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REVIEW ARTICLE

Serum iodine reference ranges and their correlations with urinary iodine and thyroid function: A systematic review and meta-analysis

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Abstract

Background: Serum iodine mainly exists in the form of iodine and iodide ions in thyroid hormones and does not change immediately due to variations in external factors. It is an important indicator reflecting iodine metabolism and actual iodine levels in the body. Given the significant differences in serum iodine among different countries and populations, the standard range of SIC has not yet reached a consensus. To the best of our knowledge, this systematic review and meta-analysis are the first to explore the serum iodine nutritional status of different populations across the country and its correlation with thyroid function. **Objective:** This study aimed to assess reference ranges of serum iodine concentration (SIC) and the potential correlations among SIC, urinary iodine concentration, and thyroid function in various populations globally, providing a reference for the assessment of individual iodine nutritional status. **Methods:** This study was conducted by searching multiple databases, including PubMed, Web of Science, and China National Knowledge Infrastructure, to gather relevant studies on SIC. Two researchers independently screened the literature and extracted and synthesized the data. The data were then analyzed using Stata software to generate pooled estimates of SIC with 95% confidence intervals (CIs) using forest plots. **Results:** A total of 48 eligible studies were included, yielding a mean SIC of 88.68 μg/L (95% CI: 84.70–92.65 μg/L). The range of SIC reported across studies was 23.92–183.50 μg/L. Among these, most studies focused on the correlations between SIC and free thyroxine (FT4) (81.0%) and between SIC and FT3 (72.7%). **Conclusion:** This meta-analysis highlights the importance of SIC as a valuable indicator of individual iodine nutritional status. The findings suggest that SIC is influenced by regional, temporal, and methodological variations, emphasizing the need for standardized testing and reference values. Moreover, the observed associations between SIC and thyroid function markers underscore its clinical relevance in monitoring iodine-related health outcomes. Establishing consistent measurement protocols and population-specific reference ranges will enhance the accuracy of iodine status assessments and support more effective public health interventions. **Relevance for Patients:** This study provides a preliminary synthesis of currently non-standardized SIC reference ranges. Future large-scale, multicenter studies on SIC testing are needed to establish reference values for assessing individual iodine nutritional status, thereby enabling scientifically informed and precision-based iodine supplementation.

Keywords: Population variability; Iodine nutritional status; Serum iodine; Medical reference values; Thyroid functions

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1. Introduction

The significance of scientifically evaluating iodine nutrition status and guiding targeted iodine supplementation for populations cannot be overstated. The demand for individual iodine status assessment is increasing, particularly among individuals with specific physiological conditions, such as children, pregnant women, and patients with thyroid diseases, who require timely and accurate evaluation of iodine status.[1] Indicators used to assess iodine status include dietary iodine intake, thyroid volume, thyroid function, urinary iodine concentration (UIC), and blood iodine concentration; however, all these indicators have certain limitations. For instance, recall bias may arise when investigating dietary intake; changes in thyroid volume require a longer period to manifest and are considered long-term indicators; thyroid function indicators are typically employed for patients with thyroid diseases and can be influenced by various factors.[2,3] Numerous previous studies have examined UIC in diverse populations.[4,5] Nevertheless, UIC reflects only the excretion of iodine from the body and does not represent the level of biologically active iodine utilized by the thyroid. Moreover, UIC is easily affected by factors such as dietary iodine intake, water iodine content, and sweating, resulting in considerable fluctuations and making it difficult to accurately reflect an individual's iodine nutritional status.[6] Serum iodine concentration (SIC) mainly exists in the form of iodine and iodide within thyroid hormones, reflecting the iodine metabolism in the body and the actual iodine level. Its fluctuations are relatively minor and less susceptible to external factors when compared with UIC, making it more stable. SIC can more precisely reflect recent iodine nutritional status and has unique advantages in accurately assessing individual iodine nutritional status. However, relatively few clinical studies on SIC have been conducted both domestically and internationally, and it is gradually emerging as a research focus.[7]

In other nations, renowned laboratories such as Mayo Clinic, Quest Diagnostics, and the World Health Organization (WHO) provide SIC reference ranges of 52–109 μg/L, 40–92 μg/L, and 45–90 μg/L, respectively, measured using inductively coupled plasma-mass spectrometry (ICP-MS). However, these ranges do not differentiate between populations.[8] In China, only a limited number of studies have determined SIC reference ranges for specific regions and populations. A multicenter cross-sectional study covering six provinces reported an SIC reference range of 36.0–79.3 μg/L, measured using ICP-MS. Nevertheless, the scientific community has not yet established a comprehensive SIC reference range.[9]

Given the substantial variations in SIC among countries and populations, there is currently no consensus on standard SIC ranges for diverse populations domestically or internationally. Hence, this systematic review and meta-analysis represent the inaugural effort to explore serum iodine status and its correlation with UIC and thyroid function across different populations, regions, sampling times, and detection methods. It aims to provide reference data for the future establishment of SIC reference ranges in various populations, thereby enabling scientific and precise iodine supplementation to maintain appropriate iodine nutritional levels.

2. Materials and methods

2.1. Inclusion criteria

The studies included in this meta-analysis were selected based on predefined criteria regarding study type, research subjects, and outcome indicators. Eligible studies comprised cross-sectional studies, case–control studies, longitudinal cohort studies, and prospective studies. The research subjects included pregnant women, children, infants, healthy adults, and individuals with abnormal thyroid function. To ensure relevance to the study objectives, eligible studies were required to report quantitative indicators of iodine nutritional status, such as mean values, quartiles, medians, or 95% confidence intervals (CI).

2.2. Exclusion criteria

Studies were excluded according to the following criteria: (i) studies published in languages other than Chinese or English; (ii) duplicate publications; (iii) studies without accessible full text or with incomplete data (e.g., SIC values only reported in figures without numerical data); (iv) case reports, review articles, conference abstracts, and animal studies; (v) studies in which subjects were exposed to environmental factors that could affect SIC (e.g., a high-iodine diet, iodine-based contrast agents, radioactive iodine, povidone-iodine disinfection, or amiodarone use within 3 days before testing, potentially resulting in iodine overload); (vi) studies with apparent statistical errors.

2.3. Search strategies for literature retrieval

A computer-based search was conducted in the China National Knowledge Infrastructure (CNKI), VIP, WanFang, PubMed, Web of Science, and Excerpta Medica dataBASE (Embase) databases. The search period was set from the establishment of each database to November 1, 2024, without country restrictions, although the language was limited to Chinese or English. In addition, other relevant databases were searched, including those maintained by the WHO (www.who.int/en/), the United Nations Children's Fund (UNICEF) (www.unicef.org/), and the International Council for the Control of Iodine Deficiency Disorders (ICCIDD) (www.iccidd.org/). The search process employed a combination of subject terms and free-text words, with adjustments made according to the characteristics of each database. We also screened the reference lists of included studies (“snowballing”) to identify additional eligible publications. The Chinese search terms encompassed: “serum iodine,” “serum iodine concentration,” “iodine nutrition assessment,” “iodine nutritional status,” “iodine nutrient level,” “iodine nutrition monitoring,” “evaluation of iodine nutritional status,” “iodine nutrition survey,” “iodine nutrition of residents,” “iodine nutrition for children,” “iodine nutrition for pregnant women,” iodine nutrition in patients with thyroid disease, iodine nutrition in patients with thyroid dysfunction, and related terms. The English search terms consisted of: “serum iodine,” “serum iodine concentration,” “iodine nutrition assessment,” “iodine nutritional status,” “iodine nutrient level,” “iodine nutrition monitoring,” “evaluation of iodine nutritional status,” “iodine nutrition survey,” “iodine nutrition of residents,” “iodine nutrition for children,” “iodine nutrition for pregnant women,” “iodine nutrition in patients with thyroid disease,” “iodine nutrition in patients with thyroid dysfunction,” and similar terms. For instance, the specific search strategy employed in PubMed is presented in Figure 1.

2.4. Literature screening and data extraction

Two researchers independently screened the literature, extracted the data, and cross-checked the results. Any disagreements were resolved through discussion or consultation with a third party. If necessary, the original study authors were contacted via email to obtain information that was not explicitly stated but considered crucial to the current study. During the literature screening process, the titles of the articles were initially inspected, and those that were obviously irrelevant were excluded from the study. The abstracts and full texts were then reviewed in detail to determine eligibility for inclusion. The extracted data encompassed: (i) basic information of the included studies, such as the first author, year of publication, country and region where the study was conducted, study type, and study duration; (ii) basic characteristics of the study subjects, including the type of population studied (e.g., pregnant women, adults, children, infants), the method employed for SIC detection, and the number of individuals tested; (iii) SIC (mean, quartiles, median, 95% CI), and the correlation between SIC, UIC, and thyroid function; (iv) key elements for bias risk assessment.

#1 Serum iodine [Mesh Terms]
#2 Serum iodine concentration [Title/Abstract]
#3 Iodine nutrition assessment [Title/Abstract]
#4 Iodine nutritional status [Title/Abstract]
#5 Iodine nutrient level [Title/Abstract]
#6 Iodine nutrition monitoring [Title/ Abstract]
#7 Evaluation of iodine nutritional status [Title/Abstract]
#8 Iodine nutrition survey [Title/Abstract]
#9 Iodine nutrition of residents [Title/Abstract]
#10 Iodine nutrition for children [Title/Abstract]
#11 Iodine nutrition for pregnant women [Title/Abstract]
#12 Iodine nutrition in patients with thyroid disease [Title/Abstract]
#13 Iodine nutrition in patients with thyroid dysfunction [Title/Abstract]
#14 #1 OR #2 OR #3OR #4OR #5 OR #6 #7 #8 #9 #10 OR #11 OR #12 OR #13

Figure 1. PubMed search strategy. Image created by the authors.

2.5. Quality assessment of included studies

Two researchers independently evaluated the risk of bias for the studies included in the review and cross-checked the outcomes. In case of any disagreement, a third reviewer was consulted to resolve discrepancies. The criteria recommended by the Agency for Healthcare Research and Quality were employed to assess the risk of bias in the cross-sectional studies. Each item of the criteria was rated as “yes,” “no,” or “unclear,” with a score of 1 assigned for “yes” and 0 for “no.” The total possible score was 11, with results ranging from 0 to 3 indicating low quality, 4–7 indicating medium quality, and 8 or above indicating high quality. The Newcastle–Ottawa Scale was utilized to evaluate the quality of the included cohort studies, case–control studies, and prospective studies, with each item awarded up to two stars. The overall quality score was computed as the sum of the individual star ratings. Total scores ranged from 0 to 10; scores 2–3 were considered low quality, 4–6 moderate quality, and 7–10 high quality. The quality assessment results for the studies included in this review were mainly concentrated on scores ranging from 6 to 8 (Table S1).

2.6. Statistical analysis

A systematic review and meta-analysis of the literature were carried out, summarizing SIC levels using mean ± standard deviation, quartiles, median, and 95% CI. Stata software (17.0, StataCorp, USA) was utilized for data cleaning and statistical analysis, and the “meta” command was employed to generate forest plots of the average SIC values and their corresponding 95% CI. Subgroup analyses were further conducted based on detection year, region, method, and population characteristics. The results were presented in forest plots to compare between-group heterogeneity. Heterogeneity was assessed using the I^2 statistic. An I^2 value of 0% indicates no observable heterogeneity, while values of 25%, 50%, and 75% represent low, moderate, and high heterogeneity, respectively. A random-effects model was applied when $I^2 > 50\%$; otherwise, a fixed-effects model was used. Statistical significance was set at $p<0.05$.

3. Results

3.1. The process and results of literature screening

Initially, a total of 2,394 relevant articles were identified for the following sources: PubMed ($n = 488$), Web of

Science ($n = 358$), Embase ($n = 421$), CNKI ($n = 164$), VIP ($n = 466$), WanFang Data ($n = 472$), and other sources ($n = 25$). NoteExpress (version 2.0, China) was employed to eliminate duplicate articles ($n = 276$), articles in languages other tn Chinese or English ($n = 41$), articles not pertinent to the research theme, case reports, systematic reviews, conference abstracts, and animal studies ($n = 1915$), as well as articles that were inaccessible in full, lacked complete data, or involved high iodine exposure before testing ($n = 114$). After sequential screening, a total of 48 studies[1-47] were ultimately included, as depicted in Figure 2.

3.2. Basic characteristics of the included studies

A total of 48 eligible studies were included, comprising 33 cross-sectional studies, four case–control studies, three longitudinal cohort studies, four prospective studies, two single-center studies, and two multicenter studies. Twenty studies reported the serum iodine nutritional status of pregnant women; 25 studies reported the serum iodine nutritional status of healthy adults (of which 16 additionally evaluated serum iodine nutritional status across early, middle, and late pregnancy stages, as indicated in Table S2); eight studies reported the serum iodine nutritional status in children or infants; and 11 studies reported the serum iodine nutritional status of patients with thyroid function disorders. The study populations encompassed pregnant women ($n = 11{,}354$), healthy adults ($n = 13{,}563$), children ($n = 4{,}413$), infants ($n = 287$), and patients with thyroid function disorders ($n = 3{,}975$). The quality score range of the studies incorporated in this meta-analysis was 5–9 points (Table S1).

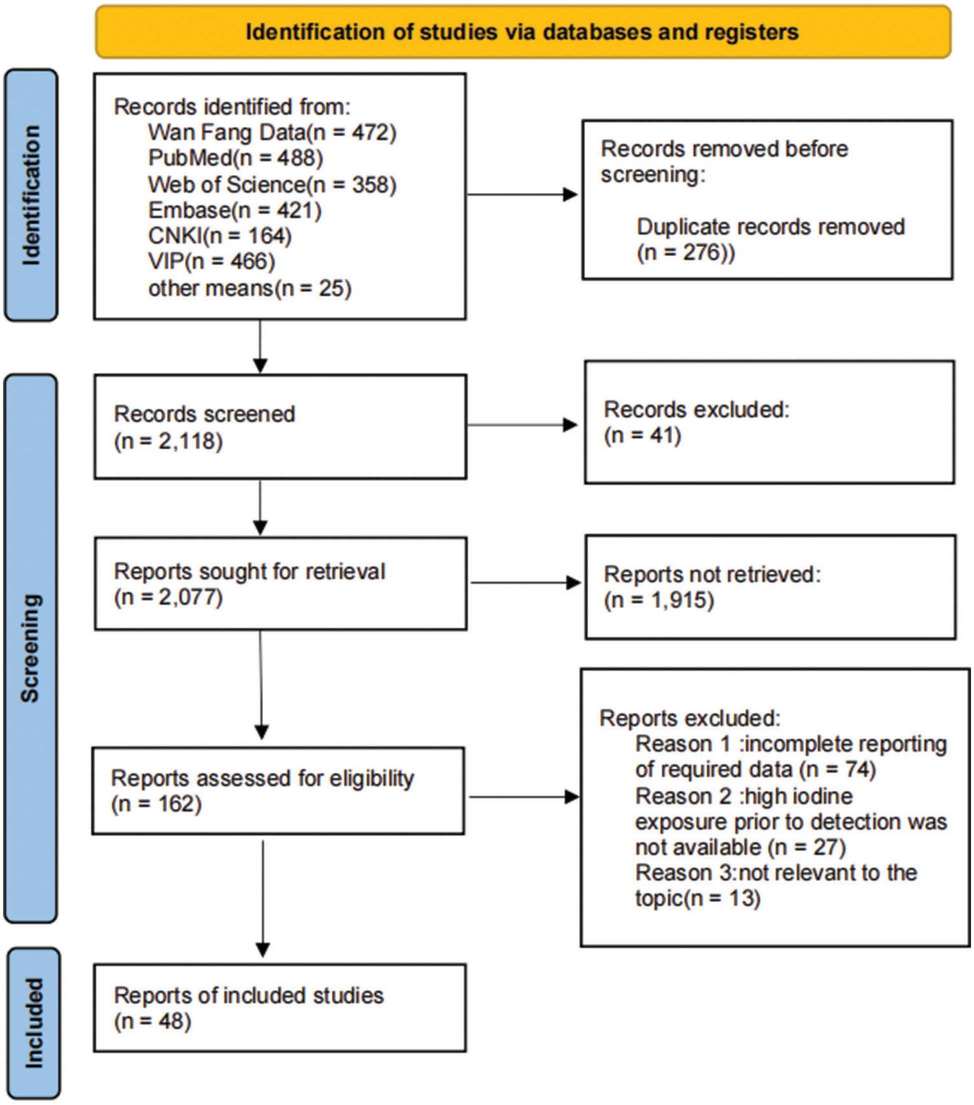


Figure 2. Flowchart illustrating the literature screening process and results. Image created by the authors.

3.3. Results of meta-analysis

3.3.1. Summary of average SIC values and 95% CIs across all populations

A meta-analysis was carried out to evaluate SIC levels across diverse populations, regions, detection times, and detection methods. The results were presented in a forest plot showing the average SIC values and corresponding 95% CI for each population (Figure 3). The analysis revealed heterogeneity among the studies (I^2 = 11.6%, *p*=0.238); therefore, a fixed-effects model was adopted. The average SIC concentration was 88.68 µg/L (95% CI: 84.70–92.65 µg/L) across all studies.

3.3.2. Subgroup analysis of average SIC values and 95% CIs by detection year

The forest plot in Figure 4 presents the average SIC values and 95% CIs by year of measurement. The results were as follows: 2017–84.02 µg/L (95% CI: 66.98–101.05 µg/L); 2019–85.54 µg/L (95% CI: 75.69–95.39 µg/L); 2020–113.85 µg/L (95% CI: 87.09–140.61 µg/L); 2021–103.31 µg/L (95% CI: 96.37–110.26 µg/L); 2022–68.50 µg/L (95% CI: 48.20–

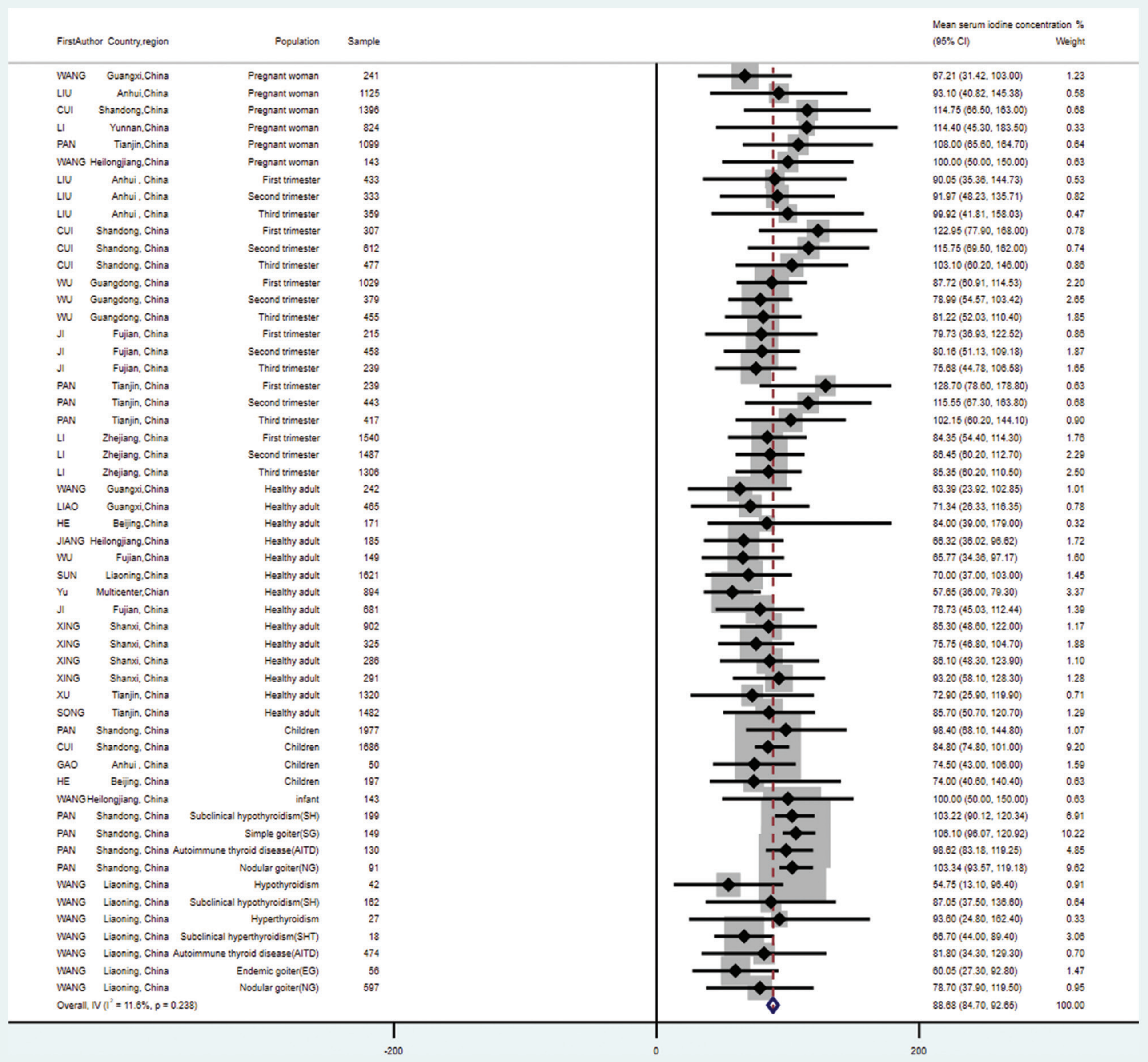


Figure 3. Forest plots showing the average serum iodine (SIC) concentration values and 95% confidence intervals (CIs) for different populations. Image created by the authors.

Notes: The hollow diamonds represent the pooled estimates for each study and the overall SIC concentration, while the solid diamonds represent point estimates (horizontal lines indicate 95% CIs). The size of the squares is proportional to the relative weight of each study.

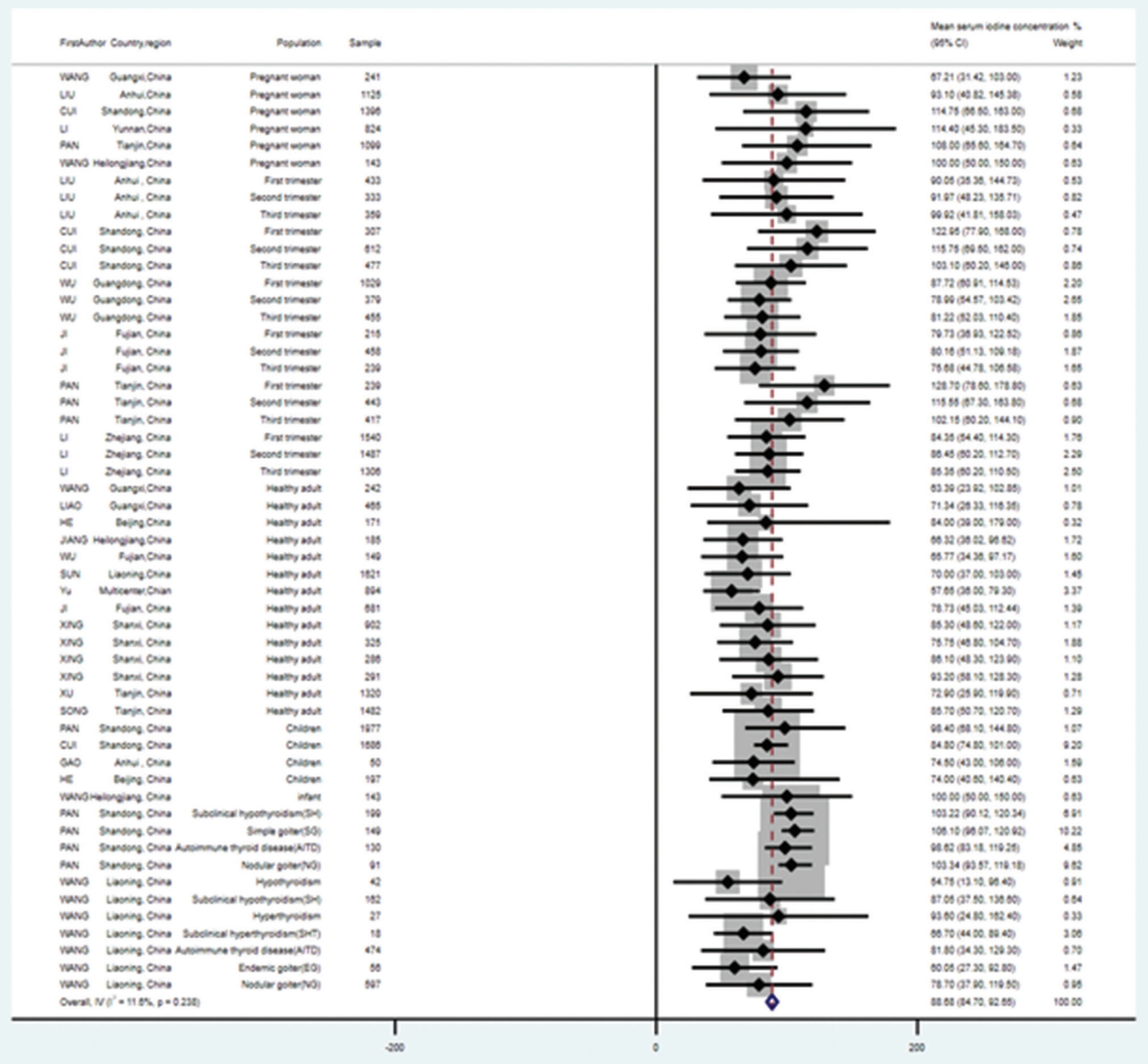


Figure 4. Forest plots showing the average serum iodine concentration (SIC) values and 95% confidence intervals (CIs) for different detection years. Image created by the authors.

Notes: The hollow diamonds represent pooled estimates for each study and the overall SIC concentration, while the solid diamonds represent point estimates (horizontal lines indicate 95% CIs). The size of the squares is proportional to the relative weight of each study.

88.81 μg/L); 2023–82.92 μg/L (95% CI: 71.44–94.40 μg/L); 2024–78.41 μg/L (95% CI: 70.19–86.63 μg/L). There was significant heterogeneity among the subgroups ($I^2 = 0.00\%$, $p<0.001$; Figure 4).

3.3.3. Subgroup analysis of average SIC values and 95% CIs in different detection areas

ArcGIS 10.8 mapping software (Esri, USA) was used to generate a weighted map of SIC detection levels for different populations across provinces in China (Figure 5). The studies involved the following provinces: Beijing (*n* = 8), Tianjin (*n* = 5), Shanghai (*n* = 1), Hebei (*n* = 1), Shanxi (*n* = 2), Liaoning (*n* = 2), Jilin (*n* = 1), Heilongjiang (*n* = 7), Jiangsu (*n* = 1), Zhejiang (*n* = 1), Anhui (*n* = 4), Fujian (*n* = 2), Shandong (*n* = 6), Henan (*n* = 1), Hubei (*n* = 2), Guangdong (*n* = 6), Hainan (*n* = 1), Guizhou (*n* = 1), Yunnan (*n* = 2), Guangxi Zhuang autonomous region (*n* = 3), Xinjiang Uygur autonomous region (*n* = 2). We found that Beijing, Heilongjiang, and Shandong had the most SIC detection studies, while no reports were found from Chongqing,

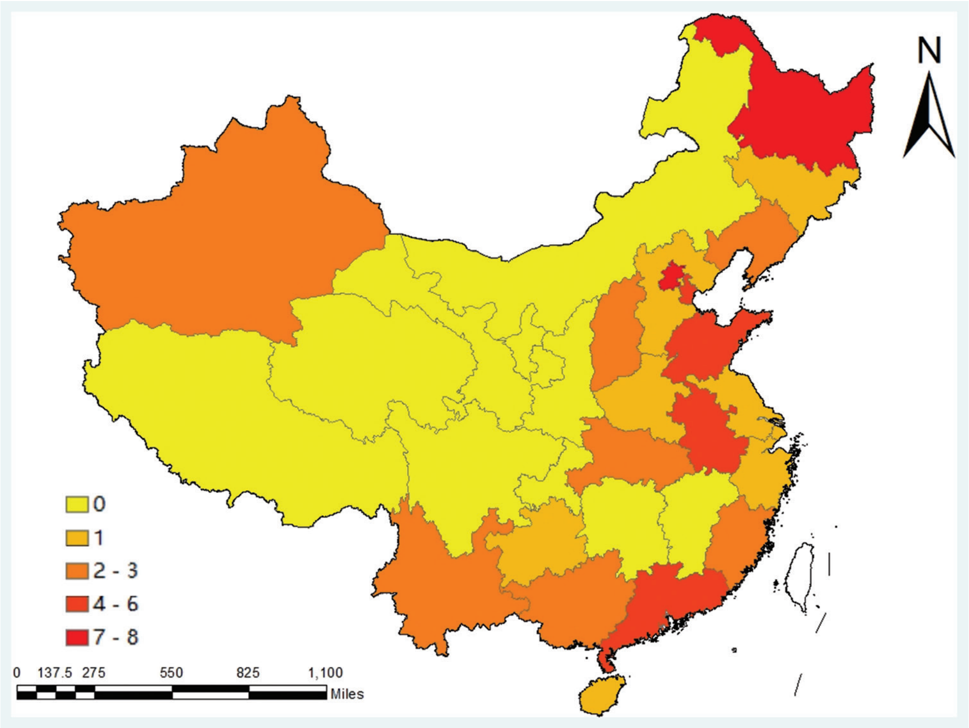


Figure 5. Serum iodine concentration detection levels for different populations in each province across China. Image created by the authors.

Hunan, Jiangxi, Sichuan, Shaanxi, Gansu, Qinghai, Inner Mongolia, Tibet, Ningxia, Hong Kong, and Macao.

The forest plots present the average values and 95% CIs of SIC across different provinces through subgroup analysis. We found that the average SIC in Guangxi Zhuang autonomous region was 66.99 μg/L (95% CI: 44.15–89.84 μg/L); in Anhui province, 85.84 μg/L (95% CI: 65.95–105.74 μg/L); in Shandong province, 100.24 μg/L (95% CI: 94.31–106.16 μg/L); in Tianjin municipality, 99.56 μg/L (95% CI: 81.52–117.60 μg/L); in Heilongjiang province, 80.56 μg/L (95% CI: 57.58–103.59 μg/L); in Guangdong province, 82.47 μg/L (95% CI: 67.12–97.83 μg/L); in Fujian province, 75.72 μg/L (95% CI: 61.09–90.34 μg/L); in Zhejiang province, 85.47 μg/L (95% CI: 69.94–100.99 μg/L); in Beijing municipality, 77.37 μg/L (95% CI: 36.74–116.00 μg/L); in Liaoning province, 69.65 μg/L (95% CI: 56.78–82.53 μg/L); and in Shanxi province, 84.02 μg/L (95% CI: 66.98–101.05 μg/L). The SIC varied among provinces (*p*<0.001; Figure 6).

3.3.4. Subgroup analysis of average SIC values and 95% CIs in different population groups

The forest plots in Figure 7 present the average SIC values and 95% CIs for different population groups. We observed that the average SIC for pregnant women was 94.02 μg/L (95% CI: 74.38–113.66 μg/L); for healthy adults, 72.88 μg/L (95% CI: 63.78–81.97 μg/L); for children, 84.11 μg/L (95% CI: 72.87–95.35 μg/L); for subclinical hypothyroid, 101.84 μg/L (95% CI: 87.39–116.30 μg/L); for autoimmune thyroid disease, 96.50 μg/L (95% CI: 79.64–113.36 μg/L); and for nodular goiter, 101.13 μg/L (95% CI: 88.91–113.35 μg/L). The SIC varied among different groups (*p*=0.007; Figure 7).

3.3.5. Average SIC values and 95% CIs during different pregnancy periods: Subgroup analysis results

The forest plots in Figure 8 present the average SIC values and 95% CIs for different trimesters of pregnancy in subgroups. We found that the average SIC for pregnant women in the first trimester was 93.88 μg/L (95% CI: 78.59–109.17 μg/L); in the second trimester, 88.04 μg/L (95% CI: 74.83–101.24 μg/L); in the third trimester, 88.99 μg/L (95% CI: 73.13–100.84 μg/L). Heterogeneity between groups (I^2 = 0.0%, *p*=0.784) was observed in the forest plots. Subgroup analysis of SIC averages and 95% CI for early, middle, and late pregnancies showed no statistically significant heterogeneity (I^2 = 0.0%, *p*=0.784) (Figure 8 and Table S3).

3.3.6. Subgroup analysis of average SIC values and 95% CIs by different detection methods

The forest plots in Figure 9 present the average SIC values and 95% CIs obtained using different detection methods.

Figure 6. Forest plots showing the average serum iodine concentration (SIC) values and 95% confidence intervals (CIs) for studies from different detection regions. Image created by the authors.

Notes: The hollow diamonds represent the pooled estimates for each study and the overall SIC concentration, while the solid diamonds represent point estimates (horizontal lines indicate 95% CIs). The size of the squares is proportional to the relative weight of each study.

We found that the average SIC detected by arsenic cerium catalytic spectrophotometry was 79.02 μg/L (95% CI: 70.85–87.18 μg/L), while that detected by ICP-MS was 91.67 μg/L (95% CI: 87.12–96.22 μg/L). There was heterogeneity between groups (I^2 = 0.0%, p=0.008; Figure 9).

3.3.7. Summary of the mean and 95% CIs of serum non-protein-bound iodine

According to the available statistics, only five studies have reported the nutritional status of serum non-protein-bound iodine (SnbI) in different populations. Figure 10 presents a forest plot summarizing the means and 95% CI values of SnbI for different populations, revealing an overall average SnbI value of 58.20 μg/L (95% CI: 54.28–62.11 μg/L; I^2=0.0%, p=0.512).

3.3.8. Relationship among SIC, UIC, and thyroid function

This meta-analysis also summarizes the correlations between SIC, UIC, and thyroid function. The range of SIC values reported was 23.92–183.50 μg/L. Within this range, we found the following: Studies reporting a positive correlation between SIC and UIC (n = 8), negative correlation (n = 0), and no correlation (n = 3); studies reporting a positive correlation between SIC and free thyroxine (FT) 3 (n = 8), negative correlation (n = 2), no correlation (n = 3); studies reporting a positive correlation between SIC and FT4 (n = 17), negative correlation (n = 1), no correlation (n = 3); studies reporting a positive correlation between SIC and total triiodothyronine (TT) 3 (n = 8), negative correlation (n = 0), and no correlation (n = 3); studies reporting a positive correlation between SIC and TT4 (n = 4), negative correlation (n = 0), and no correlation (n = 1); studies

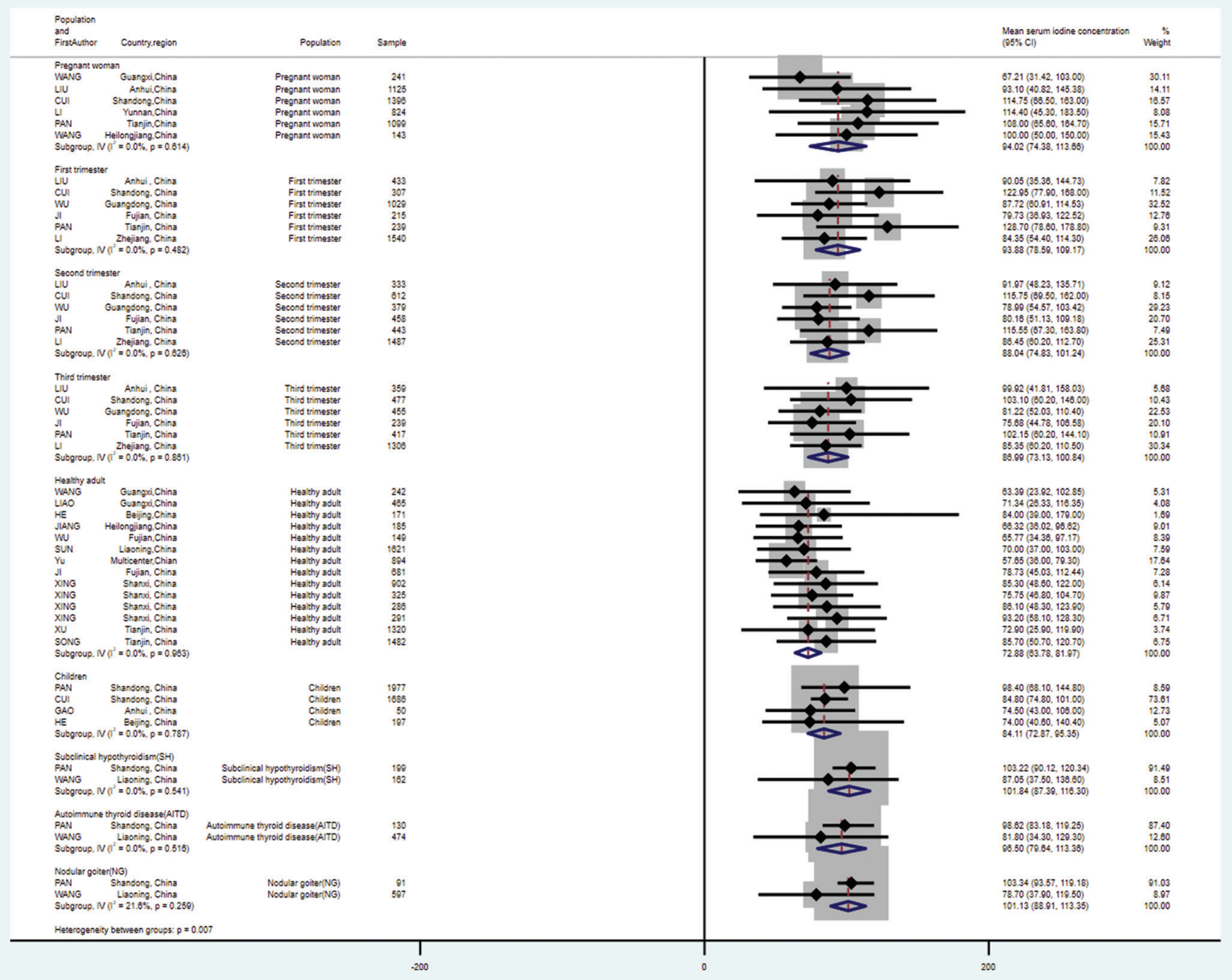


Figure 7. Forest plots showing the average serum iodine concentration (SIC) values and 95% confidence intervals (CIs) for different population groups. Image created by the authors.

Notes: The hollow diamonds represent the pooled estimate for each study and the overall estimate of SIC concentration, while the solid diamonds represent point estimates (horizontal lines indicate 95% CIs). The size of the squares is proportional to the relative weight of each study.

reporting a positive correlation between SIC and thyroid-stimulating hormone (TSH; *n* = 5), negative correlation (*n* = 8), and no correlation (*n* = 11); studies reporting a positive correlation between SIC and thyroglobulin antibody (TgAb; *n* = 0), negative correlation (*n* = 1), and no correlation (*n* = 7); and studies reporting a positive correlation between SIC and thyroglobulin (Tg; *n* = 2), negative correlation (*n* = 0), and no correlation (*n* = 4); and studies reporting a positive correlation between SIC and thyroid peroxidase antibody (TPOAb; *n* = 0), negative correlation (*n* = 1), and no correlation (*n* = 7) (Table S4 and Figure 11).

4. Discussion

It is of great significance to scientifically assess iodine nutritional status and provide precise guidance for iodine supplementation in the population. There is a growing demand for individualized iodine nutritional status assessment, particularly among individuals with specific physiological needs, such as children, pregnant women, and patients with thyroid diseases, who require accurate, personalized evaluation of their iodine levels. Previous studies have established reference ranges for UIC. According to the standards set by WHO/UNICEF/ICCIDD, UIC values are classified as follows: Deficient iodine intake (<100 μg/L), adequate iodine intake (100–200 μg/L), more than adequate iodine intake (200–300 μg/L), and excessive iodine intake (>300 μg/L). However, the medical reference range of SIC remains undefined.[8] This systematic review and meta-analysis is the first to conduct a comprehensive analysis of SIC

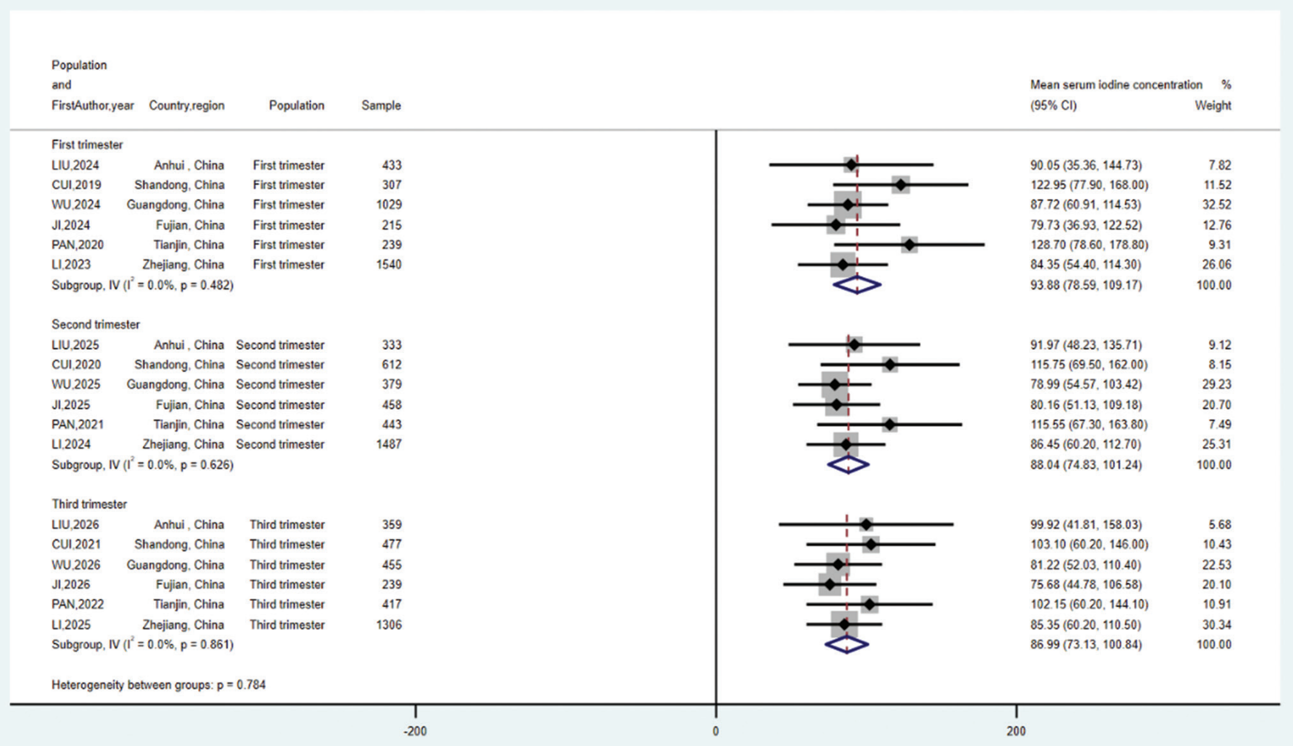


Figure 8. Average serum iodine concentration values and 95% confidence intervals for different gestational periods in pregnant women. Image created by the authors.

across different populations, regions, detection times, and detection methods. The range of SIC values reported in the included studies was 23.92–183.50 μg/L, and the average value and 95% CI of SIC in different populations were presented using forest plots (Figure 3). The meta-analysis found that the mean SIC value was 88.68 μg/L (95% CI: 84.70–92.65 μg/L). The reference ranges provided by the WHO, Mayo Clinic, and Quest Diagnostics, three internationally renowned laboratories, were 45–90 μg/L, 52–109μg/L, and 40–92μg/L, respectively, with validation rates of 80.6%, 80.6%, and 93.5%. A multicenter cross-sectional study in China preliminarily determined the reference range of SIC for healthy adults in China to be 36.0–79.3 μg/L.[6,7] Our pooled mean and its 95% CI are consistent with that study's reference range. However, due to limitations in study quality and quantity, a uniform standard reference range for SIC in medicine cannot be determined at present. In the future, both domestically and internationally, as well as across all provinces in China, a large number of multicenter, high-quality studies are needed to provide evidence for establishing a standard medical reference range for SIC.

This systematic review also performed a subgroup analysis of the average values and 95% CI of SIC for various detection years. The results indicated that the mean SIC and 95% CI of SIC were as follows: 2017, 84.02 μg/L (95% CI: 66.98–101.05 μg/L); 2019, 85.54 μg/L (95% CI: 75.69–95.39 μg/L); 2020, 113.85 μg/L (95% CI: 87.09–140.61 μg/L); 2021, 103.31 μg/L (95% CI: 96.37–110.26 μg/L); 2022, 68.50 μg/L (95% CI: 48.20–88.81 μg/L); 2023, 82.92 μg/L (95% CI: 71.44–94.40 μg/L); and 2024 78.41 μg/L (95% CI: 70.19–86.63 μg/L), with significant heterogeneity among the groups ($I^2 = 0.0\%$, $p<0.001$). We found that the SIC levels varied across years. The SIC in 2020 was higher than in other years, which might be attributed to the fact that the population consisted entirely of pregnant women. During pregnancy, the body's metabolism and iodine consumption accelerate, while dietary intake also increases. The relatively higher SIC in 2021 may be related to the inclusion of patients with thyroid diseases, as iodine is closely associated with thyroid function. The SIC in 2022 was the lowest among the study years, possibly because the included populations were all healthy adults whose serum iodine levels were within the recommended range.

There was significant heterogeneity among the groups ($I^2 = 0.0\%$, $p<0.001$). By employing ArcGIS mapping software to present a weighted map of the SIC survey results for each province throughout the country, we observed more studies from coastal and northern regions, while relatively fewer reports are available from the central and northwest regions of China. Among the reported studies, the largest amount of research was carried out in

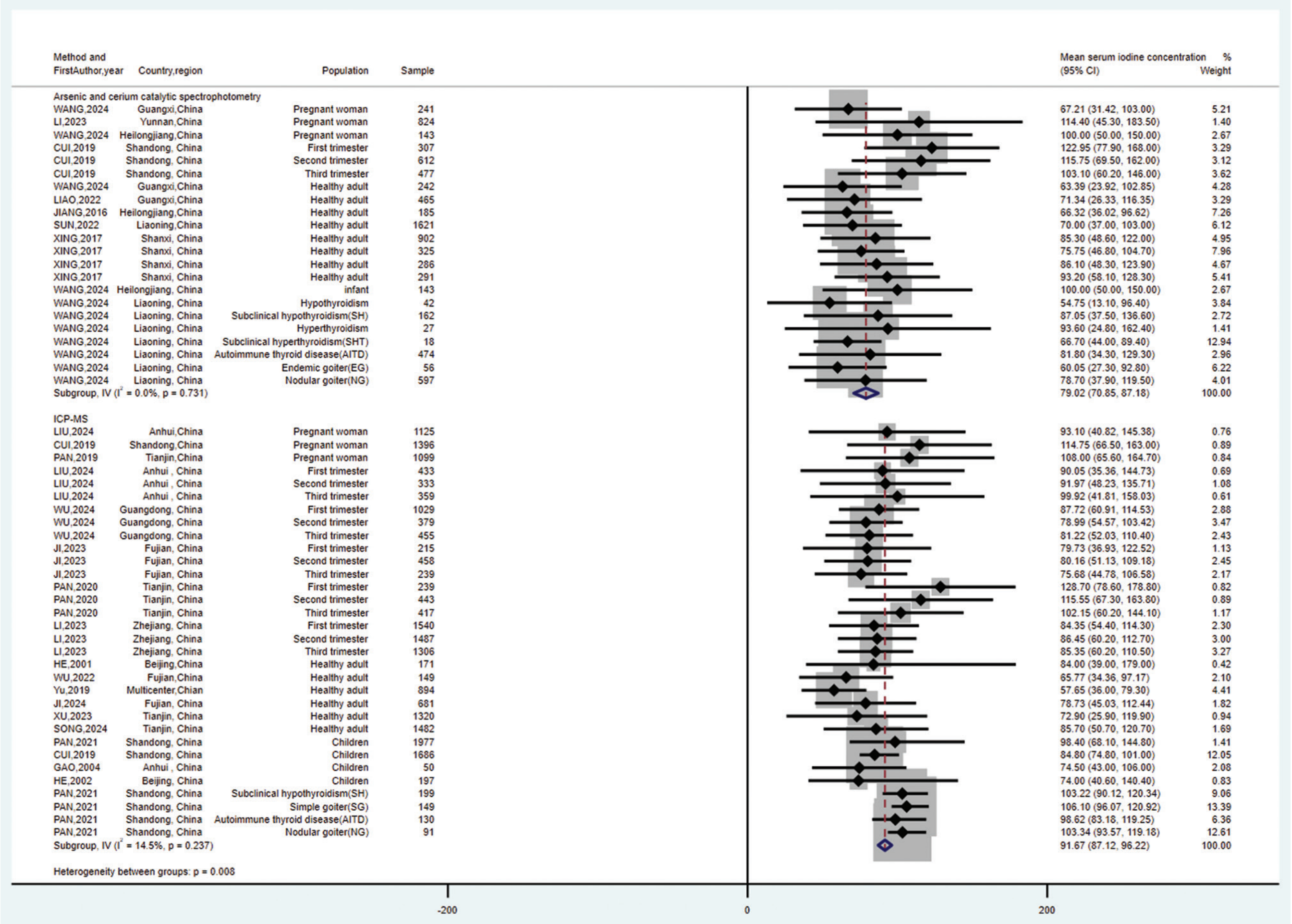


Figure 9. Forest plots depicting the average serum iodine concentration (SIC) values and 95% confidence intervals (CIs) for different detection methods. Image created by the authors.

Notes: The hollow diamonds represent the pooled estimates for each study and the overall SIC concentration, while the solid diamonds represent point estimates (horizontal lines indicate 95% CIs). The size of the squares is proportional to the relative weight of each study.

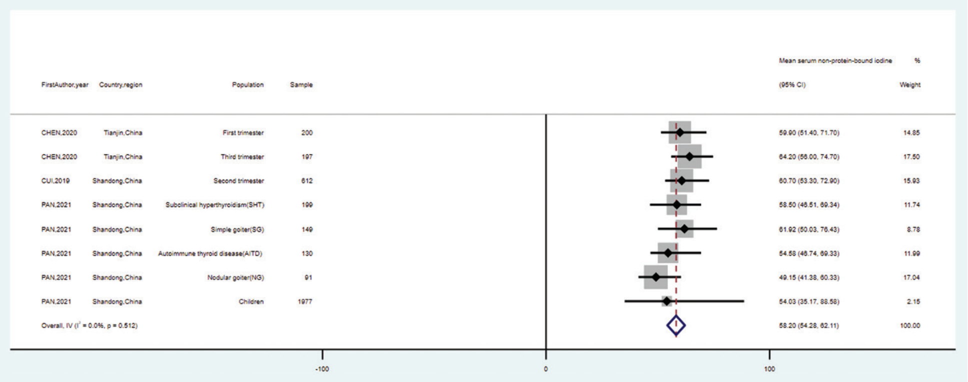
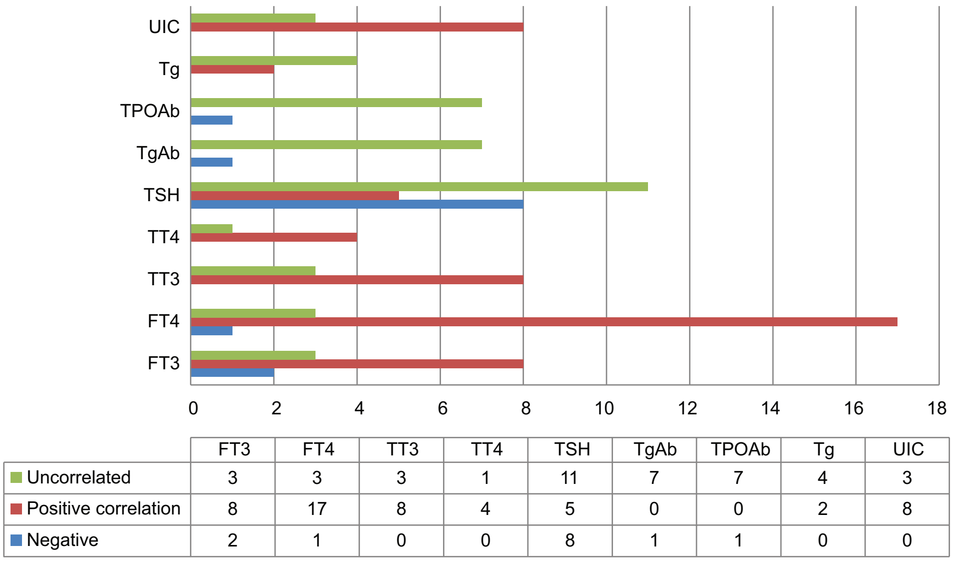


Figure 10. Means and 95% confidence intervals (CIs) of non-protein-bound serum iodine concentration (SIC) for different populations. Image created by the authors.

Notes: The hollow diamonds represent the pooled estimates for each study and the overall SIC concentration, while the solid diamonds represent point estimates (horizontal lines indicate 95% CIs). The size of the square is proportional to the relative weight of each study.

Beijing, Heilongjiang province, and Shandong province. In contrast, no eligible studies were identified from Chongqing, Hunan province, Jiangxi province, Sichuan province, Shaanxi province, Gansu province, Qinghai province, Inner Mongolia autonomous region, Tibet autonomous region, Ningxia Hui autonomous region,



	FT3	FT4	TT3	TT4	TSH	TgAb	TPOAb	Tg	UIC
🟩 Uncorrelated	3	3	3	1	11	7	7	4	3
🟥 Positive correlation	8	17	8	4	5	0	0	2	8
🟦 Negative	2	1	0	0	8	1	1	0	0

Figure 11. Summary chart of the relationship between serum iodine concentration (SIC), urinary iodine concentration (UIC), and thyroid function. Image created by the authors.
Abbreviations: FT: Free thyroxine; Tg: Thyroglobulin; TgAb: Thyroglobulin antibody; TPOAb: Thyroid peroxidase antibody; TSH: Thyroid-stimulating hormone; TT: Total triiodothyronine.

Hong Kong, or Macao special administrative region. Based on the reported studies, we observed that Tianjin and Shandong had higher SIC levels compared with other provinces, and most of the studies included thyroid disease patients and pregnant women. Nevertheless, these levels were all within the internationally recommended range of SIC. China implemented a universal salt iodization policy in 1996, which gradually resolved the long-standing issue of iodine nutritional deficiency and iodine deficiency disease in the country, making significant contributions to the prevention and control of iodine deficiency disorders worldwide. By 2010, 28 provinces had successfully eliminated iodine deficiency disease as a public health problem.[5] This study revealed that there was a statistically significant disparity in SIC levels among different regions; however, all were considered iodine-sufficient areas. Hence, it is essential to carry out nationwide SIC testing in the future to facilitate the establishment of a national reference range and support individualized iodine supplementation.

This systematic review conducted a subgroup analysis of the average SIC values and 95% CI values for different detection populations. The results showed that the average SIC value and 95% CI for pregnant women were 94.02 μg/L (95% CI: 74.38–113.66 μg/L); for the first trimester, 93.88 μg/L (95% CI: 78.59–109.17 μg/L); for the second trimester, 88.04 μg/L (95% CI: 74.83–101.24 μg/L); for the third trimester, 88.99 μg/L (95% CI: 73.13–100.84 μg/L); for healthy adults, 72.88 μg/L (95% CI: 63.78–81.97 μg/L); for children, 84.11 μg/L (95% CI: 72.87–95.35 μg/L); for subclinical hypothyroid, 101.84 μg/L (95% CI: 87.39–116.30 μg/L); for autoimmune thyroid disease, 96.50 μg/L (95% CI: 79.64–113.36 μg/L); and for nodular goiter, 101.13 μg/L (95% CI: 88.91–113.35 μg/L), with significant heterogeneity among the groups (I^2 = 0.0%, p=0.007). We determined that the SIC level of pregnant women was higher than that of healthy adults and children. In addition, when subgroup analysis was performed based on different stages of pregnancy, we observed that the SIC level was relatively higher in early pregnancy; however, there was no statistically significant difference among the groups (p=0.784). Nevertheless, most previous studies have found a statistically significant variance in SIC levels across different pregnancy periods (H = 26.20, p<0.05), with the median SIC in early pregnancy being significantly lower than that in middle and late pregnancy (z = −4.285, −2.880, p<0.05).[10,11] At present, due to the challenges associated with sample collection from infants, assessing iodine nutritional status in infants remains difficult. Thus, no optimal standard for evaluating the nutritional status of infants using SIC has been established, and future research should focus on this population. Iodine is an indispensable element for the synthesis of thyroid hormones, and both excessive and deficient iodine can lead to thyroid diseases of varying degrees. We observed that the SIC level of patients with thyroid diseases was generally elevated. Jin *et al.*[39] investigated the relationship between SIC and thyroid diseases and concluded that SIC >100 μg/L was associated with thyroid disorders. By drawing receiver operating characteristic curves to verify the consistency between thyroid function and serum iodine, it was found that SIC has significant diagnostic value for thyroid dysfunction and higher accuracy than UIC. Previous studies have demonstrated that thyroid diseases can be triggered by either insufficient or excessive iodine intake. However, current research on thyroid diseases remains relatively scarce, and no studies have comprehensively examined the SIC levels of patients with various types of thyroid diseases. Future research focusing on this aspect could facilitate individualized management for thyroid disease patients.[48]

This systematic review performed a subgroup analysis of the average SIC values and 95% CI values for different detection methods. The results indicated that the average SIC value and 95% CI of arsenic–cerium catalytic spectrophotometry were 79.02 μg/L (95% CI: 70.85–87.18 μg/L), while those of ICP-MS were 91.67 μg/L (95% CI: 87.12– 96.22 μg/L), with significant heterogeneity among the groups (I^2 = 0.0%, p=0.008). We observed that the average SIC value and 95% CI determined via ICP-MS were higher than those determined by arsenic–cerium catalytic spectrophotometry. It is hypothesized that this difference might be influenced by factors such as sample size, detection time, personnel, and reagent types. At present, there are numerous methods for determining SIC, including chromatographic methods (gas chromatography, ion chromatography, high-performance liquid chromatography), the neutron activation method, the alkali ash method, and the graphite furnace atomic absorption method. Nevertheless, the instruments employed in these methods are costly, the conditions for sample decomposition are stringent, and the technical requirements for operators are high, making it challenging to control the precision of results and hindering their widespread application in China.[29,34] Arsenic–cerium catalytic spectrophotometry, a classic method for trace iodine detection recommended by the health industry, offers the advantages of low instrument cost, simple operation, high detection sensitivity, and good accuracy. It is well-suited for large-scale testing of numerous samples in basic laboratories. ICP-MS, a widely utilized micro-iodine detection and analysis technique in the current analysis field, requires no sample digestion and is characterized by rapid analysis, high sensitivity, and excellent precision and accuracy. The iodine standard curve range set by this method is 0–300 μg/L, which can meet the detection needs for low-, normal-, and high-iodine serum levels and fulfill the requirements for individualized iodine nutritional evaluation in clinical practice.[45] Future research trends will likely continue to focus on the detection and analysis of SIC using arsenic–cerium catalytic spectrophotometry or ICP-MS.

This systematic review also summarized the average values and 95% CI of SIC for different detection sample types. The results revealed that five articles reported the nutritional status of SnbI in different groups. We found that the average SnbI value and 95% CI were equivalent to the overall average SnbI value and 95% CI of 58.20 μg/L (95% CI: 54.28–62.11 μg/L) (I^2 = 0.0%, p=0.512). There are extremely few studies on SnbI, protein-bound serum iodine, plasma iodine, and whole blood iodine; thus, more extensive research in this field is warranted in the future. The SnbI levels during the various trimesters of pregnancy were 60.3 (51.0–67.8) μg/L, 54.0 (47.0–62.6) μg/L, and 54.4 (45.7–62.4) μg/L, respectively, showing a decline as pregnancy progressed (p<0.001). The serum total iodine concentration and the SnbI concentration were negatively correlated. SnbI was positively correlated with TSH in children (p<0.05) and with serum Tg concentration (p<0.05). SnbI was negatively correlated with TSH in pregnant women (p<0.05) and positively correlated with serum Tg concentration in both pregnant women and children. Nevertheless, the number of such studies was too limited for further discussion in this meta-analysis. Finally, this review summarized the correlation between SIC and thyroid function, as well as the level of UIC. The range of SIC values examined was 23.92–183.50μg/L. Within this range, the number of studies investigating the correlation between SIC level and FT4 or FT3 was the largest, with the proportions of positive correlation being 81.0% and 72.7%, respectively. This can be explained by the fact that iodine serves as a substrate for the synthesis of thyroid hormones and plays a key role in regulating and maintaining normal thyroid function. The correlations between SIC level and UIC, TT4, TT3, and Tg were either positive or not significant, with no negative correlations reported. The correlations between SIC and TPOAb or TgAb were mostly not significant (87.5% for both), indicating that the association between serum iodine and thyroid antibodies is weak. The correlation between SIC and TSH was inconsistent, with proportions of positive, negative, and no correlation being 20.8%, 33.3%, and 45.8%, respectively, making it difficult to determine whether SIC is a directional marker of thyroid function. Future studies with larger sample sizes should be conducted to explore this further.

The main advantage of this study is that it conducted subgroup analyses for different populations, regions, detection years, and methods, which facilitated the summarization and analysis of reference value ranges for SIC across various levels and populations. However, due to the influence of research methods, study populations, sample sizes, and other factors on the different subgroups, the sources of heterogeneity could not be determined through meta-analysis. The use of different measurement instruments, standards, and personnel in SIC assessment may lead to discrepancies in study results, and there is a lack of survey data on other possible influencing factors. Therefore, in the future, it is necessary to redefine the reported iodine nutritional status using unified standards, and more studies are needed to establish a comprehensive medical reference range for SIC.

In summary, this systematic review encompassed all studies reporting SIC mean values and 95% CI summary results: 88.68 μg/L (95% CI: 84.70–92.65μg/L) (I^2 = 11.6%; p=0.238), and the mean value and 95% CI of all SnbI were 58.63μg/L (95% CI: 54.74–62.52 μg/L) (I^2 = 20.1%, p=0.284). The meta-analysis results indicated that the mean value and 95% CI of SIC differed across different detection years, regions, and populations (p<0.001) and also varied according to detection methods (p=0.008). Furthermore, the included studies in this systematic review reported SIC levels ranging from 23.92 to 183.50 μg/L. Within this range, the largest number of studies examined the relationship between SIC levels and FT4 and FT3, with proportions of positive correlation being 81.0% and 72.7%, respectively. The correlations between SIC levels and UIC, TT4, TT3, and Tg were all positive or not significant, with no studies reporting negative correlations. SIC was mostly unrelated to TPOAb and TgAb, while its correlation with TSH was inconsistent, with proportions of positive, negative, and no correlation being 20.8%, 33.3%, and 45.8%, respectively. Limitations of this study include: (i) Due to factors such as research methodology, study population source, and sample size, the inclusion of non-randomized or heterogeneous studies may have introduced selection bias; (ii) differences in measurement instruments, standards, and personnel for serum iodine assessment may have led to variations in study results; (iii) there was a lack of survey data on other potential influencing factors.

In summary, this systematic review preliminarily highlighted the current absence of a complete and uniform medical reference range for SIC. However, due to the limited quality and quantity of the included studies, these findings still require validation through high-quality, large-scale epidemiological studies. Future studies should be conducted across multiple centers with large sample sizes to provide reference data for individualized iodine nutrition assessment, thereby supporting scientific and precise iodine supplementation.

5. Conclusion

The pooled analysis showed that the mean SIC value and 95% CI were 88.68 μg/L (95% CI: 84.70–92.65 μg/L). The average value and 95% CI of SIC vary depending on the testing year, region, population and testing method. The range of SIC included in this meta-analysis was 23.92–183.50 μg/L. Among them, most studies investigated the correlation between SIC and FT4 or FT3, of which 81.0% and 72.7% demonstrated positive correlations.

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Conflict of interest

The authors declare that they have no competing of interests.

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Visualization: Na Lv
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Writing–review & editing: Hong Qiao, Shengnan Gao

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

Not applicable.

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