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ORIGINAL RESEARCH

The Association Between Serum Thyrotropin Within the Reference Range and Metabolic Syndrome in a Community-Based Chinese Population

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Purpose: We aimed to ascertain the association between thyrotropin (TSH) levels in euthyroid state and the prevalence of metabolic syndrome (MetS) in a community-based Chinese population.

Participants and Methods: Based on a large and well-characterized community cohort in Beijing, China, 1831 men and 1742 women with serum TSH levels within the reference range (0.50–4.78 μIU/mL) were stratified by quartiles of TSH (Q1-4). MetS was identified according to the criteria of International Diabetes Federation guidelines. Poisson regression models were used to estimate the association between serum TSH and the prevalence of MetS and its components before and after adjustment for potential confounding factors. The reported association was measured using the prevalence ratio (PR) with its respective 95% confidence interval (95% CI).

Results: The prevalence of MetS in euthyroid population across TSH quartiles (Q1-4) was 38.9%, 44.6%, 41.0%, and 47.7%, respectively, in men (P = 0.045), and 47.7%, 46.6%, 46.9%, and 54.6%, respectively, in women (P = 0.032). Compared with the reference group TSH-Q1, the prevalence of MetS was higher among TSH-Q4 group both in men (PR = 1.27; 95% CI: 1.09, 1.48, P = 0.002) and women (PR = 1.21; 95% CI: 1.07, 1.37, P = 0.003) even after adjustment for age, lifestyle factors, serum levels of free triiodothyronine (FT3), and free thyroxine (FT4). Most of the components of MetS were common in higher serum TSH levels within the normal range.

Conclusion: The prevalence of MetS and most of its components increased in the higher TSH group in euthyroid Chinese population.

Keywords: thyroid hormones, obesity, hypertension, hyperglycemia

The Plain Language Summary

- Why was the Study Done?

Metabolic syndrome (MetS) is increasing throughout the world, and thyroid function has an influence on systematic metabolism. However, the association between MetS and thyrotropin (TSH) was elusive. We aimed to investigate the association between MetS and TSH in euthyroid subjects from a large community-based Chinese population.

- What Did the Researchers Do?

We performed a large and well-characterized community cohort in Pinggu (PG), Beijing, China. The PG cohort is to study the course and pathogenesis of metabolic diseases. During

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the survey, we have collected detailed demographic and clinical, biochemical data, and determined the strata of glucose homeostasis, lipid metabolism and thyroid function.

- What Did We Find?

Based on the database of community-based population, we found that the prevalence of MetS and most of its components increased in the higher TSH group in euthyroid Chinese population.

- What Do These Results Mean?

The assessment of thyroid function may contribute to early identification of chronic metabolic diseases and initiate personalized treatment strategies. Further research into the causality on the association between TSH and MetS is to be warranted.

Introduction

Metabolic syndrome (MetS) representing a cluster of metabolic abnormalities that include abdominal obesity, hyperglycemia, hypertension, hypertriglyceride and low-high-density lipoprotein cholesterol (HDL-C) levels has increased all over the world and become a major public health care concern.[1,2] Thyroid hormone, as one of the most fundamental hormones in humans, is the root of systemic metabolism, energy balance and cardiovascular function.[3,4] Mounting studies have shown that overt hypothyroidism and subclinical hypothyroidism have association with an increased risk for hypertension, obesity, dyslipidemia, diabetes, cardiovascular disease and mortality.[4–9] However, whether the level of thyroid function in the normal range is related to MetS and to what extent remain inconclusive. The HUNT Study in Norway and the DanThyr Study in Denmark have reported the association between higher thyrotropin (TSH) levels within the reference range and the presence of obesity, less favorable lipid profiles and high blood pressure.[10–12] Some studies also reported that subjects with high normal TSH had an increased likeliness of MetS.[13–15] However, Mehran et al failed to find the association between TSH and MetS.[16] The studies on the association between them in Chinese population are mostly conducted among healthy examination populations, with inconsistent results. Recently, in a large population taking healthy examinations in Taiwan, elevated TSH levels within the normal range were identified as a cardiometabolic risk marker associated with MetS and other metabolic risk factors.[14] In contrast, Huang et al found no significant correlation between TSH and MetS after adjustment of confounders (smoking and age) in euthyroid Taiwanese adults.[17] Another study conducted among Chinese adolescents did not find any correlation between the prevalence of MetS and its components and normal TSH.[18] Two other Chinese studies identified the relationship between TSH and MetS components,[19,20] and they did not consider MetS as a whole in the study conducted in a southwest city.[19] As we know, the definitions of MetS were distinct in these studies. In addition, the research design, different subjects, reference range of TSH, and the potential confounders were also attributed to the conflicting results. To date, there are few studies addressing the association between TSH in the normal range and the prevalence of MetS in Chinese general community-based population.

As community-based population, the Pinggu (PG) cohort was established in northern China to study the course and pathogenesis of metabolic diseases. During the cohort survey, we have collected detailed epidemic, clinical and biochemical data, and determined the strata of glucose homeostasis, lipid metabolism and thyroid function. Here, we tried to investigate whether the serum TSH levels within the reference range were associated with the prevalence of MetS and its components, including central obesity, high blood pressure, hypertriglyceride, low-HDL-C and hyperglycemia.

Participants and Methods

Study Population

Participants of this study were from a community-based cohort established for the Pinggu Metabolic Disease Study (PMDS) in Pinggu district of Beijing, northern China from September 2013 to July 2014. The protocol has been described previously.[21,22] Briefly, based on the national Civil Registration system, a total of 6583 PG participants aged 26–76 years were randomly selected according to gender and age compositions, and finally 4002 individuals finished the survey, with a response rate of 60.8%.

In this study, we excluded (1) participants who have received thyroid surgery or thyroid medications (i.e., thyroid hormone, anti-thyroid drugs, or radioiodine therapy) (N = 115); (2) those diagnosed as hyperthyroidism or TSH < 0.55 μIU/mL at the baseline (N = 74); (3) those diagnosed as hypothyroidism or TSH > 4.78 μIU/mL at the baseline (N = 237); and (4) those taking medications or in other abnormal status that could affect thyroid function (N = 3). After these exclusions, a total of 1831 men and

1742 women with complete information were analyzed (Figure S1). PMDS was approved by the ethics committee of Peking University Medical Center. All participants gave written informed consent.

Questionnaire and Physical Examination

All participants accepted face-to-face interview and standardized questionnaires, including demographics, lifestyle, information on history of thyroid disease, diabetes, hypertension, dyslipidemia and related chronic diseases, the associated treatments, and other health-related issues. The smoking status was divided into never smoked, ex-smoker or current smoker. In dietary questions, the participants reported the frequency of food intake. Here we choose the frequency of red meat as the parameter of dietary habit and classified as 0 when consumed less than seven times per week, or 1 when consumed more than seven times per week. Alcohol consumption was divided into 0, >0 and ≤140, >140, ≤210, and >210 g/week in men and 0, >0 and ≤70, >70, ≤140, and >140 g/week in women. Sedentary time per day was also recorded, and daily sedentary time was categorized into <1.5, 1.5–2.5, 2.5–3.5, 3.5–4.5, or ≥4.5 hours/day.[23] Women were determined to be postmenopausal if their menstrual periods had stopped for at least one year. The studied postmenopausal individuals here did not receive estrogen treatment.

In addition, anthropometric data were collected by trained physicians according to standardized protocols. Height and weight were measured when subjects stood without shoes and light clothing. Body mass index (BMI) was calculated: BMI = weight (kg)/height^2 (m^2). Waist circumference (WC) was measured around the abdomen at the middle point between the anterosuperior iliac crest and the inferior margin of 12th ribs. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured three times after a 5-minute rest with the participant in the sitting position, and the mean value of the three measurements was used.

Laboratory Measurements

Fasting blood samples after overnight were collected. Fasting plasma glucose (FPG) was measured by the glucose oxidase method. Serum total cholesterol, TG, HDL-C, low-density lipoprotein cholesterol (LDL-C) and uric acid were measured by an automated clinical chemistry method (UnicelDxC 800; Beckman Coulter, Miami, FL, USA). Haemoglobin A1c (HbA1c) was measured using cation-exchange high-pressure liquid chromatography (Adams A1c HA-8160; Arkray, Kyoto, Japan). Serum insulin was tested by a radioimmunoassay method (China Institute of Atomic Energy, Beijing, China). The thyroid hormones and thyroid-related antibodies were tested using a supersensitive electrochemiluminescence immunoassay (Siemens Centaur XP, Germany). The intra-assay coefficient of variation (CV) was less than 8%, and the inter-assay CV less than 10% for all these parameters. The HOMA-IR score was calculated using the following formula: HOMA-IR = (FPG [mmol/L] × insulin[μU/mL])/22.5.

Diagnostic and Grouping Criteria

The reference range for serum thyrotropin (TSH) is 0.55–4.78 μIU/mL. The reference intervals were 11.45–23.17 pmol/L for free thyroxine (FT4), 3.50–6.50 pmol/L for free triiodothyronine (FT3), <60 IU/mL for thyroid peroxidase antibodies (TPOAb) and <15 IU/mL for thyroglobulin antibody (TGAb). Euthyroidism was defined as serum TSH in the range of 0.55–4.78 μIU/mL, regardless of the FT4 concentration. The Pinggu population is considered to have sufficient iodine intake. Participants who considered euthyroid were further divided into four groups: Q1 (TSH 0.55–1.30μIU/mL), Q2 (TSH 1.31–1.85μIU/mL), Q3 (TSH 1.85–2.58μIU/mL), and Q4 (2.59–4.78μIU/mL) groups.

Metabolic syndrome was defined according to the International Diabetes Federation (IDF 2005) criteria:[24] the diagnosis of central obesity (WC ≥90 cm in men or ≥80 cm in women), plus any two of the following four factors: (1) TG levels ≥1.7 mmol/L, (2) HDL-C <1.03 mmol/L in men or <1.29 mmol/L in women, (3) SBP ≥ 130 mmHg or DBP ≥85 mmHg or previous diagnosis with hypertension, (4) FBG ≥ 5.6 mmol/L, or previous diagnosis with type 2 diabetes mellitus. The components of MetS included central obesity, hypertriglyceride, low-HDL-C levels, hypertension, and hyperglycemia. Obesity was also defined as BMI ≥28kg/m^2 according to the Chinese-specific BMI cut-off point.[25]

Statistical Analysis

Data processing and statistical analysis were performed with SPSS 21.0 software. Continuous variables were presented as mean with standard deviation (mean ± SD) or median (25th, 75th). Categorical data were presented as number and proportion (%). Normally distributed variables were compared using *t*-tests, and variables with

skewed distribution were compared with Mann–Whitney *U*-tests between men and women groups. One-way ANOVA and Kruskal–Wallis tests were used to compare the characteristics across TSH quartiles. A Chi-square was used for categorical data. Generalized linear models from Poisson family were constructed to evaluate the association between TSH quartiles with the prevalence of MetS before and after adjustment for the confounders screening from epidemiological investigation and correlation analysis. The adjusted model 2 included the following confounding variables: age, smoking, drinking, red meat intake, sedentary time, menopause (in women); and the adjusted model 3 further included the variables: FT3 and FT4. The prevalence ratio (PR) and its 95% confidence interval (CI) were thus reported for the higher TSH levels (Q2-Q4) with the TSH-Q1 as the reference group. The p-value of <0.05 was considered as statistically significant.

Results

General Population Characteristics

A total of 3573 participants (1831 men and 1742 women) were finally included in the analysis. The demographic and clinical characteristics are listed in Table 1. Totally, the average age of the analysis population was 49.81±11.74 years. The mean BMI was 26.09±3.83 kg/m^2, with 28.5% of participants being obesity (BMI ≥ 28 kg/m^2). In this study population, 27.7% of participants were sedentary for ≥4.5 hours per day. The frequency of red meat intake was higher in men than in women. In men, 64.3% were current smokers and 70.8% drank. The vast majority of women did not have the habit of smoking and drinking.

The prevalence of MetS was 42.7%, 49.4% and 46.0% respectively in men, women and the overall study population. As shown in Figure 1A, the prevalence of MetS in men aged 25 to 29, 30 to 39, 40 to 49, 50 to 59, and ≥60 years was 34.3%, 49.2%, 47.1%, 41.7%, and 35.3% (P < 0.001), respectively, with a very significant trend of early onset. In women, it was 14.8%, 19.5%, 40.2%, 65.7%, and 71.0% (P < 0.001) (Figure 1B), respectively, increasing rapidly after menopause and even exceeding that of men.

The Prevalence of MetS Among Different TSH Quartiles

The prevalence of Mets in men from TSH-Q1 to TSH-Q4 was 38.9%, 44.6%, 41.0%, and 47.7% (P = 0.045), respectively (in Table S1a), and in women, it was 47.7%, 46.6%, 46.9%, and 54.6% (P = 0.032), respectively (in Table S1b). As shown in Figure 2, the prevalence of MetS (Figure 2A), obesity and hypertriglyceride (Figure 2C) increased along with the increased TSH levels both in men and women. The prevalence of central obesity and low-HDL-C increased significantly with the elevated TSH levels in men, but not in women (Figure 2B and D). There was no significant difference on the prevalence of hyperglycemia and hypertension among different TSH quartiles (Figure 2E and F). The proportions of positive TPOAb and TGAb were significantly highest in the TSH-Q4 group than other groups (TSH Q1-3) in men (P = 0.018) and in women (P < 0.001). We examined continuous traits across four TSH groups with P-for-trend summarized in Tables S1a and S1b. TSH levels within the normal range were positively associated with age, BMI, waist circumference, TG, and MetS in both men and women. Increased TSH levels showed significant correlations with HbA1c, fasting insulin, HOMA-IR, TC, LDL-C, uric acid (in men), and DBP (in women).

Association Between TSH Quartiles and MetS

In this analysis, a generalized linear model from Poisson family was adopted to assess the impact of TSH levels on the prevalence of Mets before and after adjustment for potential confounding factors (Table 2). Compared with euthyroid adults with the lowest serum TSH quartile (TSH-Q1), the PRs (95% CI) of MetS for TSH-Q2, TSH-Q3 and TSH-Q4 in men were 1.15 (1.00, 1.32), 1.06 (0.91, 1.24) and 1.25 (1.08, 1.46), respectively, and 0.98 (0.84, 1.14), 0.98 (0.85, 1.14) and 1.15 (1.00, 1.31) in women. After adjustments for age, postmenopausal status (for women), smoking status, drinking, red meat intake and sedentary time (model 2), compared with the TSH-Q1, the prevalence of MetS for TSH-Q4 was 23% (PR 1.23; 95% CI 1.06, 1.43, P = 0.007) in men and 17% higher in women (PR 1.17; 95% CI 1.04, 1.33, P = 0.012). In the fully adjusted model 3 that was further fitted with the levels of serum FT3 and FT4, the trend did not substantially change with higher prevalence of MetS for TSH-Q4 vs TSH-Q1 in men (PR 1.27; 95% CI 1.09, 1.48, P = 0.002) and women (PR 1.21; 95% CI 1.07, 1.37, P = 0.003).

After full adjustment for confounders, the prevalence of central obesity in TSH-Q4 was 25% and 14% higher compared with TSH-Q1 both in men (PR 1.25; 95% CI 1.10, 1.43, P = 0.001) and in women (PR 1.14; 95% CI 1.03, 1.26, P = 0.009). The similar trend was shown in the

Table 1 Characteristics of the Study Population

Characteristic	Total	Men	Women	*P*-value
Number	3573	1831	1742	/
Age (y)	49.81±11.74	49.66±11.89	49.97±11.58	0.430
BMI (kg/m^2)	26.09±3.83	26.15±3.75	26.02±3.90	0.316
Obesity (BMI ≥ 28 kg/m^2) (n, %)	1020 (28.5)	532 (29.1)	488 (28.0)	0.491
WC (cm)	86.79±10.86	89.40±10.24	84.06±10.81	**<0.001**
SBP (mmHg)	131±18	132±17	128±19	**<0.001**
DBP (mmHg)	79±11	81±12	77±11	**<0.001**
HbA1c (%)	5.82±0.93	5.83±0.99	5.81±0.86	0.450
FPG (mmol/L)	6.07±1.62	6.25±1.75	5.88±1.45	**<0.001**
FINS (μIU/mL)	9.62±6.32	9.56±6.74	9.69±5.85	0.534
HOMA-IR (mU/L mM)	2.12 (1.38, 3.26)	2.12 (1.29, 3.36)	2.12 (1.44, 3.14)	0.667
TG (mmol/L)	1.20 (0.77, 1.88)	1.29 (0.83, 2.13)	1.12 (0.72, 1.66)	**<0.001**
TC (mmol/L)	4.91±0.97	4.89±0.95	4.93±1.00	0.140
HDL-C (mmol/L)	1.16±0.31	1.11±0.32	1.21±0.29	**<0.001**
LDL-C (mmol/L)	2.86±0.80	2.83±0.79	2.89±0.81	**0.024**
UA (μmol/L)	286.58±80.72	324.29±78.41	246.93±61.96	**<0.001**
FT4 (pmol/L)	16.05 (14.66, 17.62)	16.63 (15.18, 18.24)	15.53 (14.23, 16.84)	**<0.001**
FT3 (pmol/L)	4.99 (4.65, 5.35)	5.20 (4.88, 5.54)	4.78 (4.49, 5.06)	**<0.001**
TSH (μIU/mL)	1.85 (1.31, 2.59)	1.65 (1.22, 2.33)	2.05 (1.48, 2.85)	**<0.001**
TSH Quartiles (n, %)				**<0.001**
Q1 (0.55–1.30)	885 (24.8)	558 (30.5)	327 (18.8)	
Q2 (1.31–1.85)	906 (25.4)	522 (28.5)	384 (22.0)	
Q3 (1.85–2.58)	885 (24.8)	407 (22.2)	478 (27.4)	
Q4 (2.59–4.78)	897 (25.1)	344 (38.4)	553 (31.7)	
Thyroid autoimmune antibodies (n, %)				**<0.001**
TPOAb and TGAb (-)	3035 (84.9)	1655 (90.4)	1380 (79.2)	
TPOAb or TGAb (+)	337 (9.4)	131 (7.2)	206 (11.8)	
TPOAb and TGAb (+)	201 (5.6)	45 (2.5)	156 (9.0)	
MetS (n, %)	1642 (46.0)	781 (42.7)	861 (49.4)	**<0.001**
Central obesity (n, %)	2006 (56.1)	908 (49.6)	1098 (63.0)	**<0.001**
Hypertriglyceride (n, %)	1051 (29.4)	632 (34.5)	419 (24.1)	**<0.001**
Low-HDL-c (n, %)	2224 (62.2)	1006 (54.9)	1218 (69.9)	**<0.001**
Hypertension (n, %)	2187 (61.2)	1208 (66.0)	979 (56.2)	**<0.001**
Hyperglycemia (n, %)	1908 (53.4)	1130 (61.7)	778 (44.7)	**<0.001**
Postmenopausal status (n, %)	–	–	850 (48.8)	/
Smoking (n, %)				**<0.001**
Nonsmoker	2097 (58.7)	373 (20.4)	1724 (99.0)	
Ex-smoker	282 (7.9)	280 (15.3)	2 (0.1)	
Current smoker	1194 (33.4)	1178 (64.3)	16 (0.9)	
Alcohol drinking (g/week) (n, %)				**<0.001**
0	2100 (58.8)	535 (29.2)	1565 (89.8)	
0.1–140 for men or 0.1–70 for women	860 (24.1)	728 (39.8)	132 (7.6)	
140.1–210 for men or 70.1–140 for women	74 (2.1)	54 (2.9)	20 (1.1)	
>210 for men or >140 for women	539 (15.1)	514 (28.1)	25 (1.4)	
Red meat consumption ≥7 times per week (n, %)	1424 (39.9)	842 (46.0)	582 (33.4)	**<0.001**
Sedentary time (hours/day) (n, %)				**<0.001**
<1.5	245 (6.9)	120 (6.6)	125 (7.2)	
1.5–2.5	831 (23.3)	405 (22.1)	426 (24.5)	

(*Continued*)

Table 1 (Continued).

Characteristic	Total	Men	Women	*P*-value
2.5–3.5	876 (24.5)	391 (21.4)	485 (27.8)	
3.5–4.5	633 (17.7)	312 (17.0)	321 (18.4)	
≥ 4.5	988 (27.7)	603 (32.9)	385 (22.1)	

Notes: Data are expressed as mean ± SD for continuous data with normal distribution, median (25th, 75th percentage) for continuous data with skewed distribution, and n (%) for categorical data. *P*-value from *t*-test, chi-squared or Mann–Whitney *U*-test comparing between men and women. *P*-value <0.05 was considered significant and in boldface.

Abbreviations: BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, haemoglobin A1c; FPG, fasting plasma glucose; FINS, fasting insulin; HOMA-IR, homeostasis model assessment of insulin resistance; TG, triglycerides; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; UA, uric acid; FT4, free thyroxine; FT3, free triiodothyronine; TSH, thyrotropin; Q, quartile; TPOAb, thyroid peroxidase antibody; TGAb, thyroglobulin antibody; MetS, metabolic syndrome.

prevalence of hypertriglyceride (men PR 1.38; 95% CI 1.15, 1.66, P = 0.001, and women PR 1.43; 95% CI 1.12, 1.82, P = 0.004). The prevalence of hypertension in TSH-Q4 was higher than TSH-Q1 only in women (PR 1.20; 95% CI 1.08, 1.33, P = 0.001). Compared with the TSH-Q1 group, the association between TSH quartiles and hyperglycemia and low-HDL-c in TSH-Q4 were not statistically significant both in men and women.

Discussion

The results of the current cross-sectional population study in euthyroid adults demonstrated a significant association between serum TSH and the prevalence of MetS. Overall, even if thyroid function is in the normal range, the prevalence of MetS and its components increased from low to high TSH quartiles.

Although numerous studies have explored the association between TSH and the prevalence of MetS, the conclusions are inconsistent. In a large population-based study involving 24,765 euthyroid subjects who underwent health examinations from Taiwan, TSH levels showed a positive association with the presence of MetS.[14] The prevalence of MetS was significantly higher in subjects with TSH levels >2.5 mU/L than the low-TSH group in German and Korean studies.[15,26] In addition, Zhou et al performed a 7.2-year longitudinal study and found the TSH levels were associated with the development of MetS.[27] These findings are supported by the results of the current study. Compared with euthyroid adults with the lowest serum TSH quartile, the prevalence of MetS increased 27% in men and 21% in women with the highest TSH quartile. Inconsistently, Mehran et al[16] found no correlation between TSH within normal range and MetS. The disappearance of the correlation may be related to the exclusion of diabetic patients from the analysis and different criteria of MetS they selected. Huang et al reported no association between TSH and MetS after stratified analyses according to sex.[17] The inconsistent results may be attributed to races, population, methodology, definitions of MetS and the varying set points of TSH for "euthyroid status". The two major criteria by the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) and the International Diabetes Federation (IDF) were widely used.

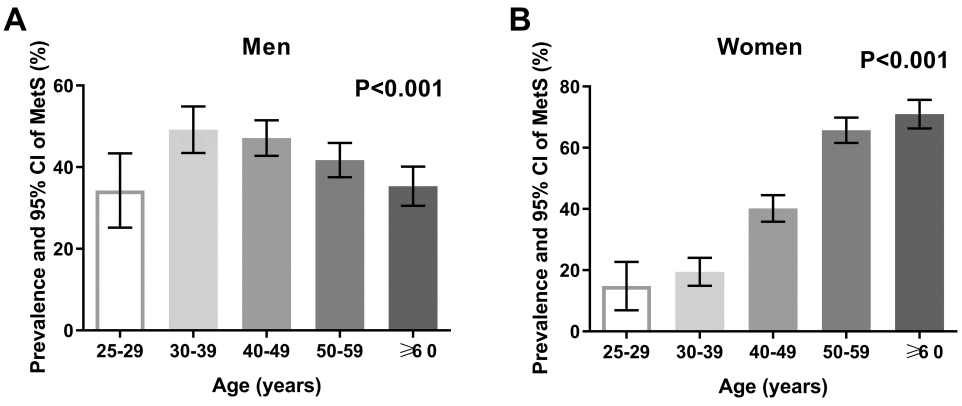

Figure 1 Prevalence of metabolic syndrome (MetS) and 95% confidence interval (CI) according to age in men (**A**) and women (**B**).
Notes: *P*-value for the difference among age groups using a chi-squared test.

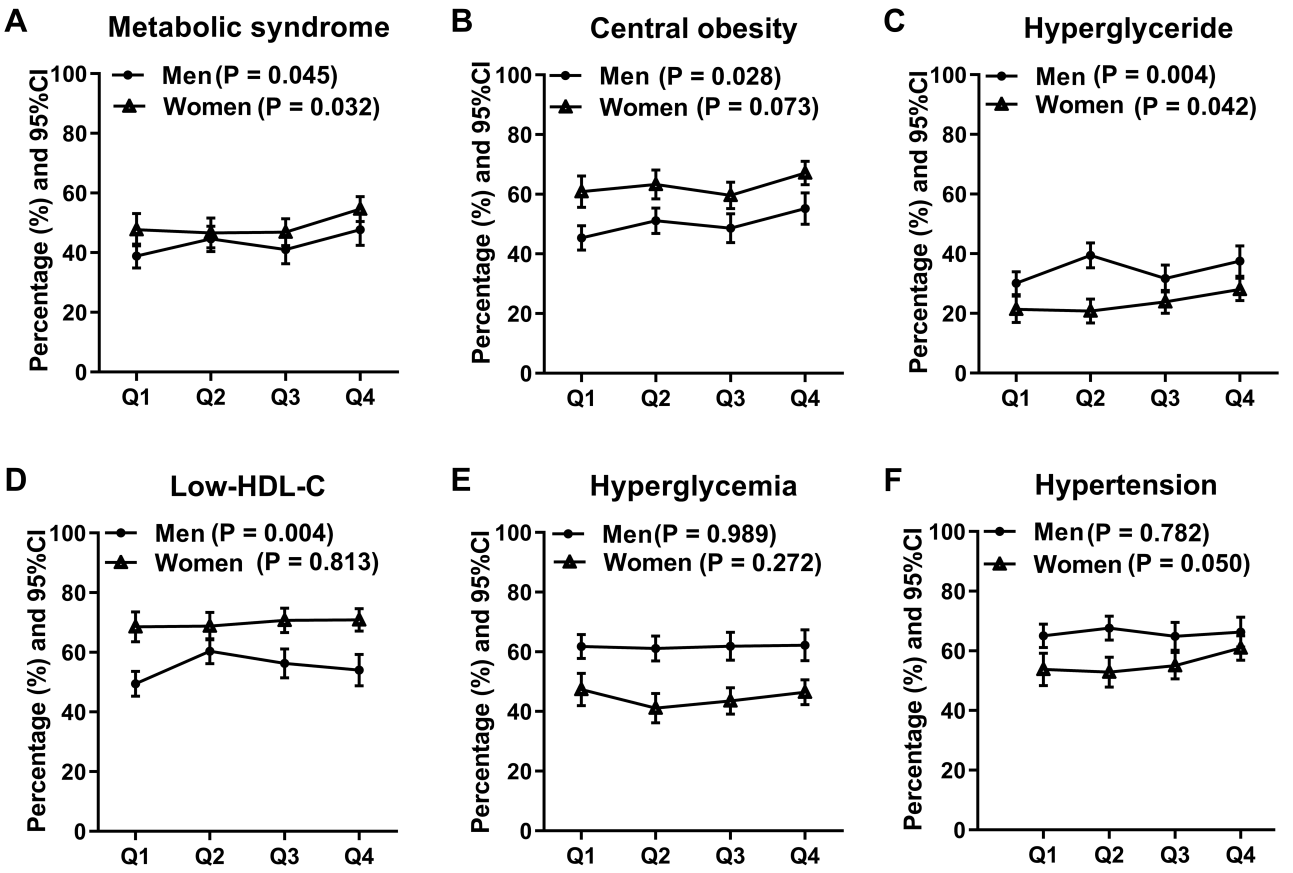

Figure 2 Percentage of metabolic disorders in men and women according to thyrotropin (TSH) quartiles.
Notes: Q1-4 indicate the TSH quartiles. *P*-value for the difference among the TSH quartiles using a chi-squared test. (**A**) Metabolic syndrome. (**B**) Central obesity. (**C**) Hyperglyceride. (**D**) Low-HDL-C. (**E**) Hyperglycemia. (**F**) Hypertension.
Abbreviation: HDL-C, high-density lipoprotein cholesterol.

Here, we prefer to choose the IDF 2005 MetS criteria because it provides a specific diagnostic cut-point for Chinese population.[24] This standard has also been adopted and confirmed by many studies from China.[14,28] Notably, most of the previous studies did not give sufficient consideration to the potential confounding factors, including sex, age, lifestyle and serum levels of thyroid hormone, such as FT3 and FT4, which may be related to metabolic disease.[29,30] Moreover, given that the occurrence of metabolic disease is characterized by gender dimorphism, we conducted analyses for men and women separately or adjusted for sex in all of the analysis models. Here we found that serum TSH was independently associated with the prevalence of MetS both in men and women after adjusting for the influence factors (including age, the intake frequency of red meat, smoking, drinking, sedentary time, and serum levels of FT4, and FT3).

Amongst the parameters of the metabolic syndrome, we also found TSH was correlated significantly with obesity and dyslipidemia. In euthyroidism, many cross-sectional studies showed the association between TSH and obesity.[10,15,26,31,32] Also besides, some longitudinal studies have established the relationship between the concentrations of thyroid hormones and changes in body weight over time.[33–35] In contrast, several studies did not detect the relation between TSH and obesity.[36,37] The variability of the maximum value in the reference range of TSH, limited sample size and the adjusting confounders might explain the differences of association between BMI and TSH. Besides adiposity, thyroid function also affected lipid metabolism.[11,13,38,39] The HUNT study found a linear and significant increase in serum TC, LDL-C, TG levels, and a linear decrease in HDL-C with increasing TSH in euthyroid subjects.[11] Similar results were observed in the PG population. There are controversial findings of the relationship between TSH and blood pressure in euthyroid subjects.[12,40,41] Here we found that TSH was just significantly correlated with blood pressure in women. Higher TSH levels within the normal range were not significantly associated with prediabetes or diabetes in most studies,[16,27]

Table 2 Association of TSH with Metabolic Syndrome by the Poisson Regression

Items	TSH Quartiles	Men			Women		
		Model 1 PR (95% CI)	Model 2 PR (95% CI)	Model 3 PR (95% CI)	Model 1 PR (95% CI)	Model 2 PR (95% CI)	Model 3 PR (95% CI)
MetS	Q2	1.15 (1.00, 1.32)	1.14 (0.99, 1.31)	1.14 (1.00, 1.32)	0.98 (0.84, 1.14)	1.03 (0.90, 1.19)	1.05 (0.91, 1.20)
	Q3	1.06 (0.91, 1.24)	1.06 (0.91, 1.24)	1.07 (0.92, 1.25)	0.98 (0.85, 1.14)	1.08 (0.94, 1.24)	1.11 (0.97, 1.27)
	Q4	1.25 (1.08, 1.46)**	1.23 (1.06, 1.43)**	1.27 (1.09, 1.48)**	1.15 (1.00, 1.31)	1.17 (1.04, 1.33)*	1.21 (1.07, 1.37)**
Central obesity	Q2	1.13 (1.00, 1.28)	1.12 (0.99, 1.26)	1.12 (1.00, 1.27)	1.04 (0.93, 1.17)	1.09 (0.98, 1.21)	1.10 (0.98, 1.22)
	Q3	1.07 (0.94, 1.23)	1.08 (0.95, 1.23)	1.09 (0.95, 1.24)	0.98 (0.87, 1.10)	1.03 (0.93, 1.15)	1.05 (0.94, 1.17)
	Q4	1.22 (1.07, 1.39)**	1.23 (1.08, 1.40)**	1.25 (1.10, 1.43)**	1.10 (0.99, 1.22)	1.12 (1.02, 1.24)*	1.14 (1.03, 1.26)**
Hypertriglyceride	Q2	1.31 (1.11, 1.55)**	1.30 (1.10, 1.52)**	1.30 (1.11, 1.15)**	0.97 (0.73, 1.29)	1.04 (0.78, 1.37)	1.06 (0.81, 1.41)
	Q3	1.05 (0.87, 1.27)	1.09 (0.90, 1.31)	1.10 (0.91, 1.32)	1.11 (0.86, 1.45)	1.23 (0.95, 1.59)	1.30 (1.00, 1.68)*
	Q4	1.25 (1.03, 1.50)*	1.33 (1.11, 1.59)**	1.38 (1.15, 1.66)**	1.31 (1.02, 1.68)*	1.33 (1.05, 1.69)*	1.43 (1.12, 1.82)**
Low-HDL-C	Q2	1.22 (1.09, 1.36)**	1.23 (1.10, 1.36)**	1.23 (1.11, 1.37)**	1.00 (0.91, 1.11)	1.01 (0.92, 1.12)	1.02 (0.92, 1.12)
	Q3	1.14 (1.01, 1.28)*	1.15 (1.02, 1.29)*	1.15 (1.02, 1.30)*	1.03 (0.94, 1.13)	1.05 (0.96, 1.15)	1.05 (0.96, 1.16)
	Q4	1.09 (0.96, 1.24)	1.12 (0.99, 1.27)	1.14 (1.00, 1.29)	1.04 (0.95, 1.13)	1.04 (0.95, 1.14)	1.04 (0.95, 1.14)
Hypertension	Q2	1.04 (0.96, 1.13)	1.03 (0.95, 1.12)	1.04 (0.96, 1.13)	0.98 (0.86, 1.13)	1.03 (0.92, 1.17)	1.05 (0.93, 1.19)
	Q3	1.00 (0.91, 1.10)	0.98 (0.89, 1.06)	0.99 (0.90, 1.08)	1.02 (0.90, 1.16)	1.13 (1.01, 1.27)*	1.16 (1.04, 1.30)*
	Q4	1.02 (0.93, 1.12)	0.96 (0.88, 1.06)	0.99 (0.90, 1.09)	1.13 (1.00, 1.28)*	1.16 (1.04, 1.29)**	1.20 (1.08, 1.33)**
Hyperglycemia	Q2	1.01 (0.91, 1.12)	0.99 (0.90, 1.08)	0.99 (0.90, 1.09)	0.87 (0.74, 1.02)	0.92 (0.79, 1.06)	0.94 (0.81, 1.09)
	Q3	1.00 (0.91, 1.11)	0.99 (0.89, 1.09)	0.99 (0.90, 1.10)	0.92 (0.79, 1.07)	1.03 (0.89, 1.18)	1.07 (0.93, 1.23)
	Q4	0.99 (0.90, 1.09)	0.96 (0.86, 1.06)	0.97 (0.88, 1.08)	0.98 (0.85, 1.13)	1.00 (0.87, 1.14)	1.05 (0.92, 1.20)

Notes: Q1-4 were grouped according to TSH quartiles. Model 1: unadjusted. Model 2: adjusted for age, smoking, drinking, red meat intake, sedentary time and menopause (in women). Model 3: further adjusted for free triiodothyronine (FT3), and free thyroxine (FT4). *P*-value <0.05 was considered significant. Significant level: **P*-value < 0.05; ***P*-value < 0.01 by Poisson regression analysis.

Abbreviations: PR, prevalence ratio; TSH, thyrotropin; Q, quartile; MetS, metabolic syndrome; HDL-C, high-density lipoprotein cholesterol.

which was consistent with our observations. One of the explanations for the lack of correlation between TSH in the normal range and blood glucose is the effect of thyroid hormone on promoting hepatic glucogenesis.[42]

The mechanism of the relationship between thyroid function and MetS does not appear to be well established. Thyroid hormones have essential physiologic roles in energy homeostasis and metabolism, and cardiovascular function. Individuals with high TSH levels within the normal range, had a higher risk of MetS and the components including obesity, dyslipidemia, and hypertension. A proinflammatory state probably contributes to the syndrome.[43–45] Obesity is an important element of MetS, and TSH is demonstrated to be independently associated with obesity in our and others' studies. TSH receptors are widely expressed in adipose tissue and this signaling pathway has been implicated in adipogenesis processes, suggesting that TSH itself may stimulate adipogenesis.[46–48] Leptin, secreted by adipocyte, has also been shown to stimulate the transcription of pro-thyrotropin-releasing hormone (TRH) and consequently also that of TSH.[49–51] A recent study has shown that leptin and adiponectin had an addictive and independent effect on the association between thyroid hormones and the components of MetS.[52] It has also been demonstrated that TSH promoted cholesterol synthesis in the liver and stimulated lipolysis in cultured adipocytes and the elevation of serum-free fatty acid levels in vivo.[53,54] Some studies found that TSH was also related to insulin resistance,[55] which was an important mediator for the effect of thyroid function on MetS.[14] In our study, we found that TSH was correlated with HOMA-IR, but this relation no longer remained significant after adjustment for age.

The strength of the present study is that we performed the analysis based on a large-scale community-based Chinese population, and evaluated the association between TSH and MetS stratified by gender before and after adjustment for the potential confounders. However, despite well-characterized covariate data allowing us to perform multivariable-adjusted analyses, the generalizability of the results needs to be cautious. In addition, as a cross-sectional study, we cannot infer causality on the association between TSH and MetS in euthyroid population. More longitudinal cohort studies and randomized clinical trials are to be warranted to confirm these associations.

Conclusion

In the present study, we found that the prevalence of MetS and its most components increased in participants with higher TSH quartile group in euthyroid population. The assessment of thyroid function may contribute to early identification and treatment of chronic metabolic diseases.

Ethical Approval and Informed Consent

The study was approved by the ethics committee of Peking University Health Science Center (No. IRB00001052-12022). All procedures in the study were performed in accordance with the ethical standards of the Declaration of Helsinki. All participants gave written informed consent.

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Disclosure

The authors report no conflicts of interest in this work.

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