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Endothelial Function in Patients with Subclinical Hypothyroidism: A Meta-Analysis

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ABSTRACT

The purpose of this meta-analysis was to determine whether patients with subclinical hypothyroidism (SCH) have impaired endothelial function, which is assessed by carotid intima-media thickness (C-IMT) and flow-mediated dilatation (FMD) of brachial artery. PubMed, Embase and Cochrane Library databases and the key studies references were searched in our study, prior to July 2017 for all language articles about FMD or C-IMT in SCH and euthyroid subjects. Two authors screened documents and extracted data by pre-established standard independently. The pooled estimate for continuous data was calculated using random-effects models. Statistical heterogeneity was evaluated using I^2 statistics. Subgroup analyses were conducted to assess the robustness of the meta-analysis. Publication bias was examined with funnel plot analysis and Egger's test. In this meta-analysis, 10 studies with 760 subjects are related to FMD with SCH and 23 studies with 1521 subjects are related to C-IMT with SCH. The pooled estimate of the weighted mean difference (WMD) has revealed that SCH correlated with increased C-IMT [WMD 0.069 mm; 95 % CI (0.042, 0.095); $p < 0.001$] and decreased FMD [WMD − 1.848 %; 95 % CI (− 2.298, − 1.399); $p < 0.001$] with high heterogeneity. Compared with EU controls, SCH was also associated with an increased diastolic blood pressure (DBP), systolic blood pressure (SBP), triglyceride (TG), total cholesterol (TC) levels, and low density lipoprotein cholesterol (LDL-C). This meta-analysis demonstrates that SCH is associated with endothelial dysfunction, which may relate with increased thyroid-stimulating hormone (TSH). Hypertension and dyslipidemia may play a crucial part in the development of endothelial dysfunction.

Introduction

Subclinical hypothyroidism (SCH) is defined by elevated serum thyroid-stimulating hormone (TSH) with normal thyroid hormones levels. The prevalence of SCH is 5–10 %, being more frequent with increased age and higher incidence in women [1–3]; the prevalence of SCH is up to 20 % in women older than 60 yrs [1]. Recently, some studies have shown that SCH associated with systolic dysfunction [4], heart failure [5], coronary heart disease and other chronic heart diseases [6, 7]. In addition, the relationship between SCH and the risk for atherosclerosis (AS) has also been reported in large population-based studies [8, 9]. Moreover, multiple lines of evidence have shown that endothelial dysfunction [10] and dyslipidemia [11] play central roles in the development of AS. The relationships between SCH with endothelial dysfunction and dyslipidemia have also been reported in some studies [12, 13].

Endothelial dysfunction is an early step for the development of AS and cardiovascular disease (CVD), which is mostly assessed by flow-mediated dilatation (FMD) and carotid intima-media thickness

(C-IMT) of brachial artery [14, 15]. A meta-analysis including 14 cohort studies with 5547 participants has shown that 1 % decrease and 1-standard deviation (SD) decrease in FMD was associated with 8 % and 22 % increase in risk of future cardiovascular events, respectively. It does illustrate that the vascular endothelium plays a critical role in various phases of the atherosclerotic disease process [16]. Studies have also demonstrated that FMD impaired the vascular, which relates to endothelium-dependent dilatation and increased the risk of AS [17, 18]. C-IMT, measured using carotid ultrasonography, plays a key role in the process of CVD [19]. A meta-analysis with 37 197 participants who were followed up for a mean of 5.5 yrs has shown that the future risk of stroke increased by 13–18 % and the myocardial infarction incidence increased by 10–15 % among the C-IMT increase of 0.1 mm. It shows that the incidence of cardiovascular events is associated with increased C-IMT [20]. In the past twelve yrs, some studies have demonstrated that SCH was associated with endothelial dysfunction which relates to the reduction of FMD and the increase of C-IMT [12, 13, 21–23], but other studies have demonstrated that FMD and C-IMT in SCH patients was not significantly different compared with controls [24–26].

This meta-analysis aims to determine the relationship between SCH and endothelial function by using FMD and C-IMT and to explore the clinical and methodological heterogeneities between studies. In addition, the studies of Gao et al., which prior to November 2011 included 3602 subjects have also revealed that C-IMT increased in patients with SCH compared with controls (the pooled estimate of the weighted mean difference (WMD)was 0.056 mm) [27]. But these clinical studies in the definition of SCH are inconsistent and the qualities of these studies are uneven, as well as the results are not consistent. Moreover, only 7 higher-quality studies with 464 subjects were included in this meta-analysis, which does not strongly explain the relationship between SCH and C-IMT. We newly included 16 related documents with 1009 subjects to more effectively illustrate these relations. Simultaneously, diastolic blood pressure (DBP), systolic blood pressure (SBP), triglyceride (TG), total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), and low density lipoprotein cholesterol (LDL-C) were also observed in this meta-analysis as important risk factors for AS.

Materials and Methods

Search strategy

PubMed, Embase and Cochrane Library databases were searched in this study, prior to July 2017 for all language articles about SCH and FMD % or C-IMT. Medical Subject Headings (MeSH) terms and free-text words used depended on the database characteristics. The detailed search strategies of each database could be found in the supplementary information ▶ **Appendix 1**. In addition, we also searched all references of relevant studies and reviews.

Inclusion criteria

Studies were included by following criteria: 1) Patients with SCH were defined as elevated serum TSH and normal free thyroid hormones concentrations; 2) C-IMT or FMD brachial artery in subjects both SCH and euthyroidism (EU) groups were detected by high-resolution ultrasound methods; FMD of the brachial artery was calculated as [(hyperemic flow diameter-baseline diameter)/baseline diameter] × 100 %, where hyperemic flow diameter is the maximal diameter in the brachial artery and baseline diameter is the diameter of the brachial artery before any flow stimulus; 3) the evaluated of C-IMT must be within the average of common carotid artery; and 4) high-resolution ultrasonography was used to detect FMD %.

Exclusion criteria

Subjects who were taking any drugs that affect the thyroid state or endothelial function were excluded (e. g., antihypertensive agents, acetylsalicylic acid, antihistamines, and multivitamins). Patients with any risk factors of the CVD and some chronic disease, which may affect blood pressure or lipids were excluded (e. g., diabetes mellitus, chronic renal failure, chronic hepatic failure and hypertension). Obese (BMI > 30 kg/m^2) people and pregnancy women were also excluded. The specific exclusion criteria included in the study are listed ▶ **Table 1**.

Data extraction and quality assessment

Two authors screened documents and extracted data by pre-established standard independently. First, we excluded some studies, which were duplicated in our search result. Then, we excluded those studies, which did not adapt to our research by reading title and abstracts. Also, abstracts of meetings, letters, reviews and other studies, which did not include FMD % or C-IMT data between SCH and control subjects were excluded by reading full text. All of studies comparing C-IMT and FMD % values (mean ± SD or median (interquartile range)), sample size, proportion of females, TSH value and metabolic parameters in SCH participants with euthyroid subjects were extracted. Additionally, the methodological quality of each study was evaluated with the Newcastle-Ottawa Scale (NOS), which is specifically developed to assess quality of non-randomized observational studies [28]. The scoring system encompasses three major domains, which included selection, comparability, and exposure and eight entries. The resulting score range is between 0 and 9, a higher score representing a better methodological quality. Literature with a NOS score of less than 8 are excluded as low quality documents.

Statistical analysis

Stata statistical software version 12.0 (StataCorp, College Station, TX, USA) was used for this meta-analysis. The pooled estimate of the weighted mean difference (WMD) and 95 % CI for continuous data were calculated using random-effects models [29]. C-IMT and FMD and its 95 % CIs in SCH and control groups were illustrated by a forest plot. Heterogeneity was determined by calculating the inconsistency index I^2 using the chi-squared test for significance (a p-value < 0.1 was considered statistically significant) and I^2 tests (I^2 > 50 %: high heterogeneity; I^2 < 25 %: low heterogeneity) [30], which are used for determining the percentage of total variation across these studies. We also made subgroup or sensitivity analysis for all studies, including the percent of women as ≥ 82 or < 82 %, TSH values as ≥ 10 mIU/l or < 10 mIU/l and ages (< 20 yrs, 20–30 yrs, 30–40 yrs, 40–50 yrs, and 50–60 yrs). Metabolic parameters (BMI, SBP, DBP, TC, LDL, TG, and HDL) were also calculated and combined in the meta-analysis by WMD and 95 % CIs. Publication bias was assessed using Egger's correlation test method [31].

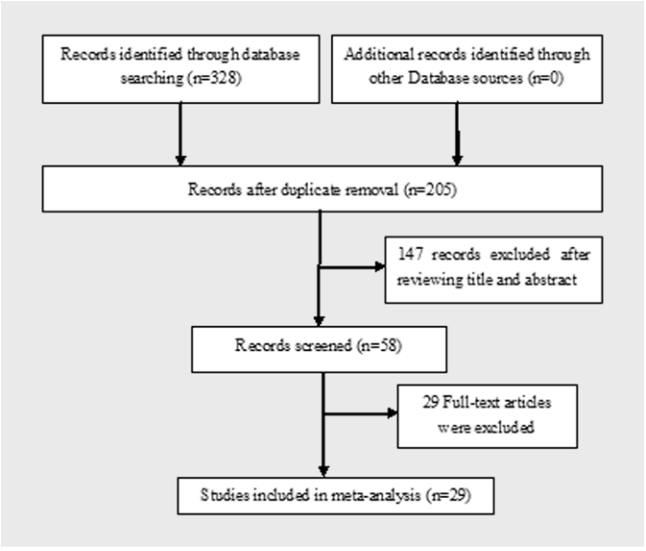
▶ **Table 1** Characteristics of included studies.

Study	Region	TSH value (mU/l)	Sample size SCH/EU	Age (years) SCH/EU	BMI (kg/m²) SCH/EU	Female (%) SCH/EU	Exclusion criteria	Matched factors	n
Cikim et al. 2004 [34] CCS	Turkey	TSH > 4.2	25/23	32.28 ± 9.67/ 35.87 ± 7.93	27.04 ± 4.95/ 26.03 ± 6.21	96/91.3	CVD, DM, CRF, postmenopausal women	Smoking habits, hypertension and family history of CVD. Age, sex, BMI	8
Monzani et al. 2004 [35] CCS	Italy	TSH > 3.6	45/32	37 ± 11/ 35 ± 10	24.7 ± 3.5/ 24.2 ± 3.7	82/84	Taking any drugs, hypertension, DM, CHF and CRF, systemic diseases, 2. Age > 55 yrs; BMI > 30 kg/m², smokers	Age, sex, BMI	8
Almeida et al. 2007 [36] CCS	Portugal	TSH > 4.0	30/27	43.07 ± 9.76/ 43.19 ± 8.39	27.32 ± 4.61/ 25.41 ± 4.38	100/100	CVD, hypertension, DM, and L-T4 treatment	Age, sex	8
Duman et al. 2007 [37] CCS	Turkey	TSH > 4.2	40/20	37 ± 12.6/ 36.7 ± 12.2	25.1 ± 4.3/ 24.7 ± 2.5	100/100	Taking any medication, DM, hypertension, CHD, CRF, CHF, age < 18 or > 60 yrs obesity (BMI > 30 kg/m²), familial hypercholesterolemia, peripheral vascular disease, and smokers	Age, sex	9
Franzoni et al. 2008 [38] CCS	Italy	TSH > 3.6	320/2818	69.0 ± 10.4/ 64.2 ± 11.3	22.84 ± 3.34/ 22.82 ± 3.11	46.2/53.9	Taking any drug and DM within the previous 3 months, the presence of atherosclerotic plaques or calcified lesions in ultrasonography; IMT > 1.2 mm	Age, sex, BMI	8
Kim et al. 2009 [39] CCS	Korea	TSH > 5.5	36/32	36 ± 6.2/ 36.1 ± 5.4	23.1 ± 2.8/ 23.3 ± 3.1	86.1/84.4	Previous thyroid disease and its treatment, DM, hypertension, serum creatinine > 1.3 mg/dl, smoking, medications (affect the lipid profile), pregnancy or postmenopausal women.	Age, sex, BMI	8
Xiang et al. 2009 [40] CCS	China	TSH > 5.5	30/27	53 ± 8/ 52 ± 7	24.7 ± 1.5/ 23.2 ± 1.6	100/100	Taking any drugs, obese (BMI > 30 kg/m²), smokers, hypertension, clinical detectable coronary artery disease	Age, sex, BMI	8
Kebapcilar et al. 2010 [41] CCS	Turkey	TSH > 5.0	38/19	49.8 ± 10/ 50 ± 8.1	28.58 ± 5.81/ 28.45 ± 5.25	81.6/63.2	Taking drugs, DM, cardiac, renal, hepatic, and other systemic diseases, morbid obesity, familial hyperlipidemias, and a history of malignancy	Age	8
Xiang et al. 2010 [42] CCS	China	TSH > 5.5	40/18	57 ± 9/ 56 ± 8	24 ± 1.44/ 23.5 ± 1.8	100/100	Taking any drugs, obese (BMI > 30 kg/m²), smokers, thyroid operation, hypertension, clinical detectable coronary artery disease	Age, sex, BMI	8
Valentina et al. 2011 [43] CCS	Macedonia	TSH > 4.2	67/30	42.4 ± 16.2/ 43.6 ± 12.8	27.8 ± 5.6/ 25.4 ± 5.1	89.9/90	DM, liver or renal disease, chronic pancreatitis, primary hyperlipidemia, ovulatory dysfunction, pregnancy and infertility.	Age, sex, BMI, smoking	8
Turemen et al. 2011 [44] CCS	Turkey	TSH > 4.2	37/23	46.35 ± 11.41/ 42.61 ± 11.61	23.68 ± 1.73/ 23.29 ± 1.23	78/82.5	Acute or chronic systemic disease, hypertension, DM, any malignant condition, use alcoholism and tobacco, and age < 20 yrs or > 69 yrs.	Age, BMI	9
Gunduz et al. 2012[45] CCS	Turkey	TSH > 4.0	16/20	40.8 ± 11.8/ 32.8 ± 5.7	26.72 ± 2.32/ 24.34 ± 2.43	81/45	To be on lipid lowering drugs, DM, hypertension, CAD, and familial hypercholesterolemia, and BMI < 20 kg/m² or > 30 kg/m²	Age	9
Xiang et al. 2012 [46] CCS	China	TSH > 5.5	10/10	34.2 ± 5.8/ 34.6 ± 5.3	24.1 ± 2.3/ 23.8 ± 2	100/100	Taking any drugs, obese (BMI > 30 kg/m²), smokers, hypertension, CAD, malignant neoplasms, renal or liver diseases, DM, familial hypercholesterolemia, or endocrinological disease	Age, sex, BMI	8
Asik et al. 2013 [48] CCS	Turkey	TSH > 5.5	33/32	38.18 ± 15.06/ 39.41 ± 9.74	30.37 ± 7.67/ 27.79 ± 3.64	87.9/90.6	History of CVD, DM or any systemic disease	Age, sex	9
Knapp et al. 2013 [52] CCS	Poland	NR	40/15	34.8 ± 4.1/ 31.6 ± 9.3	24.43 ± 4.3/ 21.8 ± 1.48	100/100	Presence of any classical risk factors of the CHD	Age, sex	9
Kilic et al. 2013 [13] CCS	Turkey	TSH > 4.2	32/29	41.5 ± 12/ 38.1 ± 11.4	28.6 ± 5.9/ 24.9 ± 6.5	85/72.4	History of thyroid disease and its treatment, DM, hypertension, high serum creatinine, atherosclerotic disease, any rhythm other than sinus, and pregnancy women	Age, sex	8
Gunes et al. 2014 [49] CCS	Turkey	TSH > 4.2	39/29	40.44 ± 15.32/ 41 ± 13.82	28.79 ± 6.6/ 27.46 ± 5.35	79/69	Had a history of muscle diseases, CAD, hypertension, systemic infection, DM, or any systemic disease	Age, sex	9

▶ **Table 1** Continued

Study	Region	TSH value (mU/l)	Sample size SCH/EU	Age (years) SCH/EU	BMI (kg/m²) SCH/EU	Female (%) SCH/EU	Exclusion criteria	Matched factors	n
Karoli et al. 2014 [51] Prospective study	Indian	TSH>4.0	50/50	31.8±8.57/ 29.92±6.74	NR	72/76	Taking L-T4 or statins, DM, smokers alcohol users, pituitary-hypothalamic disorders, critically ill, oral contraceptives, patients with concomitant inflammatory disease, CAD or cerebrovascular accidents, pregnant women	Age, sex, BMI	8
Unsal et al. 2014 [53] CCS	Turkey	TSH>4.2	56/46	41.31±14.49/ 36.07±10.58	NR	91.1/54.4	Taking any drugs, had previous thyroid disease, history of alcohol use, obesity, DM, arterial hypertension, liver, or renal diseases, CVD	NR	8
Xiang et al. 2015 [56] CCS	China	TSH>5.5	204/52	55.3±11/ 56±10	23.6±3.7/ 23.3±3.9	100/100	Obese (BMI>30 kg/m²) , smokers, thyroid operation, malignant neoplasms, renal or liver diseases, anti-DNA antibody-positive subjects, and other diseases	Age, sex, BMI	8
Yazici et al. 2015 [26] CCS	Turkey	TSH>4.0	43/30	35.2±10.7/ 34.5±8.2	25.1±5.6/ 25±4.1	97.7/83.3	Chronic diseases and any rheumatologic disease or malignancy	Age, sex, BMI	8
Zha et al. 2015 [22] CCS	China	TSH>4.5	20/10	55.25±5.71/ 52±5.7	24.4±1.61/ 24±1.6	75/60	Tanking any drugs, DM, hypertension, obesity (BMI ≥28 kg/m²), ischemic heart disease, smoker, active infection, malignancy, pituitary and rheumatologic diseases	Age, sex	8
Akbaba et al. 2016 [47] CCS	Turkey	TSH>4.0	51/43	36.9±10.6/ 34.9±8.4	26.1±5.5/ 25.7±4.2	80.4/74.4	taken any thyroid medications, CVD	Age, sex	9
Cerbone et al. 2016 [21] CCS	Italy	TSH>4.5	39/39	9.18±3.56/ 9.45±3.62	NR	51.2/NR	Chronic diseases, chromosomal and genetic syndromes, previous or current thyroid diseases, use of drugs that may interfere with thyroid function, previous irradiation in the neck region, familial lipid disorders or early CVD	Age, sex	8
Franca et al. 2016 [25] CCS	Brazil	TSH>4.5	16/15	39.5±10.39/ 45±7.5	26.5±4.4/ 24.6±2.98	81.2/73.3	Using any drugs, pregnancy, renal function changes, inadequate for carotid IMT data acquisition, use radioactive treatment, malignant thyroid cancer and CVD	Age, sex	8
Mcgowan et al. 2016 [24] CSS	Ireland	TSH>4.0	28/44	47.3±8.6/ 47.3±9.7	28.4±3.96/ 28.1±4.32	64.3/63.6	Taking any medication, aspirin, hormone treatment or combined oral contraceptives	Age, sex, BMI, waist-hip ratio	8
Niknam et al. 2016 [12] CCS	Iran	TSH>4.0	25/25	35.9±7.6/ 37.5±7.3	26±2/ 25.8±2	60/60	Being under treatment for HT; having history of cardiac, kidney or liver disease, malignancies, or cerebral vascular disorders; hypertension, DM, obesity (BMI>30 kg/m²); smokers; and pregnant or lactating women.	Age, sex	8
Isik-Balci et al. 2016 [50] CCS	Turkey	NR	53/31	9.25±4.29/ 7.19±5.15	17.56±3.61/ 17.56±2.47	56.6/51.6	chronic diseases, DM, malignancy, epilepsy, obesity, hyperlipidemia and psychiatric disorders	Age, sex	8
Altay et al. 2017 [23] CCS	Turkey	NR	35/30	34.4±10.3/ 32.5±7.5	27.6±5.9/ 23.7±3.9	82.9/83.3	CVD, any systemic disease (e.g., DM, CRF, or CHF), active or chronic infection inflammatory diseases, or malignancies	Age, sex	8

TSH: Thyroid-stimulating hormone; SCH: Subclinical hypothyroidism; EU: Euthyroidism; BMI: Body mass index; CCS: Case control study; CSS: Cross-sectional study; DM: Diabetes mellitus; CRF: Chronic renal failure; CHF: Chronic hepatic failure; CVD: Cardiovascular disease; CHD: Coronary heart disease; HT: Hypothyroidism; L-T4: l-thyroxin; CAD: Coronary artery disease; NR: Not reported.



▶ **Fig. 1** Study of selection process.

Results

Study selection and characteristics

We achieved 328 studies about SCH and endothelial function or C-IMT or FMD % in the above electronic resource. Then, 123 studies were excluded by removing duplicates and 147 studies were excluded on the basis of title or abstracts. Also, we excluded abstracts of meetings, letters, reviews, and some researches where FMD % or C-IMT data between SCH and control subjects were not available. The study of Unal et al.[32] detected only that right C-IMT was excluded. We also excluded a cross-sectional study [33], which did not specify the balance of participants with other chronic diseases that could affect C-IMT (such as diabetes mellitus or hypertension, etc.). Finally, 29 original case control studies [12, 13, 21–26, 34–53, 56] with 2051 patients were included in this meta-analysis (▶ **Fig. 1**). The characteristic of these studies is shown in ▶ **Table 1**. Patient's characteristics and the results of the NOS quality assessment and metabolic parameters in both SCH and control groups are shown in ▶ **Table 2** and ▶ **Table 3**.

Changes of C-IMT and FMD in SCH and EU subjects

In 29 studies, 23 clinical studies [12, 13, 21–23, 25, 26, 34–39, 41, 43, 45, 47–53] with 1521 patients were included to explore the changes of C-IMT in SCH subjects. The pooled estimate represented a significant increase in C-IMT among subjects with SCH compared to controls [WMD 0.069 mm; 95 % CI (0.042, 0.095); p < 0.001]. Significant statistical heterogeneity was evident among the studies (I^2 = 93.1 %, p < 0.001) (▶ **Fig. 2**).

In total, 10 original studies [12, 24, 34, 40, 42, 44, 46, 54–56] with 760 subjects were included to explore the changes of FMD in SCH subjects. It was demonstrated that FMD significantly decreased in SCH compared with control groups [WMD − 1.848 %; 95 % CI (− 2.298, − 1.399); p < 0.001], with heterogeneity, I^2 = 75.5 % (▶ **Fig. 3**).

Subgroup analysis

We conducted a subgroup of women with ≥ 82 or < 82 % in SCH patients and comparing their C-IMT values with those of EU controls. C-IMT was significantly increased in SCH with a proportion of women ≥ 82 % [WMD 0.078 mm; 95 % CI (0.034, 0.122); p = 0.001] and high heterogeneity (I^2 = 88.8 %), but it also increased in subjects with SCH with a proportion of women < 82 % [WMD 0.061 mm; 95 % CI (0.028, 0.093); p < 0.001] with heterogeneity (I^2 = 93.0 %). TSH value and BMI were also conducted as another subgroups analysis. The C-IMT in patients with SCH with TSH < 10 mIU/l was statistically increased [WMD 0.060 mm; 95 % CI (0.036, 0.084); p < 0.001] and the heterogeneity was decreased (I^2 = 81.1 %) compared with controls, but there was no significant difference in SCH with TSH ≥ 10 mIU/l [WMD 0.105 mm; 95 % CI (− 0.006, 0.216); p = 0.064] and heterogeneity was I^2 = 97.2 %. However, C-IMT was significantly higher in SCH patients with TSH ≥ 10 mIU/l in WMD as compared to SCH with TSH < 10.0 mIU/l when compared to controls (WMD 0.105 mm vs. 0.060 mm). Subjects with SCH having BMI < 25 kg/m² exhibited higher C-IMT values [WMD 0.145 mm; 95 % CI (0.076, 0.213); p < 0.001] versus SCH patients with BMI ≥ 25 kg/m² [WMD 0.041 mm; 95 % CI (0.013, 0.069); p = 0.004] than EU controls. We also conducted a subgroup analysis based on age groups. The C-IMT of WMD with 95 % CI was [0.188 mm; (0.122, 0.253); p < 0.001)] for SCH subjects aged ≤ 50 to < 60 yrs and decreased heterogeneity (I^2 = 0) and [0.078 mm; (0.038, 0.119); p < 0.001) with I^2 = 94.3 % for subjects aged ≤ 30 to < 40 yrs. However, there are no significant differences in subjects aged ≤ 40 to < 50 yrs [WMD 0.037 mm; 95 % CI (− 0.008, 0.083); p = 0.107] with I^2 = 72.8 % and aged < 20 yrs [WMD 0.027 mm; 95 % CI (− 0.022, 0.076); p = 0.279] with I^2 = 87.4 %compared with EU controls (▶ **Table 3**).

FMD was significantly decreased in SCH with a proportion of women ≥ 82 % [WMD − 1.801 %; 95 % CI (− 2.171, − 1.431); p < 0.001] and the heterogeneity was I^2 = 73.2 % and in SCH with a proportion of women < 90 % [WMD − 2.144 %; 95 % CI (− 4.022, − 0.267); p = 0.025] with heterogeneity I^2 = 81.4 %. The FMD in patients with SCH with TSH ≥ 10 mIU/l was statistically decreased [WMD − 3.400 mm; 95 % CI (− 5.685, − 1.115); p = 0.004] and FMD was also decreased in SCH with TSH < 10 mIU/l [WMD − 1.794 %; 95 % CI (− 2.243, − 1.345); p < 0.001] and heterogeneity was I^2 = 76.5 %. Subjects with SCH with BMI ≥ 25 kg/m² exhibited lower FMD [WMD − 2.229 %; 95 % CI (− 3.831, − 0.627); p = 0.006] and decreased heterogeneity (I^2 = 58.5 %, p = 0.064) versus SCH patients with BMI < 25 kg/m² [WMD − 1.821 %; 95 % CI (− 2.300, − 1.341); p < 0.001] and a near heterogeneity (I^2 = 82.7 %) than EU controls. We also conducted a subgroup analysis based on age groups. The FMD of WMD with 95 % CI was [− 1.820 %; (− 2.281, − 1.360); p < 0.001] for SCH subjects aged ≤ 50 to < 60 yrs and a near heterogeneity (I^2 = 7 8.4) and [− 1.836 %; (− 2.318, − 1.354); p < 0.001] with decreased heterogeneity I^2 = 0.5 % for subjects aged ≤ 30 to < 40 yrs. However, there are no significant differences in subjects aged ≤ 40 to < 50 yrs [WMD − 2.845 %; 95 % CI (− 8.773, 3.083); p = 0.347] with I^2 = 94.3 % and aged < 20 yrs [WMD − 0.580 %; 95 % CI (− 2.438, − 1.278); p = 0.541] compared with EU controls (▶ **Table 4**).

▶ **Table 2** Endothelial function and metabolic parameters in both SCH and EU groups.

Study	C-IMT (mm)	FMD (%)	DBP (mmHg)	SBP (mmHg)	TC (mg/dl)	LDL-C (mg/dl)	TG (mg/dl)	HDL-C (mg/dl)
	SCH/EU	SCH/EU	SCH/EU	SCH/EU	SCH/EU	SCH/EU	SCH/EU	SCH/EU
Cikim et al. 2004b [34]	0.55 ± 0.14/ 0.54 ± 0.14	10.6 ± 3.71/ 15.92 ± 7.92	NR	NR	179.56 ± 30.21/ 181.04 ± 36.71	100.28 ± 24.7/ 107.70 ± 27.92	88.32 ± 38.41/ 102.26 ± 53.79	51.48 ± 12.95/ 52.65 ± 20.95
Monzani et al. 2004 [35]	0.75 ± 0.13/ 0.63 ± 0.07	NR	71 ± 10/ 70 ± 8	115 ± 14/ 112 ± 13	NR	138.0 ± 36.2/ 113.8 ± 21.1	94.5 ± 44.7/ 80.5 ± 33.1	56.6 ± 11.2/ 55.0 ± 14.3
Almeida et al. 2007 [36]	0.57 ± 0.07/ 0.58 ± 0.07	NR	NR	NR	213.00 ± 51.85/ 200.74 ± 33.30	133.73 ± 46.60/ 126.30 ± 32.07	119.07 ± 68.54/ 106.11 ± 49.46	55.20 ± 10.59/ 52.96 ± 11.92
Duman et al. 2007 [37]	0.66 ± 0.16/ 0.54 ± 0.1	NR	77 ± 10/ 73 ± 11	126 ± 13/ 123 ± 10	205 ± 27/ 184 ± 21	124 ± 28/ 109 ± 20	144 ± 82/ 104 ± 28	55 ± 12/ 54 ± 6
Franzoni et al. 2008 [38]	0.83 ± 0.21/ 0.63 ± 0.12	NR	75.7 ± 2.8/ 72.5 ± 3.1	128.4 ± 7.3/ 121.8 ± 5.4	197.99 ± 25.14/ 184.84 ± 11.6	113.3 ± 18.17/ 102.09 ± 13.15	115.99 ± 20.37/ 112.45 ± 19.48	52.2 ± 12.37/ 55.29 ± 10.83
Kim et al. 2009 [39]	0.66 ± 0.1/ 0.57 ± 0.08	NR	77.3 ± 10.3/ 76.9 ± 10.5	126.3 ± 15.1/ 116.3 ± 16.5	193.35 ± 33.26/ 162.03 ± 29.00	118.72 ± 10.83/ 85.85 ± 10.44	107.17 ± 11.63/ 92.12 ± 32.77	53.75 ± 14.69/ 56.84 ± 11.99
Xiang et al. 2009 [40]	NR	3.87 ± 0.69/ 5.9 ± 0.97	NR	NR	206.11 ± 23.98/ 170.92 ± 18.95	134.18 ± 25.14/ 92.04 ± 17.79	254.12 ± 94.74/ 129.28 ± 62.87	44.47 ± 11.21/ 51.43 ± 14.31
Kebapcilar et al. 2010 [41]	0.64 ± 0.13/ 0.57 ± 0.08	NR	85.9 ± 12.9/ 71.3 ± 10.7	131.9 ± 21.1/ 117.8 ± 20.6	206.27 ± 37.51/ 188.79 ± 32.28	120.73 ± 34.11/ 110.16 ± 27.02	120.51 ± 60.08/ 114.89 ± 50.30	61.78 ± 19.29 / 55.83 ± 19.80
Xiang et al. 2010 [42]	NR	3.88 ± 0.62/ 5.69 ± 0.79	77.7 ± 6.34/ 75.8 ± 5.9	116.6 ± 9.6/ 116.3 ± 8.3	213.07 ± 23.68/ 174.4 ± 20.49	131.09 ± 17.61/ 85.46 ± 25.52	176.2 ± 56.3/ 110.68 ± 58.44	47.18 ± 11.46/ 49.5 ± 12.37
Valentina et al. 2011 [43]	0.61 ± 0.1/ 0.56 ± 0.1	NR	81.66 ± 12.3/ 78.6 ± 9.1	128 ± 20.7/ 121.8 ± 16.5	211.14 ± 50.27/ 201.08 ± 34.80	132.25 ± 42.15/ 128.77 ± 30.55	150.58 ± 97.43/ 104.52 ± 53.14	51.43 ± 14.31/ 56.46 ± 14.69
Turemen et al. 2011 [44]	NR	11.6 ± 4.12/ 17.56 ± 4.49	NR	NR	203.75 ± 41.22/ 166.26 ± 32.75	129.11 ± 32.40/ 98.51 ± 26.55	113.45 ± 44.68/ 94.82 ± 31.56	52.16 ± 13.92/ 46.65 ± 11.23
Gunduz et al. 2012 [45]	0.61 ± 0.11/ 0.53 ± 0.08	NR	NR	NR	204 ± 41/ 164 ± 27	126 ± 34/ 111 ± 41	186 ± 127/ 104 ± 44	41 ± 8/ 42 ± 11
Xiang et al. 2012 [46]	NR	3.88 ± 0.68/ 5.68 ± 0.51	73.2 ± 5.8/ 72.7 ± 6.1	121.1 ± 6.3/ 119.8 ± 5.6	193.74 ± 18.95/ 174.79 ± 19.72	116.40 ± 23.59/ 83.91 ± 20.88	131.05 ± 82.35/ 117.76 ± 61.98	46.02 ± 8.9/ 47.18 ± 10.83
Asik et al. 2013 [48]	0.54 ± 0.14/ 0.51 ± 0.11	NR	77.58 ± 11.19/ 79.69 ± 6.95	122.12 ± 18.83/ 119.38 ± 16.64	195.9 ± 40.4/ 176.73 ± 28.50	131.0 ± 36.1/ 107.34 ± 23.96	143.0 ± 84.65/ 99.26 ± 38.6	51.86 ± 11.95/ 47.55 ± 10.48
Knapp et al. 2013 [52]	0.61 ± 0.18/ 0.33 ± 0.06	NR	81.0 ± 8.4/ 74.2 ± 8.0	127.5 ± 8.3/ 120.8 ± 7.4	213.17 ± 58.5/ 168.5 ± 6.74	133.67 ± 45.3/ 88.0 ± 9.0	120.75 ± 25.6/ 77.5 ± 21.3	55.41 ± 14.8/ 62.5 ± 8.8
Kilic et al. 2013 [13]	0.05 ± 0.01/ 0.06 ± 0.01	11.5 ± 4.9/ 14.9 ± 4.2	79.0 ± 10.8/ 74.6 ± 9	118.1 ± 16.8/ 116.9 ± 15.5	NR	NR	NR	NR
Gunes et al. 2014 [49]	0.65 ± 0.13/ 0.55 ± 0.11	NR	74.73 ± 8.25/ 74.83 ± 8.71	118.11 ± 18.87/ 119.97 ± 16.76	205.41 ± 51.12/ 191.52 ± 50.91	124.2 ± 62.21/ 115.5 ± 65.78	127.31 ± 43.92/ 119.68 ± 31.77	51.49 ± 11.54/ 59.48 ± 13.25
Karoli et al. 2014 [51]	0.62 ± 0.1/ 0.5 ± 0.08	NR	88.24 ± 13/ 82 ± 12	NR	192.8 ± 16/ 180 ± 10.6	135 ± 23/ 112 ± 12	108 ± 11.6/ 102.6 ± 14	44.2 ± 7.6/ 44.6 ± 8

▶ **Table 2** Continued

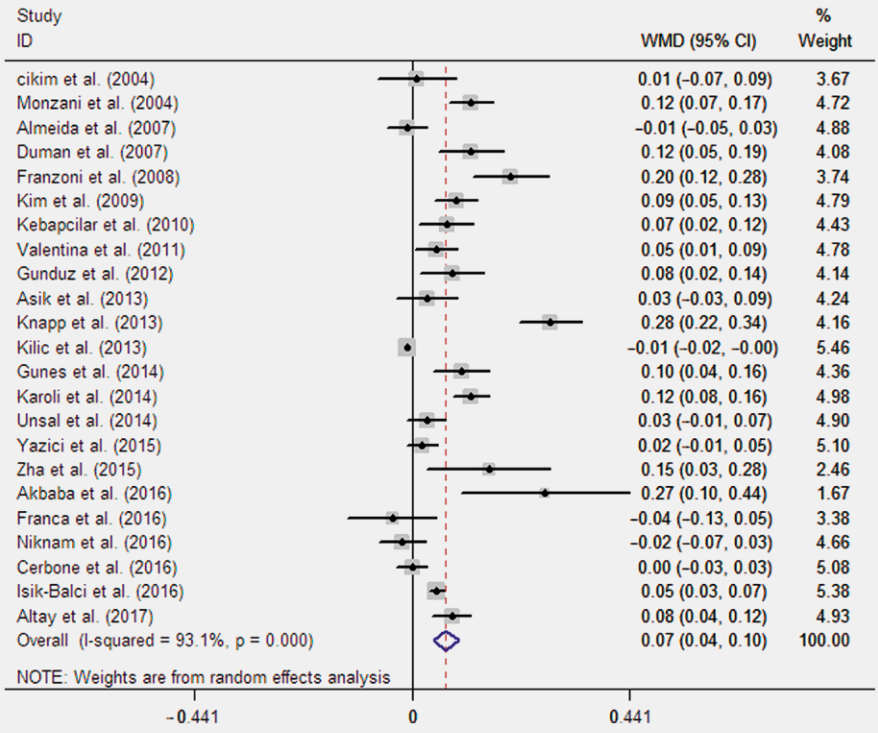
Study	C-IMT (mm)	FMD (%)	DBP (mmHg)	SBP (mmHg)	TC (mg/dl)	LDL-C (mg/dl)	TG (mg/dl)	HDL-C (mg/dl)
	SCH/EU	SCH/EU	SCH/EU	SCH/EU	SCH/EU	SCH/EU	SCH/EU	SCH/EU
Unsal et al. 2014 [53]	0.53 ± 0.11/ 0.5 ± 0.09	NR	NR	NR	NR	117.84 ± 30.27/ 111.72 ± 28.14	NR	53.76 ± 12.07/ 47.93 ± 12.15
Xiang et al. 2015 [56]	NR	4.26 ± 0.4/ 5.73 ± 0.32	74.3 ± 6.9/ 73.8 ± 6.6	120.4 ± 8.0/ 120.7 ± 7.2	187.55 ± 21.66/ 158.93 ± 17.40	113.30 ± 33.64/ 81.98 ± 13.92	167.35 ± 74.38/ 115.11 ± 68.18	46.79 ± 13.15/ 48.72 ± 14.30
Yazici et al. 2015 [26]	0.5 ± 0.09/ 0.48 ± 0.04	NR	75 ± 10/ 73 ± 8	116 ± 15/ 116 ± 13	185 36/ 177 ± 35	108 ± 33/ 100 ± 30	59 ± 10/ 54 ± 11	59 ± 10/ 54 ± 11
Zha et al. 2015 [22]	0.91 ± 0.26/ 0.75 ± 0.09	NR	77.85 ± 6.6/ 77.1 ± 8.5	128 ± 17.16/ 130 ± 17.8	235.51 ± 40.18/ 199.15 ± 16.63	127.42 ± 23.21/ 107.5 ± 13.53	102.27 ± 23.21/ 81.64 ± 6.19	60.13 ± 49.72/ 49.72 ± 5.8
Akbaba et al. 2016 [47]	0.74 ± 0.3/ 0.47 ± 0.5	NR	NR	NR	NR	114.3 ± 5.5/ 120.9 ± 48	111.9 ± 67.6/ 136.7 ± 42.0	46.9 ± 14.9/ 49.1 ± 17.0
Cerbone et al. 2016 [21]	0.44 ± 0.08/ 0.44 ± 0.06	12.64 ± 4.4/ 13.22 ± 3.96	64.98 ± 9.09/ 66.50 ± 9.98	101.33 ± 10.82/ 102.36 ± 10.79	74.56 ± 39.35/ 65.32 ± 24.21	94.33 ± 22.25/ 87.19 ± 19.43	159.72 ± 23.36/ 160.40 ± 21.20	50.47 ± 11.43/ 61.06 ± 13.83
Franca et al. 2016 [25]	0.62 ± 0.11/ 0.66 ± 0.14	NR	75.4 ± 8.54/ 74.0 ± 7.37	114.4 ± 13.2/ 112.7 ± 9.61	185 ± 46.1/ 189.3 ± 19.3	96.9 ± 36.8/ 119.7 ± 17.3	113.5 ± 45.4/ 97.8 ± 26.3	60.3 ± 17.3/ 50.1 ± 8.23
Mcgowan et al. 2016 [24]	NR	5.92 ± 3.3/ 5.79 ± 3.9	NR	NR	NR	114.46 ± 34.8/ 118.33 ± 31.71	132.82 ± 67.29/ 131.05 ± 95.63	NR
Niknam et al. 2016 [12]	0.56 ± 0.09/ 0.58 ± 0.08	4.95 ± 2.02/ 6.5 ± 2.57	NR	NR	177.4 ± 25.2/ 186.1 ± 36.9	108.6 ± 26.7/ 102.9 ± 30.1	152.3 ± 91.6/ 149.8 ± 93.1	49.2 ± 9.3/ 54.0 ± 11.2
Isik-Balci et al. 2016 [50]	0.48 ± 0.04/ 0.43 ± 0.03	NR	NR	NR	157.20 ± 22.41/ 149.00 ± 15.75	NR	93.93 ± 34.13/ 85.10 ± 25.19	NR
Altay et al. 2017 [23]	0.63 ± 0.1/ 0.55 ± 0.05	NR	76.9 ± 9.9/ 70.2 ± 6.9	115.4 ± 12.7/ 111.7 ± 9.4	192 ± 37.5/ 176.5 ± 31.4	118.3 ± 32/ 107.6 ± 25.9	158.5 ± 109.28/ 103.5 ± 60.48	50.3 ± 11.3/ 52.4 ± 10.4

SCH: Subclinical hypothyroidism; EU: Euthyroidism; C-IMT: Carotid intima-media thickness; FMD: Flow-mediated dilatation; DBP: Diastolic blood pressure; SBP: Systolic blood pressure; TG: Triglyceride; TC: Total cholesterol; HDL-C: High density lipoprotein cholesterol; LDL-C: Low density lipoprotein cholesterol; NR: Not reported.

▶ **Table 3** Subgroup analysis for C-IMT in SCH.

	No. of studies	No. of patients	WMD (95% CI) mm	p-Value	I^2 (%)
Total	23	1521	0.069 mm (0.042, 0.095)	0	93.1
Women ≥ 82%	10	558	0.078 mm (0.034, 0.122)	0.001	88.8
Women < 82%	13	963	0.061 mm (0.028, 0.093)	0	93.0
TSH ≥ 10 mIU/l	4	241	0.105 mm (−0.006, 0.216)	0.064	97.2
TSH < 10 mIU/l	19	1280	0.060 mm (0.036, 0.084)	0.000	81.1
BMI ≥ 25 kg/m^2	14	865	0.041 mm (0.013, 0.069)	0.004	84.7
BMI < 25 kg/m^2	6	376	0.145 mm (0.076, 0.213)	0	92.5
BMI (NR)	3	280	0.050 mm (−0.023, 0.122)	0.178	92.2
Age ≤ 50 to < 60 yrs	2	102	0.188 mm (0.122, 0.253)	0	0
Age ≤ 40 to < 50 yrs	5	303	0.037 mm (−0.008, 0.083)	0.107	72.8
Age ≤ 30 to < 40 yrs	14	954	0.078 mm (0.038, 0.119)	0	94.3
Age < 20 yrs	2	162	0.027 mm (−0.022, 0.076)	0.279	87.4

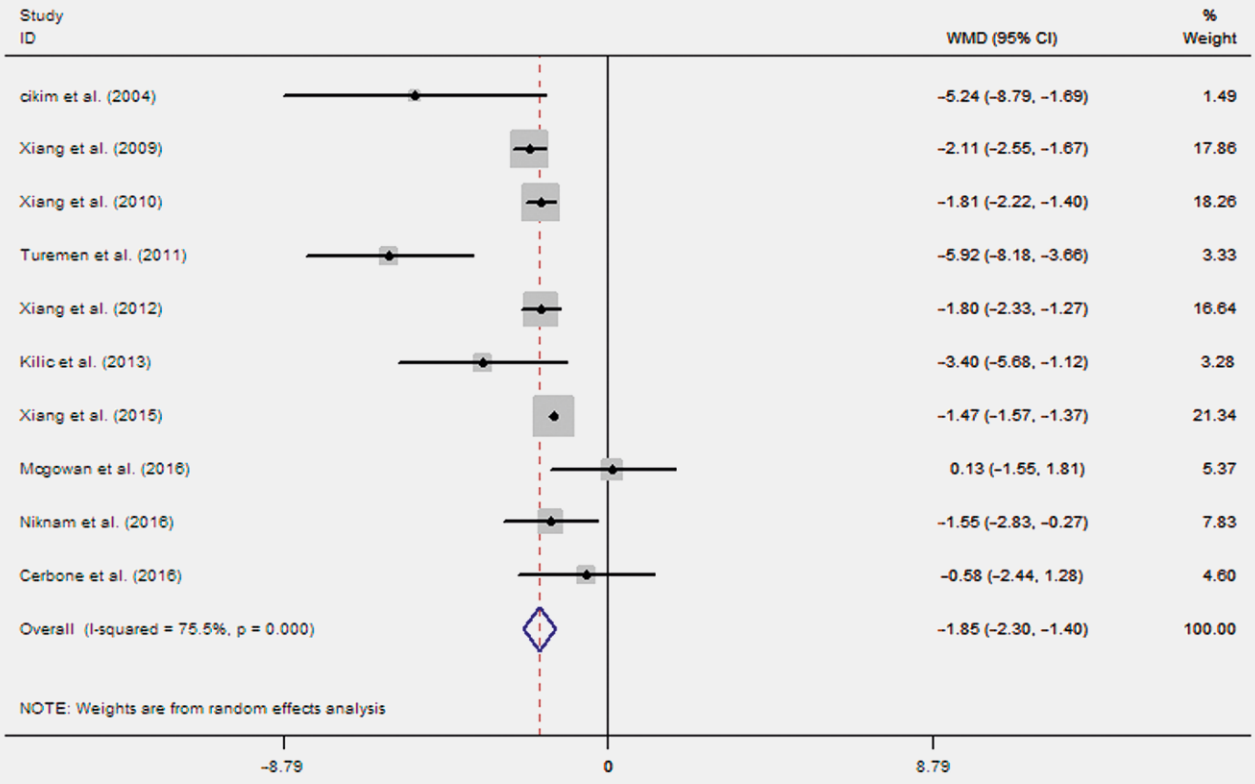
TSH: Thyroid-stimulating hormone; BMI: Body mass index.



▶ **Fig. 2** WMD with 95% CI of C-IMT in SCH and EU subjects.

Metabolic parameters changes in SCH and EU subjects

As shown in ▶ **Table 5**, the BMI [WMD 0.829 kg/m^2; 95% CI (0.457, 1.200); p < 0.001] DBP [WMD 2.537 mmHg; 95% CI (1.171, 3.903); p < 0.001], SBP [WMD 2.401 mmHg; 95% CI (0.456, 4.345); p = 0.016], TC [WMD 19.118 mg/dl; 95% CI (13.734, 24.503); p < 0.001], LDL-C [WMD 16.206 mg/dl; 95% CI (10.336, 22.077); p < 0.001], and TG [WMD 20.917 mg/dl; 95% CI (12.674, 29.159); p < 0.001] levels were significantly increased in SCH patients compared with control subjects, but the HDL-C [WMD −1.224 mg/dl; 95% CI (−3.020, 0.573); p = 0.182] level was not significantly different between the two groups.



▶ **Fig. 3** WMD with 95 % CI of FMD in SCH and EU subjects.

▶ **Table 4** Subgroup analysis for FMD in SCH.

	No. of studies	No. of patients	WMD (95 % CI) mm	p–Value	I^2 (%)
Total	10	760	−1.848 % (−2.298, −1.399)	0	75.5
Women ≥82 %	5	439	−1.801 % (−2.171, −1.431)	0	73.2
Women < 82 %	5	321	−2.144 % (−4.022, −0.267)	0.025	81.4
TSH ≥10 mIU/l	1	61	−3.400 % (−5.685, −1.115)	0.004	NR
TSH < 10 mIU/l	9	699	−1.794 % (−2.243, −1.345)	0	76.5
BMI ≥25 kg/m^2	4	237	−2.229 % (−3.831, −0.627)	0.006	58.5
BMI < 25 kg/m^2	6	523	−1.821 % (−2.300, −1.341)	0	82.7
Age ≤50 to < 60 yrs	4	419	−1.820 % (−2.281, −1.360)	0	78.4
Age ≤40 to < 50 yrs	2	132	−2.845 % (−8.773, 3.083)	0.347	94.3
Age ≤30 to < 40 yrs	3	131	−1.836 % (−2.318, −1.354)	0	0.5
Age < 20 yrs	1	78	−0.580 % (−2.438, −1.278)	0.541	NR

TSH: Thyroid-stimulating hormone; BMI: Body mass index; NR: Not reported

Publication bias evaluation

Egger's linear regression test used to examine publication bias indicated an absence of publication bias for FMD (p = 0.635) and a presence of publication bias for C-IMT (p = 0.045).

Discussion

In the current systematic review and meta-analysis of 29 clinical studies, it has been revealed that SCH might be correlated with endothelial dysfunction, which relates to the increase of C-IMT and the decrease of FMD. Patients with SCH were also associated with significantly increased BMI, DBP, SBP, TC, TG, and LDL-C.

▶ **Table 5** Metabolic parameters.

Parameters	No. of studies	No. of patients	WMD (95 % CI)	p-Value	I^2 (%)
BMI (kg/m^2)	26	1771	0.829 (0.457, 1.200)	0	38.3
DBP (mmHg)	19	1391	2.537 (1.171, 3.903)	0	55.5
SBP (mmHg)	18	1291	2.401 (0.456, 4.345)	0.016	51.8
TC (mg/dl)	25	1715	19.118 (13.734, 24.503)	0	76.2
LDL-C (mg/dl)	27	1899	16.206 (10.336, 22.077)	0	85.0
TG (mg/dl)	27	1881	20.917 (12.674, 29.159)	0	79.0
HDL-C (mg/dl)	25	1718	−1.224 (−3.020, 0.573)	0.182	53.1

BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; TC: Total cholesterol; LDL-C: Low density lipoprotein cholesterol; TG: Triglyceride; HDL-C: High density lipoprotein cholesterol.

Some epidemiological studies have shown that the prevalence of SCH is higher in women [1]. Our subgroup analysis was conducted according to the proportion of women showing a higher C-IMT in SCH patients consisting of ≥ 82 % women and a lower FMD in SCH patients consisting of < 82 % women with a near heterogeneity. This result may indicate that gender is not associated with impairment of endothelial function in SCH. Serum TSH concentration greater than 10 mIU/l is regarded as severe SCH [57]. Although C-IMT had no statistical difference in patients with SCH with TSH ≥ 10.0 mIU/l compared with EU controls in our meta-analysis, C-IMT was significantly increased and FMD was significantly decreased in SCH with TSH ≥ 10.0 mIU/l compared to SCH patients with TSH < 10.0 mIU/l. The studies of Gao et al. [27] with 7 higher-quality studies with 464 subjects have also demonstrated that C-IMT was higher in SCH patients with TSH ≥ 10.0 mIU/l. The 11 prospective cohort studies of Rodondi et al. [58] with 55 287 patients have also demonstrated that higher TSH levels associated with the increased coronary heart disease events its mortality. This indicates that the severity of SCH is closely related to the degree of damage to endothelial function but other confounding factors cannot be ruled out (e. g., illness time, complications, and patient ages).

C-IMT and FMD are not other common indicators to evaluate endothelial function, but they can also predict the occurrence and development of CVD. The studies of van den Oord et al. [59] with 15 available articles have shown that C-IMT was associated with future stroke HR (hazard ratio) of 1.31 per 1-SD increased CIMT and HR of 1.17 per 0.1 mm increased C-IMT and was also associated with future myocardial infarction with HR of 1.26 per 1-SD increase in C-IMT and HR of 1.15 per 0.1 mm increased in C-IMT. A meta-analysis including 14 cohort studies with 5547 participants has shown that 1 % decrease and 1-SD decrease in FMD was associated with 8 % and 22 % increase in risk of future cardiovascular events, respectively. It was illustrated that the vascular endothelium plays a critical role in various phases of the atherosclerotic disease process [16]. Another meta-analysis, which has indicated the overall CVD risk was 0.92 per 1 % increased FMD and observed a significant decrease of FMD in diseased populations compared to asymptomatic populations. Furthermore, it was illustrated that decreased FMD is strongly related with future risk of CVD [60].

Obesity plays a key role in the development of CVD, and thus we also conducted a subgroup analysis with BMI values. Analysis results show that C-IMT was significantly increased in SCH with BMI < 25 kg/m^2 patients compared with patients with BMI ≥ 25 kg/m^2 and the heterogeneity still high, but FMD was significantly decreased in SCH with BMI ≥ 25 kg/m^2 and the heterogeneity was significantly reduced. We also performed subgroup analyses based on the patient's age. The C-IMT was significantly increased in SCH subjects aged ≤ 30 to < 40 yrs and ≤ 50 to < 60 yrs with decreased heterogeneity. The FMD was significantly decreased in SCH subjects aged ≤ 50 to < 60 yrs with a near heterogeneity and patients aged ≤ 30 to < 40 yrs with decreased heterogeneity. However, C-IMT and FMD were not significantly different in subjects aged ≤ 40 to < 50 yrs and < 20 yrs compared with EU controls. This result suggests that the occurrence of SCH may be closely related to the people's age and the heterogeneity is associated with the level of BMI and patients age in patients with SCH.

Hyperlipidemia is an important risk factor for CVD. Being consistent with our findings, meta-analysis of Liu et al. including 16 studies with 41 931 adults has shown that TC, LDL-C, and TG levels were significantly increased and HDL-C level was not significantly different in SCH patients compared with EU individuals [61]. In addition, hypertension is strongly associated with endothelial function and C-IMT can predict the development of hypertension [62]. Noisy living environment contribute to the prevalence of hypertension [63]. In this meta-analysis, we also found that increased SBP and DBP were associated with SCH subjects. However, the DBP level was not significantly different in other meta-analysis [27]. This difference may be associated with the numbers of participants and the basic of characteristics.

Our meta-analysis has also some limitations. First, all of included studies were observational rather than randomized controlled trials. Thus, potential confounding factors may have affected the findings. Second, the detected methods for C-IMT or FMD are not entirely consistent and the definitions of SCH with serum TSH concentrations are different in different studies, and the results may not be generalizable to different populations. Third, although we were unable to identify its source by either meta-regression or subgroup analysis, there was some evidence of heterogeneity and pub-

lic bias among the studies. The total sample size in this meta-analysis was relatively small, large clinical studies stratified by basic characteristics are essential.

Conclusions

Our meta-analysis has demonstrated that SCH patients are strongly related with endothelial dysfunction, hypertension, and hyperlipidemia. Higher level of TSH plays a key role in the development of those diseases. Large randomized controlled trial should be confirmed in SCH patients in different age levels and different TSH levels. The impact of L-T4 treatment and L-T4 dosages on these also should be explored. Further mechanisms should be investigated to explain the role of evaluated TSH in endothelial dysfunction with SCH.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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