The association between subclinical hypothyroidism and metabolic syndrome: an update meta-analysis of observational studies

Xi Ding1) *, Yang Zhao1) *, Chun-Ying Zhu2), Li-Ping Wu1), Yue Wang1), Zhao-Yi Peng1), Cuomu Deji1), Feng-Yi Zhao1) and Bing-Yin Shi1)

1) Department of Endocrinology, First Affiliated Hospital of Xi’an Jiaotong University, Xi’an, 710061, China
2) Department of Disease Prevention And Control, Shaanxi Xi’an Electric Power Center Hospital, Xi’an 710000, China

Abstract. The association between subclinical hypothyroidism (SCH) and metabolic syndrome (MetS) has been widely discussed. This study aimed to conduct an update and comprehensive meta-analysis to reveal the risk of MetS and its components in SCH. PubMed, Embase and ISI Web of Knowledge were searched to identify relevant studies through February 20th, 2020. Review Manager 5.3 and Stata 14.0 were used to conduct the meta-analysis. Both fixed-effects and random-effects models were used. In total, 18 articles (19 studies) incorporating 79,727 participants were included. The pooled OR for MetS comparing subjects with SCH with euthyroid subjects was 1.28 (95% CI: 1.19 to 1.39, p = 0.04, I^2 = 40%). Subgroup analysis results showed significant associations of SCH and MetS in the adult subgroup (OR = 1.28, 95% CI: 1.18–1.40), Asian population subgroup (OR = 1.30, 95% CI: 1.19–1.42) and cross-sectional study design subgroup (OR = 1.31, 95% CI: 1.16–1.47). Significant associations of SCH and MetS also existed in all MetS definition criteria subgroups except the Chinese Diabetes Society (CDS) subgroup. SCH was correlated with MetS and was not affected by the subgroup analysis stratified by the proportion of females in the total population, the TSH cutoff value in SCH diagnostic criteria, or the adjustment for confounding factors. SCH was identified to be associated with an increased risk of obesity, hypertension, high triglyceride (TG) levels and low high-density lipoprotein cholesterol (HDL-C) levels. In conclusion, SCH is significantly associated with an increased risk of MetS and four out of five components of MetS.

Key words: Subclinical hypothyroidism, Metabolic syndrome, Meta-analysis, Observational study

SUBCLINICAL HYPOTHYROIDISM (SCH) is defined as an increased serum thyroid-stimulating hormone (TSH) level with normal free thyroxine concentrations (FT4). This condition affects up to 10% of the adult population worldwide [1]. The debate about the relationship between SCH and cardiovascular disease (CVD) is ongoing. A number of evidence-based studies have shown that SCH is associated with an increased risk of CVD [2, 3]. Furthermore, a meta-analysis of prospective cohort studies revealed that SCH is associated with an increased risk of CVD and all-cause mortality [4]. These observational studies suggest that SCH may be a predictive biomarker for the risk of CVD and its metabolic risk factors.

On the other hand, metabolic syndrome (MetS), characterized by a cluster of risk factors for CVD, including central obesity, hypertension, high triglyceride (TG) levels, low high-density lipoprotein cholesterol (HDL-C) levels, and hyperglycemia, is a common disease in the general population [5]. MetS is associated with a 2-fold increased risk of CVD and a 5-fold increased risk of developing type 2 diabetes mellitus [5]. Until now, the association between SCH and MetS has been widely explored with controversial results for more than a decade [6-12]. Most of the studies reported that SCH leads to an increased risk of MetS, as well as its components [6-9], while others suggested opposite views [10-12].

To date, three previous meta-analyses investigating the relationship between SCH and MetS have been published [13-15]. However, the first was conducted in 2013 [13], and the other two were conducted in 2016 [14, 15]. The latest dataset collected data up to September 2015 [15]. Since then, five more observational studies examining the association between SCH and MetS and its...
components have emerged [6, 7, 9, 10, 16], and three were relatively large-scale and well-designed studies [6, 7, 9].

Thus, we performed an updated systematic review and meta-analysis of all available data to investigate the association between SCH and MetS and its five components.

Materials and Methods

This meta-analysis was conducted and reported according to the Meta-Analysis of Observational Studies in Epidemiology guidelines.

Data sources and search strategy

Two authors (Ding and Zhao) independently searched relevant articles in three databases, PubMed, Embase and ISI Web of Knowledge, from inception up to February 20th, 2020. The search strategy comprised the following terms: “subclinical hypothyroidism” or “subclinical thyroid disease” or “thyroid dysfunction” or “thyroid hormones” or “thyrotropin” and “metabolic syndrome”. The search had no population restriction or language limits. The primary retrieval resulted in 902 articles from Pubmed, 869 from Embase, and 450 from ISI Web of Science. References of included articles and relevant reviews were also manually reviewed for eligible studies.

Inclusion criteria

Studies were identified as eligible if they met the following inclusion criteria: (1) a published observational study having clear definitions of SCH, euthyroidism and MetS; (2) individuals in the study population did not have diseases other than SCH and MetS; (3) the incidence or prevalence of MetS in groups of SCH and euthyroid subjects was clearly presented or could be calculated or converted; and (4) the odds ratio (OR), relative risk (RR) or hazard ratio (HR) and the corresponding 95% confidence interval (CI) were reported or could be calculated or converted (some studies may provide only case numbers of MetS in groups of SCH and euthyroid patients). Studies that used animal models or cell cultures, were written as reviews, case reports, or conference abstracts, and were published in languages other than English or Chinese were excluded. There were no cases of overlapping studies.

Data extraction and quality assessment

The following data were extracted: the first author’s name, year of publication, region, study design, sample size of the study, mean age of the study population, characteristics of the study population, female proportion of the study population, diagnostic criteria of SCH, diagnostic criteria of MetS, and adjustment for study covariates. Two reviewers (Ding and Zhao) independently conducted study selection and data extraction. Disagreements about assessments between reviewers were resolved by discussion.

The Agency for Healthcare Research and Quality (AHRQ) test was used for the quality assessment of cross-sectional studies, while the Newcastle-Ottawa Scale (NOS) was used to assess the quality of case-control studies and cohort studies.

Statistical analysis

The meta-analysis was performed with Review Manager 5.3 (Nordic Cochran Centre, Copenhagen, Denmark) and Stata 14.0 (Stata Corp. LP, College Station, TX). The study had two outcomes: the first outcome was the risk of MetS in SCH, and the second outcome was the risk of each component of MetS in SCH. ORs were considered the most common measure of the association between SCH and MetS, and HRs in studies exploring associations between SCH and MetS were assumed to have approximately the same effect estimate as ORs. To combine the ORs and 95% CIs of all included studies into mean ORs and 95% CIs, the present study converted ORs to log ORs and then chose log ORs and standard errors (SEs) as final effect estimates. The log OR and SE of every study were calculated by RevMan’s own calculator and were pooled to aggregate a mean log OR and 95% CI. Statistical heterogeneity across studies was assessed through the Q and I² statistics. An I² statistic ≤50% was proposed to indicate low heterogeneity and recommend the use of a fixed-effects model, while an I² statistic >50% was considered to indicate high heterogeneity and recommend the use of a random-effects model. This study assessed the combined risk estimates through either fixed-effects models or random-effects models with the presence of heterogeneity. Publication bias was evaluated through Egger’s test and Begg’s test. A two-tailed p-value less than 0.05 was considered indicative of statistical significance.

Results

Literature search and study selection

The flowchart of the literature search and study selection progress is displayed in Fig. 1. The database search initially yielded 2,221 articles: 902 articles from PubMed, 869 articles from Embase and 450 articles from ISI Web of Knowledge. After the preliminary screening, 143 articles remained. After reading the titles and/or the abstracts, 116 articles were excluded. A total of 27 articles underwent full-text review. Nine articles were excluded for the reasons listed in Fig. 1. Finally, 18 articles were included in this meta-analysis [6-12, 16-26].
Study characteristics and quality assessment

The characteristics of the 18 included articles are shown in Table 1. Eighteen articles (19 observational studies: 15 cross-sectional studies, 3 case-control studies and 1 cohort study; the article by Waring et al. included both a cross-sectional study and a cohort study) involving 79,727 participants were included. The SCH group comprised 6,149 individuals, and the euthyroid group consisted of 73,578 subjects. The study sample sizes ranged from 92 (Luboshitzky et al. [25]) to 19,006 (Rui-cen Li et al.) [9].

Among the 19 studies, 13 studies were conducted in Asian countries, and 6 were conducted in non-Asian countries. Regarding the age of the population, two studies (Min-Kyung Lee et al. and Jingfan Zhang et al.) [10, 17] focused on adolescents, the studies by Waring et al. [22] were limited to older adults (70–79 years old), and the rest were about the general adult population. For the definition of MetS, 9 studies chose the National Cholesterol Education Program’s Adult Treatment Panel III (NCEP-ATP III) criteria, three chose the International Diabetes Federation (IDF) criteria, three selected the China Diabetes Society (CDS) criteria, two selected the American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI) statements, and two used the Joint Interim Statement (JIS) criteria. Regarding the female proportion of the study population, six studies had populations that were fewer than 50% female, seven studies had populations that were between 50% and 60% female, and the other six studies included populations that were more than 60% female.

Most studies defined SCH as an elevated TSH level with a normal FT4 concentration. Four studies identified the TSH level to be elevated above the cutoff value of 4.0–4.5 mU/L with a normal FT4 concentration, nine studies had a TSH cutoff value of 4.5–5.0 mU/L, three studies had a TSH cutoff value above 5.0 mU/L, and three studies did not have a defined cutoff value of TSH.
| Author/ Publication year | Region/study design | Sample size/SC/ euthyroid | Mean age | Characteristics of population/ Women (%) | SCH diagnosis criteria | Severity classification of SCH | MetS diagnosis criteria | ORs/HRs/RRs; 95% CI | Adjustment for Covariates | Iodine intake | Autoantibodies |
|--------------------------|---------------------|---------------------------|----------|---------------------------------------|----------------------|---------------------------|---------------------|---------------------|---------------------|----------------|----------------|
| Li. RC (10) 2020         | China/CS            | 19,006 2,811/16,195       | 42.9 ± 9.08 | Adults/43.2%                          | An elevated TSH level with normal FT4 | /                       | NCEP ATP III         | 1.216 (1.056, 1.401) | Not mentioned                   | /                | /              |
| Lee. MK (11) 2019        | Korea/CS            | 1,006 143/863             | 14.2 ± 2.5  | Adolescents/47%                        | TSH > 4.5 mIU/ml with normal FT4 | /                       | IDF                 | 1.20 (0.54, 4.11)  | Age, gender, and BMI                | /                | /              |
| Liu. FH (8) 2018         | Taiwan/CS           | 16,146 203/15,945         | 42.9 ± 9.08 | Adults/39.8% (in Total) 50.2% (in SCH) 39.7% (in EU) | Elevated TSH levels (5.5–10 mIU/L) | /                       | NCEP ATP III         | 1.738 (1.298, 2.327) | Age and BMI                    | /                | /              |
| Bermúdez. V (17) 2018    | Venezuela/CS        | 391 41/350                 | /         | Adults/52.9%                           | TSH > 12 mIU/L with normal FT4 | /                       | JIS                 | 2.06 (1.72, 3.959) | None                                      | Iodine sufficient area | /              |
| Mehran. L (7) 2017       | Iran/CS             | 5,042 294/4,748           | 40.3 ± 14.4 | Adults/57.2%                           | TSH = 5.06 mIU/L and 0.91 ≤ FT4 ≤ 1.55 | /                       | JIS                 | 1.76 (1.04, 2.97) | Age, gender, smoking and BMI       | Iodine sufficient area | TPOAb was measured |
| Zhang. J (18) 2014       | China/CS            | 895 29/866                 | /         | Adolescents/46.6%                      | TSH = 5.73 mIU/L with normal FT4 | /                       | IDF                 | 1.908 (0.645, 5.644) | Age, gender, HOMA-IR, and BMI | /                | TPOAb was measured |
| Posadas-Romero (19) 2014 | Mexico/CS           | 753 133/620               | SCH 56.1 ± 8.4 EU 52 ± 9.6 | Adults/54.1%                           | High serum TSH with normal FT4 | /                       | AHA/NHLBI            | 0.89 (0.53, 1.53) | Age, gender, BMI, visceral adipose tissue, high sensitivity C-reactive protein, free thyroxine, and LDL-C | /                | /              |
| Pesic. M (20) 2014       | Serbia/CC           | 129 60/60                  | SCH 52.0 ± 8.79 EU 51.07 ± 10.50 | Adults/71.7%                           | TSH > 4.0 mIU/L (repeated in a three-month period) with normal FT4 | /                       | NCEP ATP III         | 1.75 (0.836, 3.662) | None                                      | TPOAb and TgAb were measured | /              |
| Sun. Y (21) 2014 (Chinese paper) | China/CS            | 1,846 146/1,700          | 62.3 ± 9.1 | Adults/62.9%                           | TSH > 4.5 mIU/L with normal FT4 | /                       | CDS                 | 1.211 (0.855, 1.716) | None                                      | Iodine sufficient area | /              |
| Gan. X (22) 2014 (Chinese Paper) | China/CS            | 2,160 110/2050          | 47.2 ± 13.3 | Adults/52.9%                           | TSH > 4.78 mIU/L with normal FT4 | /                       | CDS                 | 1.708 (1.063, 2.638) | None                                      | Iodine sufficient area | /              |
| Nakajima. Y (9) 2013     | Japan/CS            | 10,350 454/9,896         | 48 ± 9 | Adults/38.4%                           | TSH > 4.0 mIU/L with normal FT4 | /                       | NCEP ATP III         | 2.70 (1.10, 5.60)  | Age                                       | Iodine sufficient area | /              |
| Author/ Publication year | Region/study design | Sample size/SCH/ euthyroid | Mean age | Characteristics of population/ Women (%) | SCH diagnosis criteria | Severity classification of SCH | MetS diagnosis criteria | ORs/HRs/RRs; 95% CI | Adjustment for Covariates | Iodine intake | Autoantibodies |
|--------------------------|---------------------|-----------------------------|----------|-----------------------------------------|-----------------------|--------------------------------|----------------------|----------------------|--------------------------|--------------|---------------|
| Waring. A (23) 2012      | US/CS               | 2,047 268/1,779             | 73.6 ± 2.9 | Older adults: 53%                        | TSH 4.5–20 mIU/L with normal FT4 | Mild SCH (TSH 4.5–9.9 mIU/L, normal FT4) | NCEP ATP III | 1.00 (0.70, 1.50) | Age, gender, race, smoking status, BMI, and HOMA-IR | /            | /             |
|                         | US/Cohort           | 2,047 268/1,779             | 73.6 ± 2.9 | Older adults: 53%                        | TSH 4.5–20 mIU/L with normal FT4 | Mild SCH (TSH 4.5–9.9 mIU/L, normal FT4) | NCEP ATP III | 2.30 (1.00, 5.00) | Age, gender, race, smoking status, BMI, and HOMA-IR | /            | /             |
| Wang. CY (13) 2012       | Taiwan/CS           | 8,816 412/8,404             | SCH 53.01 ± 11.55 | EU 51.62 ± 11.67 | Adults: 42.7% | TSH 4–10 mIU/L | / | NCEP ATP III | 1.047 (0.760, 1.443) | Age and gender | /             |
| Liu. C (12) 2011         | China/CS            | 6,339 538/5,801             | 48.9 ± 13.7 | Adults: 62.1%                           | TSH >4.5 mIU/L with normal FT4 and FT3 | / | IDF | 1.274 (1.040, 1.562) | None                  | /             |
| Lai. Y (24) 2011         | China/CS            | 1,385 102/1,283             | SCH 46 ± 12 | EU 45 ± 14 | Adults: 60.3% | TSH >4.8 mIU/L with normal FT4 and FT3 | / | CDS | 1.426 (0.889, 2.287) | Age, gender, HOMA-IR and BMI. | /             |
| Erdogan. M (25) 2010     | Turkey/CC           | 500 100/200                 | SCH 42.36 ± 14.06 | EU 42.47 ± 13.05 | Adults: 89% | High serum TSH with normal FT4 and FT3 | / | NCEP ATP III | 1.093 (0.659, 1.813) | None                  | TPOAb and TgAb were measured |
| Luboshitzky. R (26) 2010 | Israel/CC           | 92 43/49                    | SCH 55.9 ± 7.4 | EU 52.0 ± 8.1 | Adults: 100% | TSH >4.5 mIU/L with normal FT4 (8.7–22.6 nmol/L) | / | AHA/NHLBI | 5.160 (1.811, 14.704) | Age, BMI and waist size | TPOAb and TgAb were measured |
| Garduno-Garcia (27) 2010 | Mexico/CS           | 3,033 262/2,771             | 42.3 ± 10  | Adults: 51.2%                           | 4.5 ≤ TSH <10 mIU/L with normal FT4 (10–25 pmol/L) | Mild SCH (TSH 4.5–9.9 mIU/L, normal FT4) | NCEP ATP III | 1.021 (0.778, 1.339) | None                  | /             |

Abbreviations: CS, Cross-sectional study; CC, Case-control study; SCH, Subclinical hypothyroidism; EU, Euthyroidism; FL, Fatty liver; MeS, Metabolic syndrome; TSH, Thyroid stimulating hormone; FT4, Free thyroxine; FT3, Free Triiodothyronine; NCEP-ATP III, National Cholesterol Education Program-Adult Treatment Panel III; IDF, International Diabetes Federation; CDS, Chinese Diabetes Society; AHA/NHLBI, American Heart Association/National Heart, Lung, and Blood Institute; JIS, IDF/AHA/NHLBI/WHF/IAS/IASO-2009 criteria; BMI, Body mass index; HOMA-IR, Homoeostasis model of insulin resistance; TPOAb, thyroid peroxi.dase antibody; TgAb, thyroglobulin antibody.
Out of the 19 studies, one did not mention whether the odds ratios were adjusted or not, 7 provided the specific number of people who had MetS in both the SCH and euthyroid groups, 8 provided the adjusted odds ratios adjusted for factors including “gender”, and 3 provided the adjusted odds ratios adjusted for factors not including “gender”.

The AHRQ test was used for the quality assessment of cross-sectional studies, while case-control studies and cohort studies were assessed by the NOS. Every item question of the quality assessment form was listed in turn, and a “Yes” was a confirmation of the question. The results in Table 2 indicated that the quality of the 19 included studies was relatively high.

### Subclinical hypothyroidism and the risk of metabolic syndrome

The pooled ORs for the association between SCH and MetS showed that the risk of MetS was significantly increased in SCH subjects (OR = 1.28, 95% CI: 1.18 to 1.39, p < 0.00001, I² = 40%). (Fig. 2) Because the heterogeneity was relatively low (I² = 40% <50%), we chose the fixed-effects model.

The subgroup analysis was performed based on seven factors: age, geographical region, study design, the definition criteria for MetS, the proportion of females in the total population, the TSH cutoff value in the SCH diagnostic criteria, and the adjusted confounding factors. The results of the associations between SCH and the risk of MetS according to the subgroup analysis are shown in Table 3.

When stratified by the age of the study population, the results revealed a significant association between SCH and MetS in both adults (OR = 1.28, 95% CI: 1.18 to 1.40, p < 0.00001, I² = 48%) and older adults (OR = 2.27, 95% CI: 1.13 to 4.58, p = 0.02, I² = 0%), with the exception of adolescents (OR = 1.16, 95% CI: 0.86 to 1.56, p = 0.34, I² = 0%) (Supplementary Fig. 1).

The results of the subgroup analysis based on geographical region showed that SCH was significantly associated with an increased risk of MetS in the Asian population (OR = 1.30, 95% CI: 1.19 to 1.42, p < 0.00001, I² = 40%) but not in the non-Asian population (OR = 1.20, 95% CI: 0.97 to 1.47, p = 0.09, I² = 47%) (Supplementary Fig. 2).

With regard to the study design, the results of the subgroup analysis indicated that SCH was significantly correlated with MetS only in the cross-sectional study subgroup (OR = 1.31, 95% CI: 1.16 to 1.47, p < 0.00001, I² = 35%). The pooled ORs showed no significant association between SCH and MetS in the case-control study subgroup (OR = 1.92, 95% CI: 0.87 to 4.28, p = 0.11, I² = 71%) or cohort subgroup (OR = 2.20, 95% CI: 0.60 to 8.07, p = 0.23, not applicable for heterogeneity) (Supplementary Fig. 3).

To explore the effect of the definition criteria of MetS on the association, the studies were categorized into NCEP-ATP III, IDF, CDS, AHA/NHLBI and JIS subgroups according to the definition criteria. The results of the subgroup analysis showed a significantly positive association between SCH and the risk of MetS in the NCEP-ATP III subgroup (OR = 1.32, 95% CI: 1.10 to 1.58, p = 0.003, I² = 47%), IDF subgroup (OR = 1.24, 95% CI: 1.04 to 1.46, p = 0.01, I² = 0%), CDS subgroup (OR = 1.40, 95% CI: 1.10 to 1.77, p = 0.006, I² = 48%) and JIS subgroup (OR = 1.87, 95% CI: 1.24 to 2.82, p = 0.003, I² = 0%) (Supplementary Fig. 4). However, there was no association observed in the AHA/NHLBI subgroup (OR = 2.02, 95% CI: 0.36 to 11.23, p = 0.42, I² = 88%) (Supplementary Fig. 5).

Regarding the proportion of females in the total population, the results showed that SCH was significantly associated with an increased risk of MetS in all three subgroups: the <50% subgroup (OR = 1.31, 95% CI: 1.03 to 1.50, p = 0.03, I² = 0%), 50%–60% subgroup (OR = 1.45, 95% CI: 1.08 to 1.94, p = 0.01, I² = 51%) and >60% subgroup (OR = 1.37, 95% CI: 1.09 to 1.72, p = 0.008, I² = 38%) (Supplementary Fig. 5).

The results of the subgroup analysis based on the TSH cutoff value in the SCH diagnostic criteria revealed a positive relationship between SCH and an increased risk of MetS in all four subgroups: the 4.0 ≤TSH < 4.5 subgroup (OR = 1.61, 95% CI: 1.02 to 2.56, p = 0.04, I² = 56%), 4.5 ≤TSH < 5.0 subgroup (OR = 1.40, 95% CI: 1.14 to 1.72, p = 0.001, I² = 43%), TSH ≥5.0 subgroup (OR = 1.48, 95% CI: 1.08 to 2.02, p = 0.01, I² = 55%) and no definite TSH cutoff value subgroup (OR = 1.18, 95% CI: 1.04 to 1.35, p = 0.01, I² = 0%) (Supplementary Fig. 6).

According to the factors studies were adjusted for, the studies were categorized into the “None or no mentioned” subgroup, factors including the “gender” subgroup and factors not including the “gender” subgroup. The results indicated that SCH was significantly correlated with MetS in all three subgroups: the “None or no mentioned” subgroup (OR = 1.24, 95% CI: 1.12 to 1.38, p < 0.00001, I² = 8%), factors including “gender” subgroup (OR = 1.24, 95% CI: 1.03 to 1.50, p = 0.03, I² = 12%) and factors not including “gender” subgroup (OR = 2.47, 95% CI: 1.34 to 4.56, p = 0.004, I² = 55%)
Table 2  Quality assessment of included studies

| A. Quality assessment of cross-sectional studies (AHRQ) |
|------------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|
| Li RC et al. | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | No |
| Li MK et al. | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes |
| Liu FH et al. | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | No |
| Bermúdez et al. | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | No |
| Mehran et al. | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | No |
| Zhang JF et al. | Yes | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No |
| Waring et al. | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Liu C et al. | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | No |
| Posadas-Romero et al. | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Lain YX et al. | Yes | Yes | No | Yes | Yes | Yes | Yes | Yes | No | Yes | No |
| Nakajima et al. | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Wang CY et al. | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No |
| Sun Y et al. | Yes | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | No | No |
| Gan XL et al. | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | No |
| Garduno-Garcia et al. | Yes | Yes | No | Yes | Yes | Yes | Yes | Yes | No | Yes | No |

| B. Quality assessment of case-control studies (NOS) |
|---------|---------|---------|---------|---------|---------|---------|---------|
| 1 | 2 | 3 | 4 | 5A | 5B | 6 | 7 | 8 |
| Erdogan et al. | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Luboshitzky et al. | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Pesic et al. | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes |

| C. Quality assessment of case-control studies (NOS) |
|---------|---------|---------|---------|---------|---------|---------|
| 1 | 2 | 3 | 4 | 5A | 5B | 6 | 7 | 8 |
| Waring et al. (cohort) | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |

A: Quality assessment of cross-sectional studies by the Agency for Healthcare Research and Quality (AHRQ)
1, define the source of information; 2, list inclusion and exclusion criteria for exposed and unexposed subjects or refer to previous publications; 3, indicate time period used for identifying patients; 4, indicate whether or not subjects were consecutive if not population-based; 5, indicate if evaluators of subjective components of study were masked to other aspects of the status of the participants; 6, describe any assessments undertaken for quality assurance purpose; 7, explain any patient exclusion from analysis; 8, describe how confounding was assessed and/or controlled; 9, if applicable, explain how missing data were handled in the analysis; 10, summarize patient response rate and completeness of data collection; 11, clarify what follow-up, if any, was expected and the percentage patients for which incomplete data or follow-up was obtained.

B: Quality assessment of case-control studies by the Newcastle-Ottawa Scale (NOS)
1, the case definition is adequate; 2, representativeness of cases; 3, controls drawn from community; 4, no history of disease in controls; 5A, study controlled for age; 5B, study controlled for other factor(s); 6, secure record of exposure; 7, same method of ascertainment for cases and controls; 8, same non-response rate for both groups.

C: Quality assessment of cohort study by the Newcastle-Ottawa Scale (NOS)
1, truly representative of the average older white and black population in the community; 2, drawn from the same community as the exposed cohort; 3, secure record of exposed cohort; 4, outcome of interest was not present at start of study; 5A, study controlled for age; 5B, study controlled for other factor(s); 6, independent blind assessment of outcome; 7, follow-up was long enough for outcomes to occur; 8, subjects lost to follow up unlikely to introduce bias.

(Supplementary Fig. 7).

**Subclinical hypothyroidism and the risk of each metabolic syndrome-specific component**

After summarizing the results from the included studies with available data on the risk of each specific MetS component, SCH was observed to be significantly associated with four out of five components of MetS: central obesity, hypertension, high TG level and low HDL-C level. (Table 4) The pooled OR was 1.21 (95%...
CI: 1.07 to 1.37, \( p = 0.003, \ P_{\text{heterogeneity}} = 0.18, I^2 = 28\% \) for central obesity (Supplementary Fig. 8), 1.76 (95% CI: 1.13 to 2.74, \( p = 0.01, \ P_{\text{heterogeneity}} = 0.00001, I^2 = 94\% \) for hypertension (Supplementary Fig. 9), 1.36 (95% CI: 1.13 to 1.65, \( p = 0.001, \ P_{\text{heterogeneity}} = 0.002, I^2 = 63\% \) for high triglyceride level (Supplementary Fig. 10) and 1.16 (95% CI: 1.03 to 1.31, \( p = 0.01, \ P_{\text{heterogeneity}} = 0.06, I^2 = 45\% \) for low HDL-C level (Supplementary Fig. 11) and 1.12 (95% CI: 0.99 to 1.28, \( p = 0.08, \ P_{\text{heterogeneity}} = 0.26, I^2 = 18\% \) for hyperglycemia (Supplementary Fig. 12).

Publication bias

To investigate potential publication bias, we examined Begg’s and Egger’s tests, which showed publication bias (Begg’s test: \( p = 0.025 \); Egger’s test: \( p = 0.016 \)). (Fig. 3) Then, the trim-and-fill method was used to collect the pooled ORs. After 6 studies were added (a total of 25 studies), publication bias still existed (\( p = 0.042 \)) (Supplementary Fig. 13).

Discussion

The unique strengths and novelty of the study

Our study is an updated meta-analysis. The original literature searches of the previous three meta-analyses ended in 2016, while five studies among the 19 we included were performed after 2016. These five studies incorporated 41,591 participants (SCH: 3,492; euthyroid: 38,099), which was nearly 52% of the total 79,727 patients in our meta-analysis. Moreover, the number of included studies in our meta-analysis was greater than that in any of the three previous meta-analyses (there were 6, 9 and 8 studies included in these three studies). Second, to extract the most complete and detailed data from the included studies, we did not make the inclusion criteria too restrictive. Unlike the first meta-analysis by Ye et al., which was confined only to cross-sectional studies, or the study by Eftekharzadeh et al., which applied a uniform MetS definition (NCEP-ATP III) to their data synthesis, studies eligible for our meta-analysis were not limited to a particular type of study design or specific MetS criteria. Although setting strict inclusion criteria for the literature may have the benefit of results that were not affected by potential flaws, we still believe that relatively broad but reasonable inclusion criteria combined with multiple stratification to perform subgroup analyses should be an optimal solution. With this in mind, we performed comprehensive subgroup analyses based on seven potential factors (age, geographical region, study design, the definition criteria for MetS, the proportion of females in the total population, the TSH cutoff value in the SCH diagnostic criteria, and the adjusted confounding factors), which was more than any of the three previous meta-analyses.
The association between SCH and MetS

The novel finding of our study is that SCH was associated with a 1.28-fold significantly increased risk of MetS compared with euthyroidism in our population, and for the first time, we found that the risk of MetS in SCH subjects seemed to differ according to age, ethnicity, study design and the definition criteria for MetS.

Table 3 Subgroup analysis of the association between subclinical hypothyroidism and the risk of metabolic syndrome

| Factor                                      | No. of Studies | Odds ratio | 95% CIs  | p for Difference | Model | Subgroup Difference |
|---------------------------------------------|----------------|------------|----------|------------------|-------|---------------------|
| Stratified by age                           |                |            |          |                  |       |                     |
| Adults                                      | 15             | 1.28       | 1.18, 1.40 | <0.00001         | FEM   | $\chi^2 = 33.7\%$   |
| Adolescents                                 | 2              | 1.16       | 0.86, 1.56 | 0.34             | p     | 0.22                |
| Older adults                                | 2              | 2.27       | 1.13, 4.58 | 0.02             | p     | 0.00001             |
| Stratified by geographical region           |                |            |          |                  |       |                     |
| Non-Asian                                   | 6              | 1.20       | 0.97, 1.47 | 0.09             | FEM   | $\chi^2 = 0\%$      |
| Asian                                       | 13             | 1.30       | 1.19, 1.42 | <0.00001         | p     | 0.00001             |
| Stratified by study design                  |                |            |          |                  |       |                     |
| Cross-sectional study                       | 15             | 1.31       | 1.16, 1.47 | <0.00001         | REM   | $\chi^2 = 0\%$      |
| Case-control study                          | 3              | 1.92       | 0.87, 4.28 | 0.11             | p     | 0.43                |
| Cohort study                                | 1              | 2.20       | 0.60, 8.07 | 0.23             | p     | 0.48                |
| Stratified by the definition criteria of MetS |            |            |          |                  |       |                     |
| NCEP-ATP III                                | 9              | 1.32       | 1.10, 1.58 | 0.003            |       |                     |
| IDF                                         | 3              | 1.24       | 1.04, 1.46 | 0.01             |       |                     |
| CDS                                         | 2              | 2.02       | 0.36, 11.23 | 0.42         | REM   | $\chi^2 = 0\%$      |
| AHA/NHLBI                                   | 3              | 1.40       | 1.10, 1.77 | 0.006            |       |                     |
| JIS                                         | 2              | 1.87       | 1.24, 2.82 | 0.003            |       |                     |
| Stratified by the proportion of female in the total population |            |            |          |                  |       |                     |
| <50%                                        | 6              | 1.31       | 1.08, 1.58 | 0.006            | REM   | $\chi^2 = 0\%$      |
| 50%–60%                                     | 7              | 1.45       | 1.08, 1.94 | 0.01             |       | p = 0.84            |
| ≥60%                                        | 6              | 1.37       | 1.09, 1.72 | 0.008            |       | p = 0.08            |
| Stratified by the TSH cutoff value          |                |            |          |                  |       |                     |
| 4.0 ≤TSH <4.5                               | 4              | 1.61       | 1.02, 2.56 | 0.08             | REM   | $\chi^2 = 23.0\%$   |
| 4.5 ≤TSH <5.0                               | 9              | 1.40       | 1.14, 1.72 | 0.08             |       | p = 0.27            |
| TSH ≥ 5.0                                   | 3              | 1.48       | 1.08, 2.02 | 0.11             | REM   | $\chi^2 = 0\%$      |
| No definite cutoff value                    | 3              | 1.18       | 1.04, 1.35 | 0.50             |       |                     |
| Stratified by the factors adjusted for      |                |            |          |                  |       |                     |
| None or not mentioned                       | 8              | 1.24       | 1.12, 1.38 | 0.37             | REM   | $\chi^2 = 57.6\%$   |
| Factors including “gender”                  | 8              | 1.24       | 1.03, 1.50 | 0.33             |       | p = 0.09            |
| Factors not including “gender”              | 3              | 2.47       | 1.34, 4.56 | 0.11             |       |                     |

NCEP-ATP III, National Cholesterol Education Program-Adult Treatment Panel III; IDF, International Diabetes Federation; CDS, Chinese Diabetes Society; AHA/NHLBI, American Heart Association/National Heart, Lung, and Blood Institute; JIS, IDF/AHA/NHLBI/WHF/IAS/IASO-2009 criteria; TSH, Thyroid stimulating hormone; FEM, Fixed effects model; REM, Random effects model.

and is the third strength of our study.

The novel finding of our study is that SCH was associated with a 1.28-fold significantly increased risk of MetS compared with euthyroidism in our population, and for the first time, we found that the risk of MetS in SCH subjects seemed to differ according to age, ethnicity, study design and the definition criteria for MetS.
Regarding age, the current results revealed that adults with SCH were more likely to develop MetS than adolescents. In fact, studies investigating the effect of SCH on body metabolism in adolescents are limited and remain controversial. The prevalence of SCH was estimated to be between 1.7% and 9.5% in children and adolescents [28]. The majority of the studies considered SCH to be a benign and remitting condition with a low risk of progression to overt thyroid dysfunction in children [29], while others suggested that SCH in obese children or adolescents should be carefully monitored to avoid increasing metabolic risk factors [30].

Regarding differences in ethnicity, our meta-analysis showed that Asian-SCH subjects had a higher predisposition to MetS than non-Asian-SCH participants, which is consistent with a previous study by Yang et al. [14]. Ethnicity may lead to differences in the association between SCH and MetS due to biological and sociocultural effects. TSH reference ranges were shown to vary across races [31], which results in significant differences in the prevalence of SCH among ethnic groups [32]. Some characteristics of the Asian population, such as an adequate seafood diet rich in iodine, a longer life expectancy and notable population aging progress, may also contribute to ethnic differences between Asian and non-Asian regions. However, the possibility that random error may account for this difference could not be excluded. Actually, we included only 6 studies in the non-Asian subgroup, and there were fewer participants (total: 6,344, SCH: 764, EU: 5,580) in the non-Asian subgroup than in the Asian subgroup (total: 73,380, SCH: 5,385, EU: 67,995). Thus, we expect more studies to explore the underlying reason for the racial differences occurring between Asian and non-Asian regions from biological and sociocultural aspects in the future.

In our study, a poor association between SCH and MetS was observed in the case-control study and cohort study subgroups. The small quantity of included studies in these two subgroups might account for this result, and random error cannot be excluded. Moreover, SCH was identified to be associated with MetS in all MetS

---

**Table 4** The association between subclinical hypothyroidism and each specific component of metabolic syndrome (MetS)

| MetS component      | No. of Studies | Odds ratio | 95% CIs       | p for Difference | I²         | Model  |
|---------------------|----------------|------------|---------------|-----------------|------------|--------|
| Central obesity     | 11             | 1.21       | 1.07, 1.37    | 0.003           | 0.18       | FEM    |
| Hypertension        | 12             | 1.76       | 1.13, 2.74    | 0.01            | <0.00001   | REM    |
| High triglyceride   | 12             | 1.36       | 1.13, 1.65    | 0.001           | 0.002      | REM    |
| Low HDL-C           | 10             | 1.16       | 1.03, 1.31    | 0.01            | 0.06       | FEM    |
| Hyperglycemia       | 12             | 1.12       | 0.99, 1.28    | 0.08            | 0.26       | FEM    |

CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; FEM, Fixed effects model; REM, Random effects model.

---

**Fig. 3** Egger’s publication bias plot
definition criteria subgroups except the CDS criteria subgroup in our meta-analysis, indicating that the diagnostic criteria selected for MetS may have an effect on the assessment of MetS risk in SCH. The reason may be explained from one point of view: the CDS criteria define central obesity as BMI ≥25 kg/m², while the NCEP-ATP III, IDF, AHA/NHLBI and JIS criteria all use the waist circumference threshold for MetS evaluation. Although a high BMI value is usually used to classify obesity, it is not equivalent to central obesity, which was confirmed in a study conducted by Eftekharzadeh et al. [15]. In fact, studies have demonstrated that BMI is only an imperfect measure of abnormal or excessive body fat accumulation and that using waist circumference as a measure of body fat distribution may improve visceral adiposity prediction [33, 34].

Simultaneously, three other important factors closely related to SCH should not be ignored in assessing the relationship between SCH and MetS: the severity classification of SCH, iodine intake condition and thyroid antibodies (thyroid peroxidase antibody (TPOAb) and thyroglobulin antibody (TgAb)) levels. SCH can be categorized as grade 1 (mild SCH) when TSH levels are between the upper limit of the reference range and 9.9 mU/L and as grade 2 (marked SCH) if TSH levels are 10 mU/L or higher, and the guidelines recommend different approaches for each grade [35]. Although 90% of SCH subjects are in grade 1 status [35], most of the 19 current studies included in our meta-analysis did not clearly mention the grade of their SCH subjects (more details can be seen in Table 1). For iodine intake, after the World Health Organization recommended the use of iodized salt to prevent iodine deficiency, the current iodine intake status has been sufficient or even excessive in many countries or regions, including China, Korea, Taiwan, Mexico, the U.S., and Europe (which are exactly the countries or regions in which the 19 studies in our meta-analysis were conducted) [36-45]. However, more than adequate iodine intake may increase the risk of SCH and autoimmune thyroiditis [36, 46] and has a 17.3% prevalence in SCH subjects [47]. Moreover, thyroid antibodies could be predictors of SCH in the risk of progression to overt hypothyroidism [48, 49], and MetS is reported to be more prevalent in children of TPO-Ab-positive mothers [50], indicating that positive thyroid antibodies may be associated with an adverse cardiovascular health profile [51]. However, due to incomplete information about the iodine intake condition and thyroid antibody measurement in the 19 included studies (more details are shown in Table 1), subgroup analysis could not be performed to study in depth the impact that these three factors may have on assessing the relationship between SCH and MetS. In summary, more well-designed studies considering more potential factors in the correlation between SCH and MetS are expected to verify our findings or hypothesis.

**The association between SCH and the components of MetS**

In addition, we found that SCH is associated with four out of five components of MetS: obesity, hypertension, a high TG level and a low HDL-C level. SCH has been extensively reported to be associated with obesity [52], high triglyceride levels [53, 54], low HDL-C levels [53] and increased insulin resistance [55, 56]. Among these metabolic parameters, obesity is the most indispensable component of MetS, and insulin resistance is assumed to be both the key feature and the major underlying cause of MetS. Our results revealed a positive correlation between SCH and lipid dysfunction, including high tri-glyceride levels and low HDL-C levels. This can be explained by the fact that a lack of thyroid hormones (THs) to some extent in SCH may decrease the transcription of the low-density lipoprotein (LDL) receptor gene and suppress essential enzyme activity involved in the metabolism of lipoproteins, ultimately leading to dyslipidemia [53, 57].

Our meta-analysis illustrated a propensity for hypertension in SCH, which is consistent with a previously established conclusion. Two large-scale studies have demonstrated the association between TSH levels above the upper normal limit and hypertension [58, 59], and a meta-analysis showed that replacement therapy with levothyroxine could reduce blood pressure in SCH patients [60]. However, no significant association between SCH and hyperglycemia was found in our study.

**Limitations of the study**

Two limitations should be acknowledged when interpreting the present findings. First, except for one cohort study, the majority of our included studies were cross-sectional (15/19) and case-control (3/19) designs, which might make it difficult to discern causality from the association between SCH and MetS. More longitudinal large-scale prospective cohort studies are needed to demonstrate these results. Second, publication bias was present, as evidenced by Begg’s and Egger’s tests (Begg’s test: \( p = 0.025 \); Egger’s test: \( p = 0.016 \)). Publication bias may arise because studies with statistically significant results are more likely to be accepted and published. This result suggested that studies that do not support a positive correlation between SCH and MetS may be less likely to be published. The results of our trim-and-fill method confirmed this point: after adding six potentially unpublished studies/datasets on this issue, publication bias still existed. This is consistent with
previous research conducted by Ye et al. In conclusion, our meta-analysis indicated that SCH was associated with an increased risk of MetS, as well as four out of five of its components: central obesity, hypertension, high TG levels and low HDL-C levels. The risk for MetS in SCH subjects seemed to differ according to age, ethnicity, study design and the definition criteria for MetS.

Acknowledgments

This research was supported by Grant 81873638 from the National Natural Science Foundation of Shaanxi Province and Grant 2018YFC1311500 from the National Key R&D Program of China.

Author Disclosure Statement

No competing financial interests exist.

References

1. Gomez-Izquierdo J, Filion KB, Boivin JF, Azoulay L, Pollak M, et al. (2020) Subclinical hypothyroidism and the risk of cancer incidence and cancer mortality: a systematic review. BMC Endocr Disord 20: 83.
2. Rhee CM, Curhan GC, Alexander EK, Bhan I, Brunelli SM (2013) Subclinical hypothyroidism and survival: the effects of heart failure and race. J Clin Endocrinol Metab 98: 2326–2336.
3. Kannan L, Shaw PA, Morley MP, Brindimarto J, Fang JC, et al. (2018) Thyroid dysfunction in heart failure and cardiovascular outcomes. Circ Heart Fail 11: e005266.
4. Moon S, Kim MJ, Yu JM, Yoo HJ, Park YJ (2018) Subclinical hypothyroidism and the risk of cardiovascular disease and all-cause mortality: a meta-analysis of prospective cohort studies. Thyroid 28: 1101–1110.
5. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, et al. (2009) Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation 120: 1640–1645.
6. Mehran L, Amouzegar A, Rahimabad PK, Tohidi M, Tahmasebinejad Z, et al. (2017) Thyroid function and metabolic syndrome: a population-based thyroid study. Horm Metab Res 49: 192–200.
7. Liu FH, Hwang JS, Kuo CF, Ko YS, Chen ST, et al. (2018) Subclinical hypothyroidism and metabolic risk factors association: a health examination-based study in northern Taiwan. Biomed J 41: 52–58.
8. Nakajima Y, Yamada M, Akuzawa M, Ishii S, Masamura Y, et al. (2013) Subclinical hypothyroidism and indices for metabolic syndrome in Japanese women: one-year follow-up study. J Clin Endocrinol Metab 98: 3280–3287.
9. Li RC, Zhang L, Luo H, Lei Y, Zeng L, et al. (2020) Subclinical hypothyroidism and anxiety may contribute to metabolic syndrome in Sichuan of China: a hospital-based population study. Sci Rep 10: 2261.
10. Lee MK, Kim YM, Sohn SY, Lee JH, Won YJ, et al. (2019) Evaluation of the relationship of subclinical hypothyroidism with metabolic syndrome and its components in adolescents: a population-based study. Endocrine 65: 608–615.
11. Liu C, Scherbaum WA, Schott M, Schinner S (2011) Subclinical hypothyroidism and the prevalence of the metabolic syndrome. Horm Metab Res 43: 417–421.
12. Wang CY, Chang TC, Chen MF (2012) Associations between subclinical thyroid disease and metabolic syndrome. Endocr J 59: 911–917.
13. Ye YC, Xie HZ, Zhao XL, Zhang SY (2013) Subclinical hypothyroidism and the metabolic syndrome: a meta-analysis of cross-sectional studies. World J Meta-Anal 1: 90–96.
14. Yang L, Lv X, Yue F, Wei D, Liu W, et al. (2016) Subclinical hypothyroidism and the risk of metabolic syndrome: a meta-analysis of observational studies. Endocr Res 41: 158–165.
15. Eftekharzadeh A, Khamseh ME, Farshchi A, Malek M (2016) The association between subclinical hypothyroidism and metabolic syndrome as defined by the ATP III criteria. Metab Syndr Relat Disord 14: 137–144.
16. Bermudez V, Salazar J, Anez R, Rojas M, Estrella V, et al. (2018) Metabolic syndrome and subclinical hypothyroidism: a type 2 diabetes-dependent association. J Thyroid Res 2018: 8251076.
17. Zhang J, Jiang R, Li L, Li P, Li X, et al. (2014) Serum thyrotropin is positively correlated with the metabolic syndrome components of obesity and dyslipidemia in Chinese adolescents. Int J Endocrinol 2014: 289503.
18. Posadas-Romero C, Jorge-Galarza E, Posadas-Sanchez R, Acuna-Valerio J, Juarez-Rojas JG, et al. (2014) Fatty liver largely explains associations of subclinical hypothyroidism with insulin resistance, metabolic syndrome, and subclinical coronary atherosclerosis. Eur J Endocrinol 171: 319–325.
19. Pesic MM, Radojkovic D, Antic S, Kocic R, Stankovic-Djordjevic D (2015) Subclinical hypothyroidism: association with cardiovascular risk factors and components of metabolic syndrome. Biotechnol Biotechnol Equip 29:
157–163.
20. Sun Y, Liang K, Ma Z, Zhang X, Jiang M, et al. (2014) An epidemiologic study on subclinical hypothyroidism in community-based adults aged 40 years or older in Shan-dong Province. *Chinese Journal of Endocrinology and Metabolism* 30: 601–603 (In Chinese).
21. Gan X, Chen Q, Chen J, Liao B, Li Y (2014) Relationship of subclinical hypothyroidism with metabolic syndrome and its components. *Chinese Journal of Endocrinology and Metabolism* 30: 213–215 (In Chinese).
22. Waring AC, Rodondi N, Harrison S, Kanaya AM, Simonseck EM, et al. (2012) Thyroid function and prevalent and incident metabolic syndrome in older adults: the health, ageing and body composition study. *Clin Endocrinol (Oxf)* 76: 911–918.
23. Lai Y, Wang J, Jiang F, Wang B, Chen Y, et al. (2011) The relationship between serum thyrotropin and components of metabolic syndrome. *Endocr J* 58: 23–30.
24. Erdogan M, Canataroglu A, Ganidagli S, Kulaksizoglu M (2011) Metabolic syndrome prevalence in subclinical and overt hypothyroid patients and the relation among metabolic syndrome parameters. *J Endocrinol Invest* 34: 488–492.
25. Luboshitzky R, Ishay A, Herer P (2010) Metabolic syndrome and insulin resistance in women with subclinical hypothyroidism. *Endocrinologist* 20: 29–32.
26. Garduno-Garcia Jde J, Alvirde-Garcia U, Lopez-Carrasco G, Padilla Mendoza ME, Mehta R, et al. (2010) TSH and free thyroxine concentrations are associated with differing metabolic markers in euthyroid subjects. *Eur J Endocrinol* 163: 273–278.
27. Mullur R, Liu YY, Brent GA (2014) Thyroid hormone regulation of metabolism. *Physiol Rev* 94: 355–382.
28. Catli G, Abaci A, Buyukgebiz A, Bober E (2014) Subclinical hypothyroidism in childhood and adolescence. *J Pediatr Endocrinol Metab* 27: 1049–1057.
29. Monzani A, Prodrom F, Rapa A, Moia S, Agarla V, et al. (2013) Endocrine disorders in childhood and adolescence. Natural history of subclinical hypothyroidism in children and adolescents and potential effects of replacement therapy: a review. *Eur J Endocrinol* 168: R1–R11.
30. Jin HY (2018) Prevalence of subclinical hypothyroidism in obese children or adolescents and association between thyroid hormone and the components of metabolic syndrome. *J Paediatr Child Health* 54: 975–980.
31. Surks MI, Boucai L (2010) Age- and race-based serum thyrotropin reference limits. *J Clin Endocrinol Metab* 95: 496–502.
32. Hennessey JV, Espaillat R (2015) Subclinical hypothyroidism: a historical view and shifting prevalence. *Int J Clin Pract* 69: 771–782.
33. Nimptsch K, Konigorski S, Pischon T (2019) Diagnosis of obesity and use of obesity biomarkers in science and clinical medicine. *Metabolism* 92: 61–70.
34. Ping Z, Pei X, Xia P, Chen Y, Guo R, et al. (2018) Anthropometric indices as surrogates for estimating abdominal visceral and subcutaneous adipose tissue: a meta-analysis with 16,129 participants. *Diabetes Res Clin Pract* 143: 310–319.
35. Biondi B, Cappola AR, Cooper DS (2019) Subclinical hypothyroidism: a review. *JAMA* 322: 153–160.
36. Teng X, Shan Z, Chen Y, Lai Y, Yu J, et al. (2011) More than adequate iodine intake may increase subclinical hypothyroidism and autoimmune thyroiditis: a cross-sectional study based on two Chinese communities with different iodine intake levels. *Eur J Endocrinol* 164: 943–950.
37. Shan Z, Chen L, Lian X, Liu C, Shi B, et al. (2016) Iodine status and prevalence of thyroid disorders after introduction of mandatory universal salt iodization for 16 years in China: a cross-sectional study in 10 cities. *Thyroid* 26: 1125–1130.
38. Kim HI, Oh HK, Park SY, Jang HW, Shin MH, et al. (2019) Urinary iodine concentration and thyroid hormones: Korea National Health and Nutrition Examination Survey 2013–2015. *Eur J Nutr* 58: 233–240.
39. Ahn J, Lee JH, Lee J, Baek JY, Song E, et al. (2020) Association between urinary sodium levels and iodine status in Korea. *Korean J Intern Med* 35: 392–399.
40. Tang KT, Wang FF, Pan WH, Lin JD, Won GS, et al. (2016) Iodine status of adults in Taiwan 2005–2008, 5 years after the cessation of mandatory salt iodization. *J Forms Med Assoc* 115: 645–651.
41. Tang KT, Pan WH, Wang FF, Lin JD, Won GS, et al. (2014) Iodine status of Taiwanese children before the change in national salt iodization policy: a retrospective study of the nutrition and health survey in Taiwan 2001–2002. *Asia Pac J Clin Nutr* 23: 481–487.
42. Garcia-Solis P, Solis-S SJ, Garcia-Gaytan AC, Reyes-Mendoza VA, Robles-Osorio L, et al. (2011) Iodine nutrition status in pregnant women in Mexico. *Thyroid* 21: 1367–1371.
43. Mendez-Villa L, Garcia-Solis P, Solis-S SJ, Garcia-Gutierrez DG, Perez-Mora VA, et al. (2016) High iodine and salt intakes and obesity do not modify the thyroid function in Mexican schoolchildren. *Biol Trace Elem Res* 172: 290–298.
44. Ittermann T, Albrecht D, Arohonka P, Bilek R, de Castro JJ, et al. (2020) Standardized map of iodine status in Europe. *Thyroid* 30: 1346–1354.
45. Inoue K, Leung AM, Sugiyama T, Tsujimoto T, Makita N, et al. (2018) Urinary iodine concentration and mortality among U.S. adults. *Thyroid* 28: 913–920.
46. Katagiri R, Yuan X, Kobayashi S, Sasaki S (2017) Effect of excess iodine intake on thyroid diseases in different populations: a systematic review and meta-analyses including observational studies. *PLoS One* 12: e0173722.
47. Shrestha U, Gautam N, Agrawal KK, Jha AC, Jayan A (2017) Iodine status among subclinical and overt hypothyroid patients by urinary iodine assay: a case-control study. *Indian J Endocrinol Metab* 21: 719–723.
48. Diez JJ, Iglesias P (2004) Spontaneous subclinical hypothyroidism in patients older than 55 years: an analysis of natural course and risk factors for the development of
overt thyroid failure. *J Clin Endocrinol Metab* 89: 4890–4897.

49. Li Y, Teng D, Shan Z, Teng X, Guan H, et al. (2008) Antithyroperoxidase and antithyroglobulin antibodies in a five-year follow-up survey of populations with different iodine intakes. *J Clin Endocrinol Metab* 93: 1751–1757.

50. Heikkinen AL, Pakkila F, Hartikainen AL, Vaarasmaki M, Mannisto T, et al. (2017) Maternal thyroid antibodies associates with cardiometabolic risk factors in children at the age of 16. *J Clin Endocrinol Metab* 102: 4184–4190.

51. Sieminska L, Wojciechowska C, Walczak K, Borowski A, Marek B, et al. (2015) Associations between metabolic syndrome, serum thyrotropin, and thyroid antibodies status in postmenopausal women, and the role of interleukin-6. *Endokrynol Pol* 66: 394–403.

52. Sami A, Iftekhar MF, Rauf MA, Sher A (2018) Subclinical hypothyroidism among local adult obese population. *Pak J Med Sci* 34: 980–983.

53. Rastgooye Haghi A, Solhjoo M, Tavakoli MH (2017) Correlation between subclinical hypothyroidism and dyslipidemia. *Iran J Pathol* 12: 106–111.

54. Pearce EN (2012) Update in lipid alterations in subclinical hypothyroidism. *J Clin Endocrinol Metab* 97: 326–333.

55. Vyakaranam S, Vanaparthy S, Nori S, Palarapu S, Bhongir AV (2014) Study of insulin resistance in subclinical hypothyroidism. *Int J Health Sci Res* 4: 147–153.

56. Srive D, Vivekanand B, Giridhar G, Mythili A, Subrahmanyan KA (2012) Insulin resistance and lipid alterations in subclinical hypothyroidism. *Indian J Endocrinol Metab* 16: S345–S346.

57. Decandia F (2018) Risk factors for cardiovascular disease in subclinical hypothyroidism. *Ir J Med Sci* 187: 39–43.

58. Ittermann T, Thamm M, Wallaschofski H, Rettig R, Volzke H (2012) Serum thyroid-stimulating hormone levels are associated with blood pressure in children and adolescents. *J Clin Endocrinol Metab* 97: 828–834.

59. Chen H, Xi Q, Zhang H, Song B, Liu X, et al. (2012) Investigation of thyroid function and blood pressure in school-aged subjects without overt thyroid disease. *Endocrine* 41: 122–129.

60. He W, Li S, Zhang JA, Zhang J, Mu K, et al. (2018) Effect of levothyroxine on blood pressure in patients with subclinical hypothyroidism: a systematic review and meta-analysis. *Front Endocrinol (Lausanne)* 9: 454.