Research Paper

Estimated change in prevalence of abnormal thyroid-stimulating hormone levels in China according to the application of the kit-recommended or NACB standard reference interval

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A B S T R A C T

Background: Both the kit-recommended and United States National Academy of Clinical Biochemistry (NACB) standard thyroid-stimulating hormone (TSH) reference intervals (RIs) are used to determine thyroid dysfunction in clinical practice and epidemiological surveys in China. However, a number of kit-recommended RIs were derived from the European or United States reference population.

Methods: A nationally representative cross-sectional study with 78,470 enrolled participants aged 18 years or older from China was performed. Serum concentrations of thyroid hormones, TSH, thyroid antibodies (by Roche Diagnostics), and urine iodine concentration (UIC) were measured.

Findings: The abnormal TSH weighted prevalence was 15.33% (95% CI, 14.24% to 16.49%) according to the kit-recommended RI and 6.89% (6.46% to 7.34%) according to the NACB standard RI. The NACB standard prevalence of abnormal TSH was associated with an absolute change in abnormal TSH prevalence of −11.20% (−12.23% to −10.18%) among women. When estimating the proportion of supranormal TSH levels according to background characteristics, the NACB standard definition decreased the prevalence by more than 10% in some categories, with the highest absolute difference of −13.92% (−15.52% to −12.33%) observed among the elderly, −12.85% (−13.68% to −12.02%) among those with UIC ≥300 μg/L, and −12.15% (−13.02% to −11.28%) among non-smokers. For subnormal TSH, with the highest absolute difference of 3.17% (2.74% to 3.61%) observed among regular smokers, 3.11% (2.49% to 3.74%) among the elderly, and 2.53% (2.29% to 2.77%) among those with BMI <25.

Interpretation: For adults in China, the NACB standard RI of TSH reveals a lower estimated prevalence of supranormal TSH levels than the kit-recommended RI. Because of the public health significance of overt and subclinical hypothyroidism and the very large population base in China, the TSH RI should be further assessed.

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1. Introduction

Thyroid dysfunction has multiple effects on public health. Previous research indicates that a large proportion of people with thyroid dysfunction are unaware of their condition [1]. In the absence of pituitary or hypothalamic disease, the thyroid-stimulating hormone (TSH) test is the best diagnostic tool for thyroid dysfunction and is recommended as a first-line test in diagnostic algorithms [2].

Supranormal TSH levels have been reported to be associated with an increased risk of higher serum lipid levels and atherosclerosis [3-5]. In addition, subnormal TSH levels have been related to increased risks of atrial fibrillation, fractures, and cardiovascular mortality [6-9]. Some professional thyroid societies recommend screening for thyroid dysfunction in high-risk populations (such as pregnant women and elderly individuals) to promote early diagnosis and reduce morbidity and mortality [10,11].

The diagnostic accuracy of thyroid dysfunction is mainly affected by the validity of the serum TSH reference interval (RI). The accurate definition of an RI is extremely important in laboratories, but the use of reference values still remains unsatisfactory [12,13]. The TSH RI was reported to be influenced by age, coexistent acute or chronic

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Research in context

Evidence before this study

We searched PubMed for studies published up to 1 Oct 2020 with the search terms "abnormal TSH" and "China" and "reference interval" with no language or date restrictions. The estimated changes in abnormal thyroid-stimulating hormone (TSH) prevalence among adults in China following application of the kit-recommended and National Academy of Clinical Biochemistry (NACB) standard reference interval (RI) was unknown.

Added value of this study

Using data from a nationally representative survey conducted in China, the estimated prevalence of abnormal TSH levels was 15.33% according to the kit-recommended RI; this value is 8.45% higher than that according to the NACB standard RI (6.89%).

Implications of all the available evidence

Implementing the NACB standard RI of TSH results in a lower estimated prevalence of abnormal TSH levels; the TSH RI should be further assessed to avoid overdiagnosis and overtreatment.

illness, type of assay used, iodine status, and ethnicity [14]. The United States National Academy of Clinical Biochemistry (NACB) proposed the criteria for the establishment of new TSH RI, including individuals with no detectable thyroid autoantibodies, thyroid peroxidase antibodies (TPOAb), or thyroglobulin antibodies (TgAb); individuals with no personal or family history of thyroid dysfunction; individuals with no visible or palpable goiter; and individuals who did not receive any medications except estrogen [15]. However, the kit-recommended RI was typically established by measuring the serum concentrations in an apparently healthy population without further characterization of the thyroid and clinical chemical or demographic data [16-22]. A number of studies to date have established normal serum TSH intervals based on reference populations according to the standard of the NACB criteria in some countries [15,23-25]. Although prior studies have estimated the prevalence of thyroid disorders using the NACB standard RI, numerous studies have determined the prevalence of this condition using the kit-recommended RI, which is also commonly used in epidemiological surveys [26-30]. It is estimated that a difference in the change in the prevalence of abnormal TSH levels between the two RIs could be of particular concern because there is not only a lack of national data but also an increasing burden of global medical resources.

As a country with mild-to-moderate iodine deficiency, China has already transformed the iodine intake of the population from deficient to adequate after the long-term mandatory universal salt iodization program was enacted through timely adjustments [27]. Although a decrease in the prevalence of most thyroid disorders was observed, a relatively high prevalence of subclinical hypothyroidism of 12.93% was previously reported by our group, representing 136 million patients in China [27]. Our recent study has also highlighted that the prevalence of subclinical hypothyroidism diagnosed according to the kit-recommended RI and the NACB standard RI in that population differed significantly [31]. However, it remains unclear how many of these millions of individuals have been classified as having abnormal thyroid function due to differences between the kit-recommended RI and whether applying the NACB standard RI would make a difference.

The aim of this study was to further estimate the prevalence of abnormal TSH levels among adults (aged 18 years and older) in China after applying the kit-recommended and NACB standard RIs. In addition, we compared the NACB criteria prevalence with the kit-

recommended RI prevalence to determine the absolute differences in the prevalence of this condition according to subnormal/supranormal TSH level and background characteristics.

2. Methods

2.1. Data source

This study analyzed the national cross-sectional survey dataset of the Thyroid disorders, Iodine status and Diabetes Epidemiological survey (TIDE study) [27]. The survey was implemented from 2015 to 2017 and included all 31 provinces of mainland China. The main objective of this survey was to provide updated national estimates of endocrine and metabolic indicators. The Chinese Society of Endocrinology and the Chinese Thyroid Association provided necessary assistance during the survey process. The research protocols were approved by the Medical Ethics Committee of China Medical University.

2.2. Study population and survey design

We previously described the study design in detail, and a detailed flowchart of the study design can also be found in Supplementary Figure [27,31-34]. Briefly, the study had four stages of random sampling from urban and rural locations that were conducted in parallel (Supplementary Figure 1). An updated version of the frame from the 2010 national census data of China was used in the sampling frame [35]. The inclusion criteria of the adult respondents were as follows: aged 18 years and older, residence in the selected community for at least 5 years, no use of iodine drugs or contrast agents within 3 months, and not pregnant. All subjects provided written informed consent following a thorough explanation of the research procedures. With an overall response rate of 92.08%, 80,937 participants completed the study. Among them, 2467 subjects were excluded owing to missing information on sex, age, or thyroid function tests, and 78,470 samples remained eligible for analysis (Supplementary Figure 1).
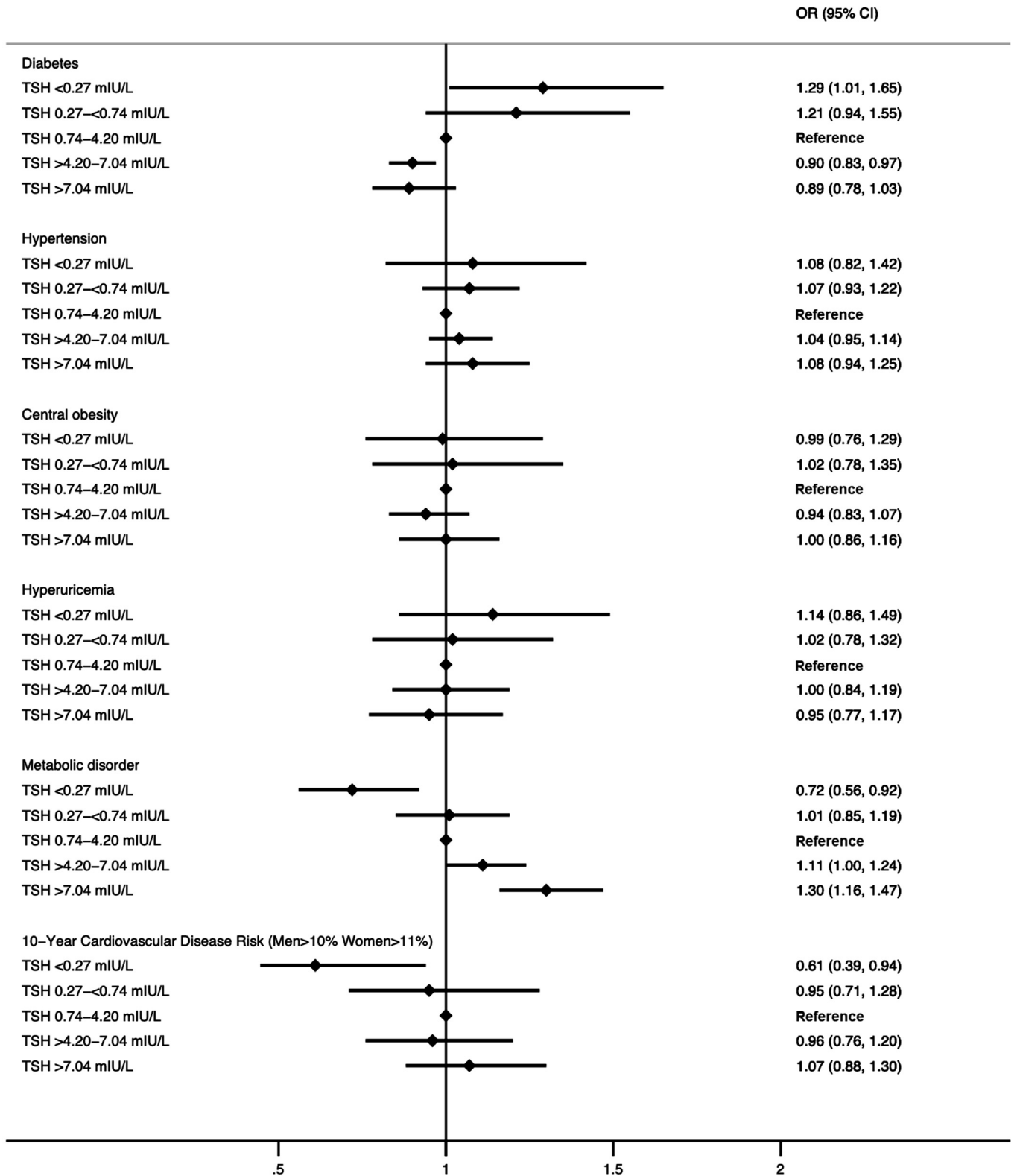
2.3. Measurements

From each participant, fasting blood and spot urine samples were collected. All participants underwent thyroid ultrasonography by qualified observers, who had trained and passed examination in the project center, using a portable instrument (LOGIQ 100 PRO; GE, Milwaukee, WI with 7.5 MHz linear transducers). Serum TSH, thyroid peroxidase antibodies (TPOAb), and thyroglobulin antibodies (TgAb) were measured using an electrochemiluminescence immunoassay on a Cobas 601 analyzer (Roche Diagnostic, Switzerland). Serum samples were also used for the measurements of fasting plasma glucose levels and two hour plasma glucose levels after carrying out an oral 75 g glucose tolerance test. HbA1c was measured in venous blood samples by high performance liquid chromatography (Bio-Rad VARIANT II Haemoglobin Analyzer). In people with self-reported diabetes, only fasting plasma glucose and HbA1c were measured. Fasting plasma glucose, two hour plasma glucose levels, serum total cholesterol (TC), low density lipoprotein cholesterol (LDL), high density lipoprotein cholesterol (HDL), and triglycerides were measured using an automatic biochemical analyser (Mindray BS-180 Analyzer) in the central laboratory in Shenyang.

The RIs for TSH, free thyroxine (fT4), free triiodothyronine (fT3), TPOAb, and TgAb were 0.27 to 4.20 mIU/L, 12.0 to 22.0 pmol/L, 3.1 to 6.8 pmol/L, $\leq$34.0 IU/mL, and $\leq$115.0 IU/mL, respectively, and were provided by the test kit manufacturers. A higher RI for TSH of $0.74-7.04$ mIU/L was established based on the NACB criteria in the reference population of the TIDE study in a previous study [22]. The RI of TSH was reported as 2.5th to 97.5th empirical percentiles from the selected reference population. Serum fT4 and fT3 levels were measured only if TSH was outside the reference range according to the kit manufacturers or the NACB criteria. Urinary iodine concentration (UIC) was

OR (95% CI)

Diabetes

TSH <0.27 mIU/L	1.29 (1.01, 1.65)
TSH 0.27–<0.74 mIU/L	1.21 (0.94, 1.55)
TSH 0.74–4.20 mIU/L	Reference
TSH >4.20–7.04 mIU/L	0.90 (0.83, 0.97)
TSH >7.04 mIU/L	0.89 (0.78, 1.03)

Hypertension

TSH <0.27 mIU/L	1.08 (0.82, 1.42)
TSH 0.27–<0.74 mIU/L	1.07 (0.93, 1.22)
TSH 0.74–4.20 mIU/L	Reference
TSH >4.20–7.04 mIU/L	1.04 (0.95, 1.14)
TSH >7.04 mIU/L	1.08 (0.94, 1.25)

Central obesity

TSH <0.27 mIU/L	0.99 (0.76, 1.29)
TSH 0.27–<0.74 mIU/L	1.02 (0.78, 1.35)
TSH 0.74–4.20 mIU/L	Reference
TSH >4.20–7.04 mIU/L	0.94 (0.83, 1.07)
TSH >7.04 mIU/L	1.00 (0.86, 1.16)

Hyperuricemia

TSH <0.27 mIU/L	1.14 (0.86, 1.49)
TSH 0.27–<0.74 mIU/L	1.02 (0.78, 1.32)
TSH 0.74–4.20 mIU/L	Reference
TSH >4.20–7.04 mIU/L	1.00 (0.84, 1.19)
TSH >7.04 mIU/L	0.95 (0.77, 1.17)

Metabolic disorder

TSH <0.27 mIU/L	0.72 (0.56, 0.92)
TSH 0.27–<0.74 mIU/L	1.01 (0.85, 1.19)
TSH 0.74–4.20 mIU/L	Reference
TSH >4.20–7.04 mIU/L	1.11 (1.00, 1.24)
TSH >7.04 mIU/L	1.30 (1.16, 1.47)

10–Year Cardiovascular Disease Risk (Men>10% Women>11%)

TSH <0.27 mIU/L	0.61 (0.39, 0.94)
TSH 0.27–<0.74 mIU/L	0.95 (0.71, 1.28)
TSH 0.74–4.20 mIU/L	Reference
TSH >4.20–7.04 mIU/L	0.96 (0.76, 1.20)
TSH >7.04 mIU/L	1.07 (0.88, 1.30)

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Fig. 1. Adjusted odds ratio for diabetes, hypertension, central obesity, hyperuricemia, metabolic disorder, and 10-year cardiovascular disease risk between different TSH groups*
* Adjusted for age, sex, BMI and smoke.

determined using inductively coupled plasma mass spectrometry (Agilent 7700x; Agilent Technologies, Santa Clara, CA). Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Positive TPOAb and positive TgAb were defined as TPOAb >34 IU/mL and TgAb >115 IU/mL, respectively.

2.4. Definition of abnormal TSH levels

According to the kit-recommended RI of TSH, individuals who had a TSH level outside of 0.27 to 4.20 mIU/L were categorized as having abnormal TSH levels, individuals who had a TSH level lower than

Table 1
Background characteristics of the weighted survey participants[a].

Characteristics	All participants (N = 78,470),% (95%CI)	Participants with subnormal TSH		Participants with supranormal TSH	
		Kit-recommended (n = 954),% (95%CI)	NACB criteria(n = 2796),% (95%CI)	Kit-recommended (n = 12,197),% (95%CI)	NACB criteria(n = 3095),% (95%CI)
Sex					
Men	50.55 (50.27 to 50.84)	35.38 (29.97 to 41.19)	47.92 (45.16 to 50.68)	38.10 (36.86 to 39.36)	35.89 (32.94 to 38.95)
Women	49.45 (49.16 to 49.73)	64.62 (58.81 to 70.03)	52.08 (49.32 to 54.84)	61.90 (60.64 to 63.14)	64.11 (61.05 to 67.06)
Age group, years					
18−39	46.02 (43.65 to 48.41)	45.08 (39.92 to 50.34)	38.26 (33.47 to 43.30)	38.46 (35.58 to 41.44)	31.57 (28.52 to 34.78)
40−59	37.10 (36.08 to 38.14)	39.57 (35.24 to 44.08)	41.79 (38.40 to 45.26)	38.47 (36.49 to 40.48)	41.12 (38.22 to 44.08)
≥60	16.88 (15.51 to 18.34)	15.35 (12.24 to 19.07)	19.95 (16.47 to 23.95)	23.07 (21.19 to 25.07)	27.31 (25.17 to 29.56)
BMI					
<25	63.03 (61.77 to 64.28)	70.52 (65.17 to 75.36)	68.73 (65.71 to 71.60))	61.88 (60.32 to 63.41)	58.61 (55.41 to 61.74)
25-<30	30.69 (29.67 to 31.73)	24.54 (20.71 to 28.82)	26.57 (24.04 to 29.27)	31.53 (30.21 to 32.88)	34.64 (31.72 to 37.68)
≥30	6.28 (5.96 to 6.61)	4.93 (3.42 to 7.07)	4.69 (3.78 to 5.82)	6.59 (5.94 to 7.30)	6.75 (5.75 to 7.90)
UIC, μg/L					
<100	17.82 (15.78 to 20.06)	18.52 (14.27 to 23.68)	18.91 (15.32 to 23.12)	17.44 (15.75 to 19.28)	19.94 (17.85 to 22.22)
100−299	63.44 (61.71 to 65.14)	52.44 (47.59 to 57.24)	58.55 (56.07 to 60.99)	60.36 (58.72 to 61.98)	58.21 (55.09 to 61.27)
≥300	18.74 (16.88 to 20.75)	29.04 (24.39 to 34.18)	22.53 (19.50 to 25.89)	22.19 (20.01 to 24.55)	21.85 (18.94 to 25.06)
BMI	23.98 (23.85 to 24.11)	23.47 (22.95 to 23.99)	23.61 (23.37 to 23.85)	24.12 (23.99 to 24.24)	24.31 (24.05 to 24.58)
UIC, μg/L	177.89 (117.99 to 263.90)	198.09 (120.90 to 326.64)	183.06 (117.67 to 281.90)	183.00 (119.79 to 281.37)	179.82 (111.57 to 274.46)
TSH, mIU/L	2.28 (1.57 to 3.31)	0.03 (0.01 to 0.10)	0.47 (0.10 to 0.63)	5.42 (4.69 to 6.88)	9.05 (7.82 to 12.34)
Positive TPOAb	10.19 (9.84 to 10.55)	48.76 (44.10 to 53.43))	23.35 (20.31 to 26.69)	22.29 (20.77 to 23.89)	39.46 (35.57 to 43.49)
Positive TgAb	9.70 (9.31 to 10.10)	40.42 (36.58 to 44.37)	19.13 (16.62 to 21.92)	20.57 (19.14 to 22.07)	35.93 (33.08 to 38.88)

[a] For categorical variables, data were presented as% (95% CI); for continuous variables (BMI), data were presented as mean (95% CI); for continuous variables (UIC and TSH), data were presented as median (interquartile ranges).

0.27 mIU/L were categorized as having subnormal TSH levels, and individuals who had a TSH level greater than 4.20 mIU/L were categorized as having supranormal TSH levels.

According to the NACB standard RI of TSH, individuals who have a TSH outside the range of 0.74 to 7.04 mIU/L were categorized as having abnormal TSH levels, individuals who have a TSH level lower than 0.74 mIU/L were categorized as having subnormal TSH levels, and individuals who have a TSH level greater than 7.04 mIU/L were categorized as having supranormal TSH levels.

2.5. Outcome assessment

Diabetes was defined as 1) self-reported diabetes or taking hypoglycemic drugs, or 2) fasting plasma glucose ≥7.0 mmol/L, or 3) 2 h plasma glucose ≥11.1 mmol/L, or 4) HbA1c ≥6.5% [36]. Hypertension was defined as 1) taking antihypertensive medications, or 2) SBP ≥140 mmHg, or 3) DBP ≥90 mmHg [37]. Central obesity was defined as waist circumference ≥90 cm in men and ≥80 cm in women [38]. Hyperuricemia was define as uric acid ≥420 μmol/L [39]. Metabolic disorder was defined as 1) triglyceride ≥1.7 mmol/L, or 2) TC ≥5.2 mmol/L, or 3) LDL ≥3.4 mmol/L, or 4) HDL <1.0 mmol/L in men and HDL <1.3 mmol/L in women [40]. The Framingham risk score (FRS) was calculated by adding the scores for the six main coronary risk factors: sex, age, HDL, TC, systolic blood pressure, and smoking habit. The 10-year Cardiovascular Disease (CVD) risk (as a percentage) was determined from the total score [41].

2.6. Statistical analysis

To account for the complex sampling design of this study, we used SUDAAN software (Research Triangle Institute) to obtain estimates of prevalence and the standard errors according to the Taylor linearization method. Estimates were weighted to reflect age, sex, and urban-rural distribution of provinces of the adults living in China. Weighting coefficients were derived from the 2010 Chinese population census data, and the sampling scheme of our survey was designed to obtain a national estimate. Categorical data are presented as percentages and 95% confidence intervals. Chi-square test was used to test differences between groups for categorical data. The POLYNOMIAL statement was used to assess significant linear trend and quadratic trend for the levels of an ordinal group. The prevalence was estimated for both RIs of TSH; we

then estimated the absolute differences between the prevalence of abnormal TSH levels according to the two RIs. The normality of the continuous variables was assessed, and variables with a skewed distribution were reported with medians and interquartile ranges (IQRs), otherwise continuous data are presented as the means and 95% CIs. Adjusted odds ratios (ORs) with 95% CIs were calculated by multivariable logistic regression to examine the association between the five TSH categories with the prevalence of diabetes, hypertension, central obesity, hyperuricemia, metabolic disorder and 10-year CVD risk. Two sets of sensitivity analysis for odds ratio were undertaken. First, three models with progressively increased adjustment of risk factors among all participants were applied. Second, considering that abnormal TSH prevalence differs according to sex and age, we stratified participants according to age and sex group for analysis. A p-value of <0.05 was considered statistically significant.

2.7. Role of the funding source

The funders had no role in the execution of this study or the interpretation of the results.

3. Results

A total of 78,470 participants were included in this analysis. The mean age of the respondents was 43 (95% CI, 42 to 44; Range, 18 to 107) years, the BMI ranged from 12.70 to 64.93, the UIC ranged from 5 to 35,177 μg/L (not shown), and 49.45% (95% CI, 49.16% to 49.73%) were women (Table 1). Overall, the median TSH was 2.28 (IQR 1.57 to 3.31; Range, 0.005 to 100) mIU/L (not shown). The kit-recommended RI identified 13,151 participants (15.33%) as having abnormal TSH levels, while the NACB criteria categorized 5891 people (6.89%) as having abnormal TSH levels (Table 2). The prevalence of positive thyroid antibodies were higher among participants categorized as having abnormal TSH levels according to the NACB criteria than those categorized as having abnormal TSH using the kit-recommended RI (Table 1).

Table 2 summarizes the weighted prevalence (95% CI) of abnormal TSH levels among men and women according to the two RIs, along with the absolute difference in prevalence according to the kit-recommended RI and the NACB criteria. The weighted prevalence of abnormal TSH levels was 15.33% (95% CI, 14.24% to 16.49%) according to the kit-recommended RI, compared with 6.89% (95% CI, 6.46% to

Table 2
Weighted prevalence and absolute changes in prevalence according to kit-recommended interval and NACB standard interval by sex.

Sex	Prevalence based on kit-recommended interval,% (95% CI)	Prevalence based on NACB standard interval,% (95% CI)	Absolute difference,% (95% CI)
Men			
Normal TSH	88.51 (87.50 to 89.45)	94.26 (93.86 to 94.63)	5.75 (4.99 to 6.51)
Abnormal TSH	11.49 (10.55 to 12.50)	5.74 (5.37 to 6.14)	−5.75 (−6.51 to −4.99)
Subnormal TSH	0.86 (0.72 to 1.03)	3.39 (3.14 to 3.66)	2.53 (2.30 to 2.77)
Supranormal TSH	10.63 (9.74 to 11.59)	2.35 (2.06 to 2.68)	−8.28 (−8.95 to −7.61)
Women			
Normal TSH	80.74 (79.33 to 82.07)	91.94 (91.25 to 92.57)	11.2 (10.18 to 12.23)
Abnormal TSH	19.26 (17.93 to 20.67)	8.06 (7.43 to 8.75)	−11.20 (−12.23 to −10.18)
Subnormal TSH	1.61 (1.39 to 1.85)	3.77 (3.40 to 4.18)	2.16 (1.92 to 2.41)
Supranormal TSH	17.66 (16.35 to 19.05)	4.29 (3.82 to 4.82)	−13.37 (−14.35 to −12.38)
Overall			
Normal TSH	84.67 (83.51 to 85.76)	93.11 (92.66 to 93.54)	8.45 (7.6 to 9.29)
Abnormal TSH	15.33 (14.24 to 16.49)	6.89 (6.46 to 7.34)	−8.45 (−9.29 to −7.60)
Subnormal TSH	1.23 (1.11 to 1.36)	3.58 (3.32 to 3.85)	2.35 (2.14 to 2.56)
Supranormal TSH	14.11 (13.05 to 15.24)	3.31 (2.98 to 3.68)	−10.8 (−11.59 to −10.01)

7.34%) according to the NACB criteria. Approximately one-fifth of women had abnormal TSH levels according to the kit-recommended RI (19.26%; 95% CI, 17.93% to 20.67%), compared with 11.49% (95% CI, 10.55% to 12.50%) of men. The prevalence of abnormal TSH levels according to the NACB criteria was 5.74% (95% CI, 5.37% to 6.14%) among men and 8.06% (95% CI, 7.43% to 8.75%) among women. According to the NACB criteria, the weighted prevalence of abnormal TSH levels was 8.45% (95% CI, 9.29% to 7.60%) lower in the overall population. Women had the highest absolute decrease in prevalence of supranormal TSH levels with a decrease of 13.37% (95% CI, 14.35% to 12.38%). A percentage decrease was observed for supranormal TSH levels in both sexes. The overall absolute increases in the prevalence of subnormal TSH levels among men and women were 2.53% (95% CI, 2.30% to 2.77%) and 2.16% (95% CI, 1.92% to 2.41%), respectively.

Among the categories of individuals with subnormal TSH levels (Table 3), a significant trend of absolute difference was seen in age and smoking groups. A higher absolute increase in prevalence was observed among people aged 60 years and older (3.11%; 95% CI, 2.49% to 3.74%), those with a BMI less than 25 (2.53%; 95% CI, 2.29% to 2.77%), and among regular smokers (3.17%; 95% CI, 2.74% to 3.61%). Regarding supranormal TSH levels, a significant trend of absolute difference was seen in age, UIC, and smoking groups. A greater prevalence reduction occurred in participants aged 60 years and older (−13.92%; 95% CI, −15.52% to −12.33%), those with a UIC of 300 μg/L or greater (−12.85%; 95% CI, −13.68% to −12.02%), and among non-smokers (−12.15%; −13.02% to −11.28%).

In order to further explain the applicability of the RI obtained in this study, we divided the population into five groups according to their serum TSH level. Group 1 contained individuals with serum TSH level less than 0.27 mIU/L; group 2 with serum TSH level 0.27 mIU/L to less than 0.74 mIU/L; group 3 with serum TSH level 0.74 mIU/L to 4.20 mIU/L; group 4 with serum TSH level more than 4.20 mIU/L to 7.04 mIU/L; and group 5 with serum TSH level more than 7.04 mIU/L. Then, we analyzed risk factor for diabetes, hypertension, central obesity, hyperuricemia, metabolic disorder, and 10-year CVD risk in the five groups. As shown in Fig. 1, compared with the reference group (group 3), no significantly higher risk of those disorders and 10-year CVD risk were observed in group 2 (TSH 0.27 mIU/L to <0.74 mIU/L) and group 4 (TSH >4.20 mIU/L to 7.04 mIU/L), however, a higher risk of diabetes was observed in group 1 (TSH <0.27 mIU/L), and a higher risk of metabolic disorders was seen in group 5 (TSH >7.04 mIU/L). Sensitivity analysis with logistic models for odds ratio was provided in Fig. 1 and Supplementary Figure 2. The results remained stable after adjustment for risk factors. Subgroup analysis was performed based on sex and age group (Supplementary Figure 3), a higher risk of metabolic disorder was found in group 4 compared with the reference group among women and individuals aged 18 to 39 years old.

4. Discussion

We investigated the change in the estimated prevalence of abnormal TSH levels in China according to the two RIs of TSH. According to the kit-recommended RI, 15.33% of adults in China were considered to have thyroid dysfunction. These findings reclassified 10.8% of adults as having supranormal TSH levels who were categorized as normal TSH levels according to the NACB criteria.

A very high RI of TSH with 0.74 to 7.04 mIU/L established based on the NACB criteria was found in this population, which is comparable to the TSH range of 0.62 to 6.84 mIU/L recently reported by a study from South Korea and is presumably due to the high iodine intake in both countries [25]. The kit-recommended RI of TSH suggested a lower TSH level threshold for the diagnosis of supranormal TSH levels based on the reference population from the European (0.27 to 4.20 mIU/L) [42]. To further explain the applicability of the NACB RI obtained in this study, we compared the risk of several metabolic disorders between individuals with different TSH groups. Individuals with serum TSH of 0.27 to 0.74 mIU/L and those with serum TSH of 4.20 to 7.04 mIU/L did not confer a higher risk. However, the results of subgroup analysis also indicated that participants with serum TSH of 4.20 to 7.04 mIU/L had an increasing risk of metabolic disorder among women and young characters. More appropriate studies are needed to confirm that whether the NACB RI reported here is safe and reasonable.

Applying the Chinese population RI of TSH should have a significant impact on hypothyroidism prevention and management in China, where more than one-eighth of the adult population was previously classified as having subclinical hypothyroidism according to the kit-recommended RIs of thyroid function [27]. In addition, the marginally raised TSH levels may be contributing to some individuals being treated unnecessarily, given the evidence of substantial overuse of levothyroxine [43].

Despite the similar absolute difference in prevalence of supranormal TSH levels regardless of background characteristics, a larger absolute difference prevalence was seen in some background characteristics, such as individuals with an older age, with a higher UIC, and non-smokers. As reported previously, the serum TSH concentration is influenced by factors such as age, sex, race, region, and method of determination [31]. The determinants of abnormal TSH levels are beyond the scope of this discussion; however, studies that investigated risk factors for thyroid dysfunctions in China found a higher likelihood of subclinical hypothyroidism among individuals who had a higher UIC [27]. It is still unclear that elevated TSH in individuals with higher UIC is a shift of the normal range although we previously concluded that upper limits of the NACB RI was acceptable. More cohort studies are needed to confirm this assumption. Therefore, these high-risk groups still require more awareness of subclinical

Table 3
Weighted prevalence of abnormal TSH in both sexes according to selected demographic characteristics.

Demographic Characteristics	Prevalence of subnormal TSH,% (95% CI)			Prevalence of supranormal TSH,% (95% CI)		
	Kit-recommended	NACB criteria	Absolute difference	Kit-recommended	NACB criteria	Absolute difference
Age group, years						
18−39	1.20 (1.06 to 1.37)	2.98 (2.67 to 3.31)	1.77 (1.52 to 2.03)	11.79 (10.97 to 12.67)	2.27 (2.00 to 2.58)	−9.52 (−10.21 to −8.83)
39−59	1.31 (1.12 to 1.53)	4.03 (3.55 to 4.58)	2.72 (2.31 to 3.13)	14.62 (13.25 to 16.12)	3.67 (3.24 to 4.15)	−10.95 (−12.03 to −9.88)
≥60	1.12 (0.86 to 1.45)	4.23 (3.52 to 5.08)	3.11 (2.49 to 3.74)	19.28 (17.25 to 21.49)	5.36 (4.69 to 6.12)	−13.92 (−15.52 to −12.33)
P for difference	0.41	0.01	0.001	<0.0001	<0.0001	<0.0001
P for linear trend	0.58	0.007	0.0002	<0.0001	<0.0001	<0.0001
P for quadratic trend	0.19	0.14	0.28	0.11	0.51	0.11
BMI						
<25	1.38 (1.25 to 1.52)	3.91 (3.66 to 4.17)	2.53 (2.29 to 2.77)	13.85 (12.67 to 15.12)	3.08 (2.68 to 3.54)	−10.77 (−11.62 to −9.92)
25-<30	0.98 (0.78 to 1.24)	3.10 (2.76 to 3.48)	2.12 (1.86 to 2.38)	14.49 (13.49 to 15.55)	3.74 (3.38 to 4.13)	−10.75 (−11.61 to −9.89)
≥30	0.97 (0.65 to 1.45)	2.68 (2.04 to 3.51)	1.71 (1.20 to 2.22)	14.81 (13.28 to 16.49)	3.56 (3.04 to 4.17)	−11.25 (−12.63 to −9.87)
P for difference	0.01	0.0001	0.005	0.25	0.0003	0.24
P for linear trend	0.05	0.02	0.76	0.35	0.97	0.12
P for quadratic trend	0.96	0.03	0.10	0.86	0.13	0.17
UIC, μg/L						
<100	1.27 (1.09 to 1.49)	3.80 (3.32 to 4.34)	2.52 (2.10 to 2.94)	13.80 (12.25 to 15.50)	3.70 (3.08 to 4.42)	−10.10 (−11.23 to −8.98)
100−299	1.01 (0.89 to 1.15)	3.30 (3.03 to 3.59)	2.29 (2.05 to 2.52)	13.41 (12.33 to 14.57)	3.03 (2.69 to 3.41)	−10.38 (−11.24 to −9.52)
≥300	1.90 (1.50 to 2.40)	4.30 (3.80 to 4.86)	2.40 (2.14 to 2.67)	16.70 (15.49 to 17.97)	3.85 (3.31 to 4.48)	−12.85 (−13.68 to −12.02)
P for difference	0.003	0.002	0.61	<0.0001	0.009	0.0001
P for linear trend	0.008	0.16	0.53	0.008	0.70	0.0009
P for quadratic trend	0.002	0.0004	0.18	<0.0001	0.003	0.0004
Cigarette smoking						
Current non-smoker	1.33 (1.18 to 1.51)	3.45 (3.16 to 3.76)	2.11 (1.91 to 2.32)	15.87 (14.69 to 17.12)	3.72 (3.33 to 4.15)	−12.15 (−13.02 to −11.28)
Occasional smoker	0.81 (0.54 to 1.20)	2.92 (1.98 to 4.28)	2.11 (1.02 to 3.19)	11.26 (9.72 to 13.00)	1.94 (1.45 to 2.61)	−9.31 (−10.71 to −7.92)
Regular smoker	0.96 (0.78 to 1.18)	4.14 (3.71 to 4.61)	3.17 (2.74 to 3.61)	8.89 (8.03 to 9.83)	2.23 (1.91 to 2.60)	−6.66 (−7.33 to −5.99)
P for difference	0.007	0.007	0.0002	<0.0001	<0.0001	<0.0001
P for linear trend	0.005	0.002	<0.0001	<0.0001	<0.0001	<0.0001
P for quadratic trend	0.10	0.18	0.35	0.08	0.001	0.87

hypothyroidism to minimize complications or negative consequences associated with thyroid dysfunction.

A determination of the prevalence of thyroid dysfunction is necessary to begin to formulate public healthcare policy and programs, especially for universal salt iodization programs. Debate over the laboratory RI of serum TSH still exists. In fact, the definition of RIs has several pitfalls. A previous study concluded that no RI is completely "right" or "wrong" [44]. In this study, the prevalence of abnormal TSH levels based on the NACB criteria ranged between 5% and 8% among men and women, which is mainly because the RI in use refers to the central 95% of the reference population of Chinese adults. By definition, approximately 5% of all results from "healthy" people will fall outside of the reported RI and, as such, will be flagged as being "abnormal". Therefore, evaluating the degree of abnormal TSH levels in China according to the two RIs may be helpful in understanding the future research requirements needed to overcome this public health challenge.

Current guidelines recommend the use of TSH alone as the best method to detect and monitor thyroid dysfunction. When serum TSH is outside of the kit-recommended RI, further fT3 and fT4 testing are commonly ordered. Therefore, knowing exactly what the normal range is, and especially what the upper limit of the normal range is, is extremely important since a patient with elevated TSH levels but a normal fT4 concentration is considered to have a disease that has been termed subclinical hypothyroidism. Unnecessary testing of fT3 and fT4 can lead to added economic burden in an era of rising healthcare costs, while rarely contributing to the evaluation or management of thyroid disorders [45].

The strengths of this study include the generalizability of the findings to the Chinese population, as this survey covered both urban and rural areas of all provinces in this country, and the use of appropriate statistical methods to estimate the weighted prevalence of abnormal TSH levels in the study sample. The limitations of the current study also warrant discussion. First, we did not obtain results of fT3 or fT4 in participants with a normal TSH level owing to the study design, which reduced our ability to explore the RIs of free thyroid hormone. Second, the general conclusion may not apply to the specific population of

pregnant women. Given increased thyroid hormone requirement during pregnancy, increase in TSH interval may not be as safe and harmless as in the general population. Third, for the current type of data, we could only present the prevalence and 95% CI for comparison.

In conclusion, the results of our study indicate that a significant proportion of the adults in China who were categorized as having abnormal TSH levels according to the kit-recommended RI may be reclassified as having normal TSH levels. Considering the overdiagnosis and overtreatment associated with subclinical hypothyroidism, this condition is a potential public health challenge for China and other countries with similar ethnic characteristics. Our results signify the importance of determining a normal range of TSH levels to estimate ethnicity-specific burdens of thyroid dysfunction.

Declaration of Competing Interest

The authors declare no conflict of interests.

Author Contributions

Drs Zhongyan Shan, Weiping Teng and Yongze Li had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Zhongyan Shan, Weiping Teng.

Acquisition, analysis, or interpretation of data: Zhongyan Shan, Weiping Teng and Yongze Li.

Drafting of the manuscript: Yongze Li.

Statistical analysis: Yongze Li.

Obtained funding: Weiping Teng.

Administrative, technical or material support: All authors.

Study supervision: Zhongyan Shan, Weiping Teng, Yongze Li.

Data sharing statement

The data used during the current study are available from the corresponding author upon reasonable request.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.eclinm.2021.100723.

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