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# Reference Range and Sociodemographic Characteristics of TSH among Reproductive Age Women in Rural China

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## Abstract

Appropriate reference range of thyroid-stimulating hormone (TSH) is important to interpreting the results of thyroid functional tests. However, the reference range and sociodemographic characteristics of TSH based on large-scale studies are yet to be declared in rural China. To clarify reference range and sociodemographic characteristics of TSH in reproductive age of women from rural China. A nationwide population-based study was conducted as The National Free Preconception Health Examination Project (NFPHEP). Nearly 400,000 ($n = 392{,}659$) of Chinese rural women aged 15–55 years were randomly recruited. Predetermined strict exclusion criteria made a number of 359,895 as the reference population. Serum TSH was evaluated with enzyme-linked immunosorbent assay (ELISA). The reference range of TSH on overall and reference population was 0.39–5.20 and 0.39–5.13 uIU/ml (2.5th–97.5th percentiles), respectively. In the reference population, the range (2.5th to 97.5th percentile) of serum TSH in different age groups was 0.40–5.03 uIU/ml, 0.39–5.15 uIU/ml, 0.37–6.10 uIU/ml, and 0.44–7.03 uIU/ml, respectively. The mean TSH value in women aged 26–35 years was 2.26 uIU/ml, significantly lower than those aged 36–45 ($p < 0.001$). The mean TSH values for eastern, central, and western regions were 2.28 uIU/ml, 2.29 uIU/ml, and 2.24 uIU/ml respectively. The mean of serum TSH concentration was significantly higher in central region than that in western region ($p \leq 0.001$). The TSH value 0.39–5.13 uIU/ml (2.5th–97.5th percentiles) was derived as a reference range of reproductive age women from rural China. We use the TSH ranges from reference population to diagnose hyperthyrotropinemia or hypothyroidism in different areas in China. The reference ranges for eastern, central, and western regions were 0.33–5.61 uIU/ml, 0.40–5.04 uIU/ml, and 0.40–4.98 uIU/ml (2.5th–97.5th percentiles) respectively. The value of serum TSH was associated with age, living region, smoking, drinking, educational level, and interpersonal tension, as well as life and economic pressure, but irrelevant to ethnicity or occupation.

**Keywords** Thyroid-stimulating hormone · Thyroid function · Reference interval · Subclinical hypothyroidism · Euthyroidism · Thyrotropin

**Abbreviations**

| | |
|---|---|
| TSH | Thyroid-stimulating hormone |
| fT4 | Free thyroxine |
| TPOAb | Thyroid peroxidase antibody |
| TgAb | Thyroglobulin antibody |
| NFPHEP | National Free Preconception Health Examination Project |
| ELISA | Enzyme-linked immunosorbent assay |
| NACB | National Academy of Clinical Biochemistry |

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## Introduction

Thyroid hormone is one of the most important hormones to ensure fetal normal growth and development. In the first 11 weeks of gestation, fetuses cannot produce thyroid hormone by themselves, so they still depend on maternal thyroid hormone. Pregnant women with hypothyroidism may exert a significantly negative impact on their children, especially during early pregnancy [1–4]. Understanding the thyroid function status of childbearing age women is vital for giving birth to healthy babies. The clinical definition of thyroid dysfunction derived from the reference ranges of TSH and thyroid hormones. Subclinical hypothyroidism or subclinical hyperthyroidism is defined as abnormally increased or decreased serum TSH level, respectively, with a normal serum-free thyroxine (fT4) level. The diagnosis of thyroid dysfunction, especially subclinical dysfunction, is heavily affected by the validity of the TSH reference range. However, the optimal reference value of serum TSH and clinical significance of subclinical thyroid dysfunction are still controversial [5]. In addition, it is difficult for the childbearing women to detect subclinical hypothyroidism in the early stage of pregnancy. The prevalence of subclinical hypothyroidism has been reported to vary from 3 to 12%, and that of subclinical hyperthyroidism to vary from 1 to 6% [6, 7]. Therefore, the National Academy of Clinical Biochemistry (NACB) suggested that the serum TSH reference range should be established in rigorously screened normal euthyroid volunteers without evidence of thyroid diseases [8].

There were several reference intervals derived from thyroid functional tests have been published [9–11]. Previously, the incidence and prevalence of hypothyroidism or hyperthyroidism of Chinese women have been reported by several studies [12–14]. However, a large nationwide epidemiological study evaluating the reference range of serum TSH has never been implemented in rural Chinese women of reproductive age. Therefore, the diagnosis and treatment of thyroid diseases in reproductive age women remain great challenges to physicians, especially in rural China. We aimed to perform a large-scale population-based study to assess the value of serum TSH in women aged 15–55 years, in order to provide valuable information on patterns of thyroid function in rural China. We also aimed to establish a universal reference range of serum TSH levels on different age groups of women in rural China based on the survey data obtained from the NFPHEP (2010 to 2012).

## Subjects and Methods

### Study Population

The data set was derived from the NFPHEP. This project was launched by the National Health and Family Planning Commission and Ministry of Finance in China, aiming to provide free health examination for rural married couples who planned to have babies. This study was a nationwide population-based data survey of the rural Chinese who were aged from 15 to 55 years living in 28 provinces of China mainland. Sample collection was performed from 1 January 2010 to 31 December 2012. Couples who planned to have a baby were randomly enrolled by local community staff and signed information consent. Free medical examination and counseling service were provided by well-trained local medical workers. Files were then recorded in a web-based electronic data collection system and sent to the NFPHEP office. The detailed protocol, organization, and implementation of this project were documented elsewhere [15, 16]. Missing data and the extreme values (e.g., TSH > 1000 uIU/ml) were excluded from the subsequent statistical analyses. Thus, the overall population included 392,659 women, while the reference population included 359,895 women.

### Study Design

For overall population, a standard questionnaire was used to collect the basic information on age, education level, occupation, ethnicity, residence address, medical history, drug history, family history, life pressure, economic pressure, and interpersonal tension. The overall population was defined as subjects that underwent thyroid function tests in the NFPHEP with a TSH value of ≤ 1000 uIU/ml. The reference population was defined as subjects without thyroid-related diseases or any other diseases that can cause changes in TSH levels, having any family diseases history, or taking any medications. Life pressure, economic pressure, and interpersonal tension were defined as socio-psychological factors which depend on participants' own feeling.

According to age distribution, the reference population was categorized into various age groups (15–25, 26–35, 36–45, and 46–55). As to residential addresses, participants from 28 provinces were divided into three regions: eastern region (including Beijing, Fujian, Guangdong, Jiangsu, Liaoning, Shandong, and Zhejiang), central region (including Anhui, Hainan, Hebei, Heilongjiang, Henan, Hubei, Hunan, Jiangxi, Jilin, and Shanxi), and western region (including Chongqing, Gansu, Guangxi, Guizhou, Inner Mongolia, Ningxia, Qinghai, Shaanxi, Sichuan, Yunnan, and Xinjiang).

### Serum Analysis

In order to evaluate serum TSH, approximately 5 ml of peripheral blood from each participate was collected. Within 30 min after separating the serum, the sample was transferred to the testing facility. Collected specimens were analyzed by ELISA kits within 24 h after collection. The ELISA kits with the same reference intervals, approved by the China Food and Drug Administration, were chosen by the local laboratories.

### Statistical Analysis

Big data set seems to follow the law of large numbers and the central limit theorem. So the whole sampled big data is normal distribution. The reference range of TSH was expressed with the 2.5th and 97.5th percentiles, as described previously [17–20]. Student's $t$ test and one-way ANOVA test were

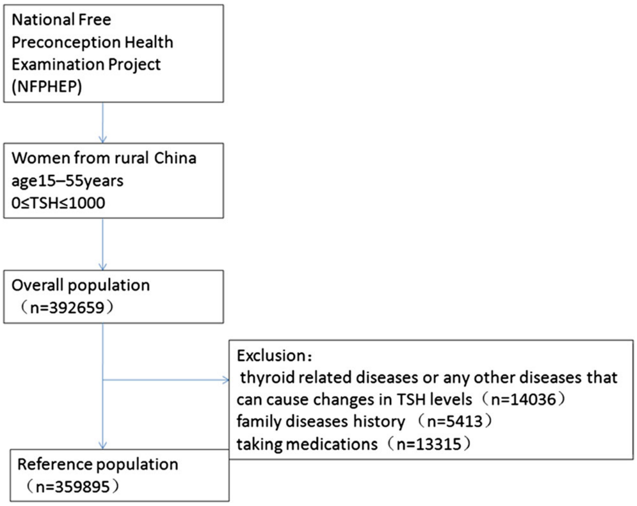


**Fig. 1** Recruitment and participation of the study subjects

applied to compare two or multiple groups, with respect to continuous and discrete variables. Comparisons of sub-data sets among different age and region groups were completed by using one-way ANOVA tests. Statistical analysis was performed using SPSS software (IBM SPSS Statistics, version 20.0; SPSS, Inc., Chicago, IL). A $p$ value of < 0.05 was considered statistically significant.

## Results

### Baseline Characteristics of the Subjects

Strict inclusion and exclusion criteria were applied to this study. Step 1, we excluded the subjects with a TSH value > 1000 uIU/ml, so the overall population aged 15–55 years who underwent thyroid function tests in the NFPHEP (from 2010 to 2012) included 392,659 subjects. Step 2, we excluded 14,036 subjects with thyroid-related diseases or any other diseases that can cause changes in TSH levels. Step 3, we excluded 5413 subjects with any family disease history. Step 4, we excluded 13,315 subjects taking any medications. Finally, the reference population comprised of 359,895 subjects (Fig. 1).

### Serum TSH Concentrations in Total Population and Reference Population

In overall population, the mean value of serum TSH was 2.28 uIU/ml, with a range (2.5th to 97.5th percentile) of 0.39–5.20 uIU/ml. In the reference population, the mean value of serum TSH was 2.27 uIU/ml, with a range of 0.39–5.13 uIU/ml (2.5th to 97.5th percentile). The reference population was categorized into four age groups (15–25, 26–35, 36–45, and 46–55 years old). The mean TSH values were increased with age ascending. The range (2.5th to 97.5th percentile) of serum TSH in different age groups was 0.40–5.03 uIU/ml, 0.39–5.15 uIU/ml, 0.37–6.10uIU/ml, and 0.44–7.03 uIU/ml, respectively. One-way ANOVA was applied to compare the variation among different age groups. In the reference population, the mean TSH value in women aged 26–35 years was 2.26 uIU/ml, significantly lower than those aged 36–45 ($p < 0.001$). No significant difference was observed between 15–25 and 26–35 age groups ($p = 0.520$) or between 36–45 and 46–55age groups ($p = 0.138$) (Table 1). We found that most of the subjects were distributed within the range of 1.01 to 2.0 with the same trend in two groups (Fig. 2). The mean value of TSH in overall population was higher than that in the reference population, divided by age groups (Fig. 3).

### Serum TSH Concentrations in Three Regions

The reference population was categorized into three region groups (eastern region, central region, and western region). In the eastern region population, the mean value of serum TSH was 2.28 uIU/ml, with a range (2.5th to 97.5th percentile) of 0.33–5.61 uIU/ml. In the central region population, the mean value of serum TSH was 2.29 uIU/ml, with a range (2.5th to 97.5th percentile) of 0.4–5.04 uIU/ml. In the western region population, the mean value of serum TSH was

**Table 1** Serum concentration of TSH in total population and reference population [a]

| Age median (range) | TSH of total population (uIU/ml) | | | | | $p$ value | TSH of reference population (uIU/ml) | | | | | $p$ value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | $N$ (%) | Mean ± SE | Percentile | | | | $N$ (%) | Mean ± SE | Percentile | | | |
| | | | 2.5th | 50th | 97.5th | | | | 2.5th | 50th | 97.5th | |
| 23 (15–25) | 211,069 (53.8) | 2.26 ± 0.008 | 0.39 | 2.00 | 5.09 | | 194,334 (54) | 2.25 ± 0.009 | 0.40 | 1.99 | 5.03 | |
| 28 (26–35) | 157,684 (40.2) | 2.28 ± 0.010 | 0.38 | 2.00 | 5.22 | 0.152 | 143,826 (40) | 2.26 ± 0.010 | 0.39 | 1.99 | 5.15 | 0.052 |
| 38 (36–45) | 22,822 (5.8) | 2.44 ± 0.027 | 0.37 | 2.00 | 6.21 | < 0.001[b] | 20,732 (5.8) | 2.41 ± 0.028 | 0.37 | 1.99 | 6.10 | < 0.001[b] |
| 47 (46–55) | 1084 (0.3) | 2.69 ± 0.113 | 0.49 | 2.10 | 7.17 | 0.045 | 1003 (0.3) | 2.60 ± 0.086 | 0.44 | 2.10 | 7.03 | 0.138 |
| Total | 392,659 | 2.28 ± 0.006 | 0.39 | 2.00 | 5.20 | | 359,895 | 2.27 ± 0.006 | 0.39 | 2.00 | 5.13 | |

[a] The $P$ value represents the mean level of this group compared with the upper group

[b] $P < 0.005$ was considered as a significant difference

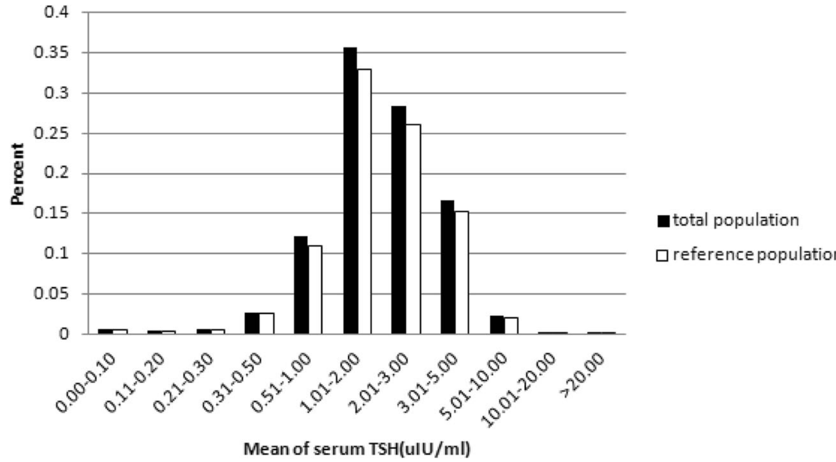


**Fig. 2** Mean of serum TSH distribution in total and reference population

2.24 uIU/ml, with a range (2.5th and 97.5th percentile) of 0.4–4.98 uIU/ml. The medians of serum TSH levels were all the same in all subgroups, 1.99 uIU/ml (Table 2). One-way ANOVA was performed to compare the TSH levels among three region groups. Serum TSH concentration was significantly higher in central region than that in western region ($p \leq 0.001$, Table 2), while there was no difference between eastern and central region (Table 2).

### Sociodemographic Characteristics of Participants

In the reference population, 359,895 women were assessed. Each participant was documented in detail on ethnicity, occupation, education level, smoking, alcohol intake, life pressure, economic pressure, and interpersonal tension. As shown in Table 3, 70.2% of the subjects only graduated from junior middle school. Most of them were Han ethnicity (95.4%), farmers (79.3%), non-smokers (99.1%), non-drinkers (95.7%), without life pressure (80.3%), without economic pressure (80.2%), or without interpersonal tension (89.0%). Serum TSH was significantly higher among women who were smoking, drinking, and uneducated ($p < 0.0001$) (Table 3).

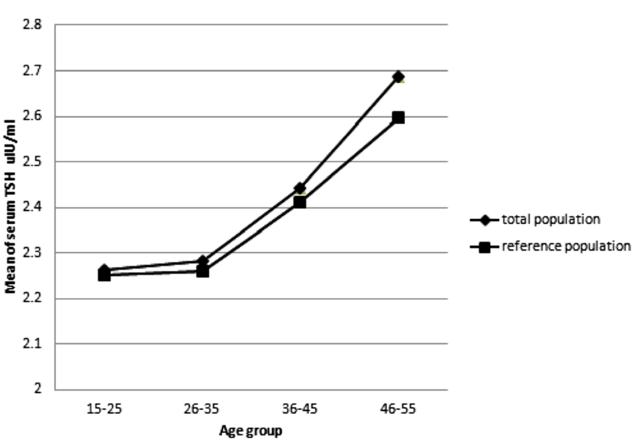


**Fig. 3** Mean of serum TSH in total and reference population of different age groups

The mean value of TSH was positively correlated with life/economic pressure and interpersonal tension ($p < 0.0001$) (Table 3 and Fig. 4). There was no significant difference in TSH distribution by ethnicity or occupation, as indicated by one-way ANOVA or Student's *t* test (Table 3).

## Discussion

This population-based epidemiologic study on TSH levels of 359,895 women from rural China was the first attempt, as far as we know. We compare the levels of serum TSH in the reference population to several other studies. The results were different among Asian, European, and American countries. For instance, Korea National Health and Nutrition Examination Survey (KNHANES) (2013 to 2015) reported the 2.5th and 97.5th percentile of serum TSH as 0.6 and 7.21 uIU/ml, respectively, in the reference population of female [21]. In Finland, the Health 2000 Survey reported the 2.5th and 97.5th percentile as 0.39 and 3.22 uIU/ml, respectively [22]. In the USA, National Health and Nutrition Examination Survey (NHANES III) (1988 to 1994) reported the 2.5th and 97.5th percentile as 0.41 and 4.09 uIU/ml, respectively [17]. In our study, the corresponding value of the reference population was 0.39–5.13 uIU/ml. Comparing with the above three studies, the difference might stem from sampling bias and non-sampling bias, such as screening strategies, laboratory assays, and immunoassay methods, as described previously [18, 22–24].

In our study, the mean value of TSH was positively correlated with age. In several relevant literatures, the TSH value was significantly affected by age [17, 25–29]; however, this was not the case in other studies [18, 30, 31]. We suggest that age-specific reference limits should be used for thyroid function tests by the NACB guidelines [8].

Other factors, such as gender, thyroidauto-antibodies, iodine intake, and investigation methods [25, 32, 33], might have contributed to different levels of serum TSH in

**Table 2** Serum concentration of TSH levels in different region of reference population[a]

| Region | $N$ (%) | TSH (uIU/ml) | | | | | | $p$ value |
|---|---|---|---|---|---|---|---|---|
| | | Mean | Percentile | | | | | |
| | | | 2.5th | 25th | 50th | 75th | 97.5th | |
| Eastern | 54,739 (15.2) | 2.28 | 0.33 | 1.20 | 1.99 | 2.69 | 5.61 | |
| Central | 162,637 (45.2) | 2.29 | 0.40 | 1.30 | 1.99 | 2.70 | 5.04 | 0.616 |
| Western | 142,519 (39.6) | 2.24 | 0.40 | 1.25 | 1.99 | 2.71 | 4.98 | 0.001[b] |

[a] The $P$ value represents the mean level of this group compared with upper group

[b] $P < 0.005$ was considered as a significant difference

**Table 3** Sociodemographic characteristics in the reference population

| Variables | $N$ (%) | TSH (uIU/ml); mean ± SE | $p$ value |
|---|---|---|---|
| ALL | 359,895 | 2.27 ± 0.006 | |
| Ethnicity | | | 0.216 ‡ |
| Han | 343,451 (95.4) | 2.26 ± 0.007 | |
| Others | 16,444 (4.6) | 2.30 ± 0.030 | |
| Smoking | | | 0.0001* ‡ |
| No | 357,037 (99.1) | 2.26 ± 0.006 | |
| Yes | 2858 (0.9) | 2.55 ± 0.210 | |
| Drinking | | | 0.0001* ‡ |
| No | 345,330 (95.7) | 2.26 ± 0.007 | |
| Yes | 14,565 (4.3) | 2.38 ± 0.032 | |
| Occupation | | | 0.600 † |
| Farmer | 285,505 (79.3) | 2.27 ± 0.007 | |
| Factory work | 28,000 (7.8) | 2.25 ± 0.040 | |
| Others | 46,390 (12.9) | 2.26 ± 0.016 | |
| Educational level | | | 0.0001* † |
| None | 1110 (0.3) | 2.55 ± 0.203 | |
| Primary school | 17,706 (4.9) | 2.38 ± 0.029 | |
| Junior middle school | 252,486 (70.2) | 2.25 ± 0.008 | |
| Senior middle school | 60,578 (16.8) | 2.32 ± 0.017 | |
| University and more | 28,051 (7.8) | 2.23 ± 0.016 | |
| Life pressure | | | 0.0001* † |
| None | 289,059 (80.3) | 2.25 ± 0.007 | |
| Little | 42,829 (12.2) | 2.31 ± 0.018 | |
| A little | 26,104 (7.5) | 2.33 ± 0.023 | |
| More | 1903 (0.5) | 2.47 ± 0.126 | |
| Economic pressure | | | 0.0001* † |
| None | 288,332 (80.2) | 2.24 ± 0.007 | |
| Little | 41,871 (11.6) | 2.33 ± 0.019 | |
| A little | 27,370 (7.6) | 2.36 ± 0.024 | |
| More | 2322 (0.6) | 2.53 ± 0.115 | |
| Interpersonal tension | | | 0.0001* † |
| None | 320,588 (89.0) | 2.25 ± 0.006 | |
| Little | 32,220 (9.0) | 2.35 ± 0.037 | |
| A little | 6904 (1.9) | 2.38 ± 0.047 | |
| More | 183 (0.1) | 2.69 ± 0.465 | |

† One-way ANOVA test

‡ Students's $t$ test

*$p < 0.005$ was considered as a significant difference

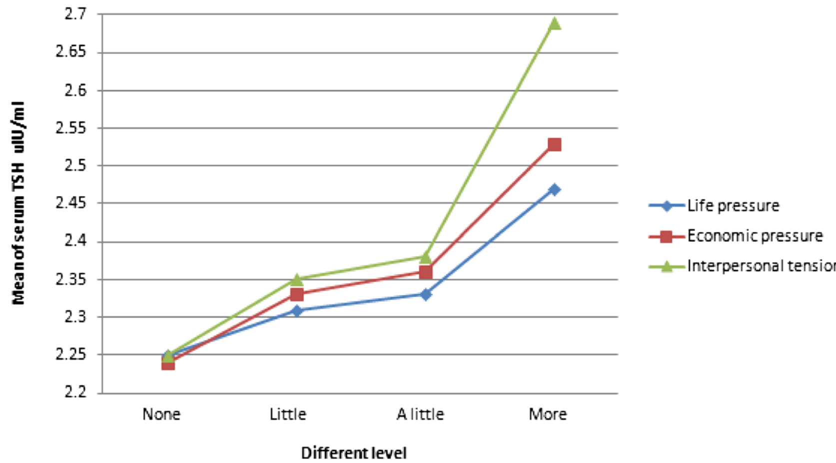


**Fig. 4** Mean of serum TSH among different levels of life pressure, economic pressure, and interpersonal tension groups in reference population

Chinese. However, limited by resource, this study did not evaluate the above factors. We evaluated the effects of resident areas on TSH levels, and found that the value of TSH was significantly higher in the central region than in the western region of China. This phenomenon could be due to different iodine intake or eating habits in the above regions. The iodine intake could contribute to differential distribution of serum TSH in rural China. Guan H et al. [34] showed "a urinary iodine-related increase of serum TSH levels in areas according to different levels of iodine intake." They also found that "iodine nutrition was an important factor associated with TSH concentration, even in the rigorously selected reference population." Rebagliato observed "an increased risk of TSH above 3.0 mIU/L in pregnant women who consumed 200 μg or more of iodine supplements daily compared with those who consumed less than 100 μg/d" [35]. Orito found "significant positive correlations between urinary iodine concentration and TSH" [36]. There may be two reasons for high TSH caused by an increased iodine intake. Firstly, Papanastasiou reported "a strong association of thyroid autoimmunity with increased serum TSH aggravated by high iodine intake has been reported due to increased iodination of thyroglobulin or direct stimulation of immune cells" [37]. Xiaoguang Shi reported that "thyroid autoimmunity might impair the thyroid sufficiently to raise TSH" [38]. Next, Li N's animal study offers another explanation "the activity of deiodinase-II in the hypothalamus and pituitary was significantly inhibited by chronically increased iodine intake, which reduced T3 production in the hypothalamus and the pituitary and resulted in increased TSH production" [39]. Rosene reported the same results in amiodarone treated mice [40].

At the same time, we found that the value of TSH was significantly associated with smoking, drinking, education, life/economic pressure, or interpersonal tension. The increase in pressure or tension may result in an increase in TSH concentration. However, the effect of cigarette smoking on thyroid function is controversial. Several studies have reported that smokers have a lower prevalence of TPOAb [41] and a lower level of TSH [41, 42]. Another study has proposed that the effect of smoking on thyroid function differs according to iodine intake [42], which suggests that compounds from cigarettes interact with iodine in the thyroid gland.

Predetermined strict exclusion criteria had excluded 32,764 (8.34%) samples and left 359,895 subjects as the reference population. To some extent, the exclusion criteria were even stricter than NACB guidelines [8]. As the value of TSH might be affected by many diseases [43–47], it might be related to family history or medications. Meanwhile, we excluded extreme values of TSH (≥ 1000 uIU/ml), since the detection range of ELISA kits was 0–1000 uIU/ml. The extreme values may be caused by input mistakes or non-sampling errors.

Our study has the following limitations, which should be improved in future studies. Firstly, the NFPHEP study targeted only on the couples who were planning to have babies in rural China. The values of TSH in single women or in the couples who were not planning to have babies in rural China could be underestimated or ignored. Meanwhile, married women who were preparing to have babies deliberately avoided smoking and drinking, so women who were smoking and drinking in the reference population were very few, only accounting for 0.9 and 4.3%, respectively. Therefore, this population may not be representative for ordinary population. In the future, we plan to recruit unmarried women to our ongoing study. Secondly, more detailed histories and physical examination findings should be collected, such as iodine intake which has been considered as an important factor associated with TSH concentration in previous studies [34]. However, in a large-scale survey, it is hard for the researchers to collect the histories completely and sufficiently. Thirdly, restricted by the funds and human resources, the serum levels of TgAb and TPOAb were not measured. As a result, we could not follow all the stringent criteria of the NACB guidelines [8]. TPOAb-positivity had a substantial effect on the TSH upper limit in some studies [18, 22, 27], yet in other studies, the effect was nonexistent or less pronounced [19, 48]. It was reported that the effect of TPOAb-positivity was apparent only among women [49]. TPOAb presented a high sensitivity for screening for thyroid related diseases [22]. Therefore, TgAb and TPOAb should be investigated in our future studies, which deserves more efforts to set up a reliable, accurate, and reproducible reference range of TSH, especially for Chinese population. Finally, there were many influential factors in ELISA measurement. Samples, reagents and operating factors all influence the test results, especially the difficulty in standardization of manual operation was one of the limiting factors in present study.

In conclusion, we collected and analyzed the TSH data and sociodemographic characteristics of 359,895 women of reproductive age in rural China. We obtained that the normal TSH reference range for them was 0.39–5.13 uIU/ml (2.5th–97.5th percentiles). We suggest that people from different regions should have different reference ranges of TSH to diagnose hyperthyrotropinemia or hypothyroidism. The reference ranges for eastern, central, and western regions were 0.33–5.61 uIU/ml, 0.40–5.04 uIU/ml and 0.40–4.98 uIU/ml (2.5th–97.5th percentiles) respectively.

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## Compliance with Ethical Standards

**Conflict of Interest** The authors declare that they have no competing interests.

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