al. Thyroid function and prevalent and incident metabolic syndrome in older adults: the Health, Ageing and Body Composition Study. *Clin Endocrinol (Oxf)* 2012; 76: 911–918.
  28. Alexander CM, Landsman PB, Teutsch SM, et al. NCEP-defined metabolic syndrome, diabetes, and prevalence of coronary heart disease among NHANES III participants age 50 years and older. *Diabetes* 2003; 52: 1210–1214.
  29. Cameron A, Magliano D, Zimmet P, et al. The metabolic syndrome as a tool for predicting future diabetes: the AusDiab study. *J Intern Med* 2008; 264: 177–186.
  30. Cai Y, Ren Y and Shi J. Blood pressure levels in patients with subclinical thyroid dysfunction: a meta-analysis of cross-sectional data. *Hypertens Res* 2011; 34: 1098.
  31. Ruhla S, Weickert MO, Arafat AM, et al. A high normal TSH is associated with the metabolic syndrome. *Clin Endocrinol (Oxf)* 2010; 72: 696–701.
  32. Roos A, Bakker SJ, Links TP, et al. Thyroid function is associated with components of the metabolic syndrome in euthyroid subjects. *J Clin Endocrinol Metab* 2006; 92: 491–496.
  33. Reinehr T, Isa A, De Sousa G, et al. Thyroid hormones and their relation to weight status. *Horm Res* 2008; 70: 51–57.
  34. Bi Y, Lu J, Wang W, et al. Cohort profile: Risk evaluation of cancers in Chinese diabetic individuals: a longitudinal (REACTION) study. *J Diabetes* 2014; 6: 147–157.
  35. Lu J, Bi Y, Wang T, et al. The relationship between insulin-sensitive obesity and cardiovascular diseases in a Chinese population: results of the REACTION study. *Int J Cardiol* 2014; 172: 388–394.
  36. Ning G and Bloomgarden Z. Diabetes and cancer: Findings from the REACTION study. *J Diabetes* 2015; 7: 143–144.
  37. Ning G and Group RS. Risk Evaluation of cAncers in Chinese diabeTic Individuals: a lONgitudinal (REACTION) study. *J Diabetes* 2012; 4: 172–173.
  38. He QY and GYH. Some definitions of terms on smoking. *Chinese Journal of Tuberculosis and Respiratory Diseases* 2009; 32: 56.
  39. World Health Organization. Global advice on the health benefits of physical activity. 2011.
  40. Aguilar M, Bhuket T, Torres S, et al. Prevalence of the metabolic syndrome in the United States, 2003–2012. *JAMA* 2015; 313: 1973–1974.
  41. Zhou YC, Fang WH, Kao TW, et al. Exploring the association between thyroid-stimulating hormone and metabolic syndrome: A large population-based study. *PLoS One* 2018; 13: e0199209.
  42. Kannan L. Hypothyroidism and the Metabolic Syndrome. *Endocrinology & Metabolism International Journal* 2017; 5. DOI: 10.15406/emij.2017.05.00115.
  43. Hamlaoui ML, Ayachi A, Dekaken A, et al. Relationship of metabolic syndrome and its components with thyroid dysfunction in Algerian patients. *Diabetes Metab Syndr* 2018; 12: 1–4.
  44. Park HT, Cho GJ, Ahn KH, et al. Thyroid stimulating hormone is associated with metabolic syndrome in euthyroid postmenopausal women. *Maturitas* 2009; 62: 301–305.
  45. Lee YK, Kim JE, Oh HJ, et al. Serum TSH level in healthy Koreans and the association of TSH with serum lipid concentration and metabolic syndrome. *Korean J Intern Med* 2011; 26: 432.
  46. Oh JY, Sung YA and Lee HJ. Elevated thyroid stimulating hormone levels are associated with metabolic syndrome in euthyroid young women. *Korean J Intern Med* 2013; 28: 180.
  47. Park SB, Choi HC and Joo NS. The relation of thyroid function to components of the metabolic syndrome in Korean men and women. *J Korean Med Sci* 2011; 26: 540–545.
  48. Zhu X and Cheng SY. New insights into regulation of lipid metabolism by thyroid hormone. *Curr Opin Endocrinol Diabetes Obes* 2010; 17: 408.
  49. Triolo M, De Boer JF, Annema W, et al. Low normal free T4 confers decreased high-density lipoprotein antioxidative

- functionality in the context of hyperglycaemia. *Clin Endocrinol (Oxf)* 2013; 79: 416–423.
50. Chin KY, Ima-Nirwana S, Mohamed IN, et al. The relationships between thyroid hormones and thyroid-stimulating hormone with lipid profile in euthyroid men. *Int J Med Sci* 2014; 11: 349.
  51. Åsvold BO, Bjøro T, Nilsen TI, et al. Association between blood pressure and serum thyroid-stimulating hormone concentration within the reference range: a population-based study. *J Clin Endocrinol Metab* 2007; 92: 841–845.
  52. Maratou E, Hadjidakis DJ, Peppas M, et al. Studies of insulin resistance in patients with clinical and subclinical hyperthyroidism. *Eur J Endocrinol* 2010; 163: 625–630.
  53. Gurevitz SL, Snyder JA, Peterson KL, et al. Hypothyroidism and subclinical hypothyroidism in the older patient. *Consult Pharm* 2011; 26: 657–64.
  54. Mehran L, Amouzegar A, Rahimabad PK, et al. Thyroid function and metabolic syndrome: a population-based thyroid study. *Horm Metab Res* 2017; 49: 192–200.
  55. Thapa BB, Bhatta BD, Tiwari M, et al. Metabolic Syndrome in Subclinical and Overt Hypothyroidism. *Medical Journal of Pokhara Academy of Health Sciences* 2018; 1: 4.
  56. Deshmukh V, Farishta F and Bhole M. Thyroid dysfunction in patients with metabolic syndrome: a cross-sectional, epidemiological, Pan-India study. *Int J Endocrinol* 2018; 2018: 2930251.
  57. Delitala AP, Scuteri A, Fiorillo E, et al. Role of Adipokines in the Association between Thyroid Hormone and Components of the Metabolic Syndrome. *J Clin Med* 2019; 8: 764.

## Appendix A

Guang Ning, Yiming Mu, Jiajun Zhao, Chao Liu, Yufang Bi, Donghui Li,

Shenghan Lai, and Zachary T. Bloomgarden comprised the advisory committee of the REACTION Study Group.

## The REACTION Study Group

Guang Ning, Shanghai Jiao Tong University School of Medicine; Yiming Mu, People's Liberation Army General Hospital; Jiajun Zhao, Shandong Provincial Hospital; Chao Liu, Jiangsu Province Hospital for the Integration of Chinese and Western Medicine, Qin Wan, University of Luzhou School of Medicine; Shengli Wu, Xinjiang Kelamayi People's Hospital; Guijun Qin, University of Zhengzhou School of Medicine; Qiang Li, University of Haerbin; Youming Wang, University of Anhui School of Medicine; Huacong Deng, University of Chongqing School of Medicine; Tao Yang, University of Nanjing School of Medicine; Li Yan, University of Zhongshan School of Medicine; Yan Liu and Guixia Wang, University of Jilin School of Medicine; Zuojie Luo, University of Guangxi School of Medicine; Xulei Tang, University of Lanzhou School of Medicine; Gang Chen, University of Fujian School of Medicine; Lixin Shi, University of Guizhou School of Medicine; Yanan Huo, Jiangxi People's Hospital; Zhengnan Gao, University of Dalian School of Medicine; Qing Su, Shanghai JiaoTong University School of Medicine; Zhen Ye, Zhejiang Centre for Disease Control and Prevention; Xuefeng Yu, Wuhan Tongji Hospital; Feixia Shen, Wenzhou University School of Medicine; Lulu Chen, Huazhong University of Science and Technology School of Medicine; and Li Chen, University of Shandong School of Medicine.