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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ABSTRACT

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% (2.29% to 2.77%) among non-smokers. For subnormal TSH, with the highest absolute difference of 3.17% (2.49% 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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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 were classified as having abnormal thyroid function due to differences between the kit-recommended RI and 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.

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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.

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**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, 2,467 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 0.2-4.20 mIU/L, 12.0 to 22.0 pmol/L, 3.1 to 6.8 pmol/L, <34.0 IU/mL, and <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 recommended RI prevalence to determine the absolute differences in the prevalence of this condition according to subnormal/supranormal TSH level and background characteristics.
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

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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.
method. Estimates were weighted to represent prevalence and the standard errors according to the Taylor linearization.  

2.6. Statistical analysis

Age group (years) was determined from the total score [41]. The 10-year Cardiovascular Disease (CVD) risk (as a percentage) was calculated by adding the scores for the six main coronary risk factors: 1) systolic blood pressure > 140 mmHg, or 2) diastolic blood pressure > 90 mmHg, 3) total cholesterol (TC) > 6.5 mmol/L, or 4) HDL cholesterol < 1.0 mmol/L in men [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 major 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].

2.7. 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 7.31%).
models for odds ratio was provided in Fig. 1 and Supplementary

Figure 2. The results remained stable after adjustment for risk fac-

Regarding supranormal TSH levels, a signi-

Table 2

| 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 | 10.61 (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)                          | 11.20 (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 (92.60 to 93.54)                          | 8.45 (7.60 to 9.29)            |
| Abnormal TSH | 15.33 (14.24 to 16.49)                            | 6.89 (6.46 to 7.34)                               | -5.45 (-6.29 to -4.70)         |
| 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)                               | -10.80 (-11.59 to -10.01)      |

4. Discussion

We investigated the change in the estimated prevalence of abnor-

mal 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. To further explain the applicability of the NACB RI obtained in this study, we compared the risk of several metabolic dis-

orders 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 signifi-
cant 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 over-

use of levothyroxine [43].

Despite the similar absolute difference in prevalence of supranor-

mal TSH levels regardless of background characteristics, a larger absolute difference prevalence was seen in some background character-

istics, 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 investigat-
ed 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
A previous study concluded that no RI is completely necessary for universal salt iodization programs. Debate over the laboratory thresholds needed to overcome this public health challenge.

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.

References
[1] Santos Palacios S, Llaverio Valero M, Brugos-Larumbe A, Díez J, Guillén-Grima F, Galafre JC. Prevalence of thyroid dysfunction in a large southern European population. Analysis of modulatory factors. The APWA study. Clin Endocrinol (Oxf) 2018;89(3):367–75.
[2] Lo Sasso B, Vidal M, Scaczone C, Agnello L, Ciaccio M. Reference interval by the indirect approach of serum thyrotropin (TSH) in a Mediterranean adult population and the association with age and gender. Clin Chem Lab Med 2019;57(10):1587–94.
[3] Selmer C, Olesen JB, Hansen ML, et al. Subclinical and overt thyroid dysfunction and risk of all-cause mortality and cardiovascular events: a large population study. J Clin Endocrinol Metab 2012;97(2):326–33.
[4] Orlando Z, Egizio R, Rebecchi L, et al. Reference interval of serum thyrotropin (TSH) in a Mediterranean adult population. Clin Chem Lab Med 2003;41(6):2438–44.
[5] Selmer C, Rebechi L, Egizio R, et al. Subclinical hypothyroidism and atrial fibrillation. Thyroid 2002;12(6):501–3.
[6] Blum MR, Bauer DC, Collet TH, et al. Subclinical thyroid dysfunction and fracture risk: a meta-analysis. JAMA 2015;313(20):2055–65.
[7] Sawin CT. Subclinical hyperthyroidism and atrial fibrillation. Thyroid 2002;12(6):501–3.
[8] Frost L, Vestergaard P, Moskilde L. Hyperthyroidism and risk of atrial fibrillation or flutter: a population-based study. Arch Intern Med 2004;164(15):1675–8.
[9] Seilm J, Olesen JB, Hansen ML, et al. Subclinical and overt thyroid dysfunction and risk of all-cause mortality and cardiovascular events: a large population study. J Clin Endocrinol Metab 2014;99(7):2372–82.
[10] Nebeker JR, Cobin RH, Gharib H, et al. Clinical practice guidelines for hypothyroidism in adults: cosponsored by the American association of clinical endocrinologists and the American thyroid association. Thyroid 2012;22(12):1200–8.
[11] Burks MR, Ortiz E, Daniels GH, et al. Subclinical thyroid disease: scientific review and guidelines for diagnosis and management. JAMA 2004;291(2):228–38.
[12] Sudanman JR, FW. Current concepts of “normal values,” “reference values,” and “discrimination values,” in clinical chemistry. Clin Chem 1975;21(13):1873–7.
[13] Gates HC. The evolution of the reference value concept. Clin Chem Lab Med 2000;42(7):692–7.
[14] Janczok M, Kottke M, Seibert K, et al. Reference intervals of serum thyroid function hormones on the ARCHITECT i2000 analyzer. Clin Chem Lab Med 2004;42:540–2.
[15] Zöllke H, Alt D, Kohlmann T, et al. Reference intervals of serum thyroid function tests in a previously iodine-deficient area. Thyroid 2005;15(3):279–85.
[16] Teng W, Shang Z, Teng X, et al. Effect of iodine intake on thyroid diseases in China. N Engl J Med 2006;354(26):2783–93.
[17] Kim M, Kim TY, Kim SH, et al. Reference interval for thyrotropin in a ultrasonography screened Korean population. Korean J Intern Med 2015;30(3):335–44.
[18] Ganie MA, Charoo BA, Sahar T, et al. Thyroid function, urinary iodine, and thyroid antibody status among the tribal population of Kashmir valley: data from endemic zone of a sub-Himalayan region. Front Public Health 2020;8:555840.
[19] Guo Y, Zynat J, Xu Z, et al. Iodine nutrition status and thyroid disorders: a cross-sectional study from the Xining autonomous region of China. Eur J Clin Nutr 2016;70:1322–32.
[20] Chobanian AV, Bakris GL, Black HR, et al. The seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure; national high blood pressure education program coordinat- ing committee. The seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure: the JNC 7 report. JAMA 2003;289(19):2506–72.
[21] Bao Y, Lu J, Wang C, et al. Optimal waist circumference cutoffs for abdominal obe- sity in Chinese. Atherosclerosis 2008;201:378–84.
[22] Hareland T, Hallden TD, Ytterberg B, et al. Reference values for thyrotropin in a Swedish population. Clin Chem Lab Med 2001;39(7):912–6.