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Review Article

The Association with Subclinical Thyroid Dysfunction and Uric Acid

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The relationship between subclinical thyroid dysfunction and uric acid was not well established. This study aimed to determine if subclinical thyroid dysfunction is associated with hyperuricemia risk and to evaluate the levels of uric acid in patients with different forms of subclinical thyroid dysfunction. A systematic search was conducted in 4 databases to obtain relevant studies on subclinical thyroid dysfunction (subclinical hyperthyroidism and subclinical hypothyroidism) and uric acid. The standardized mean difference (SMD) or odds ratio (OR) and 95% confidence interval (95% CI) were used for evaluation, and the sensitivity analysis was conducted. Publication bias was estimated by funnel plot, Egger's test, and Begg's test. A total of 73 studies were included in this meta-analysis. The results demonstrated that serum levels of uric acid in patients with subclinical hypothyroidism were significantly higher than those of controls and patients with subclinical hyperthyroidism. Patients with subclinical thyroid dysfunction had a higher prevalence of hyperuricemia compared with normal clinical thyroid function. Subclinical thyroid dysfunction was associated with the prevalence of hyperuricemia. Different types of subclinical thyroid dysfunction had varied effects on serum levels of uric acid.

1. Introduction

Thyroid hormones elicited significant effects on numerous physiological processes, such as growth, development, and metabolism. Thyroid dysfunction is a common endocrine disease and consists of overt hypothyroidism (OH), subclinical hypothyroidism (SCH), overt hyperthyroidism (OHyper), and subclinical hyperthyroidism (SCHyper). Subclinical thyroid dysfunction was characterized by high (SCH)/low (SCHyper) TSH concentrations and normal serum thyroid hormones or serum-free thyroid hormones [1, 2]. The prevalence of SCH was approximately 4–10% [3, 4], and it can be as high as 20% in people over 60 years old [5]. SCHyper was also a common thyroid disorder with a prevalence of up to 10% [6–8]. Subclinical thyroid dysfunction, which can be diagnosed by thyroid function tests before symptoms and complications occur, is viewed as a risk factor for developing hyperthyroidism and hypothyroidism complications [9]. Moreover, a growing body of observational data suggests that cardiovascular risk may also be increased in subgroups of patients with SCH or SCHyper [10]. Uric acid (UA) is the end product of the purine metabolism in the human body. Serum UA levels reflected a balance between the metabolic breakdown of purine nucleotides and UA excretion [11]. Serum UA levels have been considered as an independent predictive factor for metabolic syndrome [12, 13]. Hyperuricemia is the best-known risk factor for gout, but it is also a risk factor for hypertension, diabetes, and chronic kidney disease (CKD) [14–16]. Across the globe, hyperuricemia was becoming a critical medical problem, and its prevalence has dramatically increased in past decades [17, 18]. Many epidemiologic studies have suggested that hyperuricemia is associated with hypertension, cardiovascular diseases, diabetes mellitus, and dyslipidemia [19–23]. Uric acid as the end product of the purine metabolism can be affected by thyroid hormones.

Therefore, we hypothesized that a link between UA and thyroid function may exist. Although previous studies have investigated the association between overt thyroid dysfunction and UA [24–27], the results are quite inconsistent between subclinical thyroid dysfunction and UA. A recent study by YE Y et al. showed that subclinical thyroid dysfunction was not significantly associated with serum UA levels, either SCHyper or SCH [28]. Zhang et al. found the marked elevated risk of hyperuricemia observed among the subjects with SCH [29]. This study, therefore, aimed to evaluate the association between subclinical thyroid dysfunction and hyperuricemia and focus on variation in subclinical thyroid dysfunction styles and serum UA levels.

2. Materials and Methods

2.1. Literature Search. We adopted PubMed, Embase, Cochrane library, and China Academic Journal Full-text Database (CNKI) to search relevant literature before March 2021. A systematic search for "subclinical hyperthyroidism/hypothyroidism" and "hyperuricemia/uric acid" was carried out. Key-terms were grouped and searched within the article title, abstract, and keywords using the conjunctions "OR" and "AND." Selection of studies: after initial screening of titles and abstracts retrieved by the search, the full text of all potentially eligible studies was retrieved.

2.2. Inclusion Criteria. The inclusion criteria were as follows: the study was an observational or prospective study; data provided within the study met the needs to confirm the relationship between subclinical thyroid dysfunction and uric acid; the control group was included in the study or data for before and after therapy of subclinical thyroid dysfunction; there was no direct associations among studies; and the patient was diagnosed as subclinical hyperthyroidism, subclinical hypothyroidism, and hyperuricemia by a clear diagnosis.

2.3. Exclusion Criteria. The exclusion criteria were as follows: Animal studies, reviews, and case reports; studies that used data from a previously published study; and the data within the study which were not complete enough to meet the requirements of meta-analysis.

2.4. Literature Screening and Data Extraction. The first stage involved screening titles and abstracts to identify and exclude irrelevant articles. All full-text versions of studies that were potentially relevant were then screened in relation to the inclusion criteria. Two researchers independently searched and screened the literature and collected and cross-checked the relevant data. If the results were inconsistent, those would be discussed together or judged by a third senior researcher. Data from included studies were extracted and summarized independently using a prestandardized data extraction form. The excerpts included basic characteristics (year of publication, study area, number of participants, diagnostic criteria, the determination method of UA and thyroid hormones, and inclusion and exclusion criteria). Mean ± SD was extracted when the level of UA was used as a continuous variable, and the corresponding proportion was extracted when the level of UA was used as a binary variable. The cutoff value for the diagnosis of hyperuricemia and subclinical thyroid dysfunction was extracted.

2.5. Statistical Analysis. The data and the database were organized and checked carefully according to the requirements of the meta-analysis. The RevMan 5.3 analysis software was used for statistical analysis. Standardized mean difference (SMD) for continuous variables, with 95% confidence interval (CI), was calculated for each study. For analyses of dichotomous variables, we used risk ratios (OR) and 95% confidence intervals (95% CI). The Z-test was assessed to evaluate the significance of the pooled effect size. If $I^2 \leq 50\%$ or $P \geq 0.05$, fixed effect model analysis was used; if $I^2 > 50\%$ or $P < 0.05$, random effect model analysis was used. The sensitivity analysis was tested to determine the stability and reliability of the results in this meta-analysis. In addition, we will run subgroup analysis to explore possible sources of obvious heterogeneity. Funnel plot, Egger's test, and Begg's test were used to evaluate publication bias. $P < 0.05$ was considered statistically significant, suggesting that publication bias is not excluded. The stability of the conclusions was further evaluated after eliminating publication bias by the trim-and-fill method. Meta-regression and subgroup analysis were performed to explore the source of heterogeneity.

3. Result

3.1. Literature Search Results. The systematic literature search retrieved 1983 publications; after exclusion of duplicates and screening for relevance in title and abstract, 1429 publications were further appraised in full text. In the second step, full texts were reviewed for eligibility and relevance of their findings, and 1094 articles were excluded due to duplicate data, review articles, and insufficient relevance. Finally, a total of 73 articles were included in the meta-analysis (Figure 1). We did not exclude any studies in the review based on the comorbidities of the study participants, but we kept into account this aspect when summarizing the results. Supplementary Materials (Table S1) provide the basic characteristics of included studies.

3.2. Meta-Analysis Results

3.2.1. Relationship between SCH/SCHyper and the Prevalence of Hyperuricemia. A total of 4 studies provided a comparison of the prevalence of hyperuricemia. Among them, 2 studies were related to the comparison of the prevalence of hyperuricemia in SCHyper patients and normal thyroid function individuals. 3 studies involved the comparison of the prevalence of hyperuricemia between SCH patients and normal thyroid function people. It was shown that the prevalence of hyperuricemia of patients with subclinical thyroid dysfunction was higher than that of subjects with

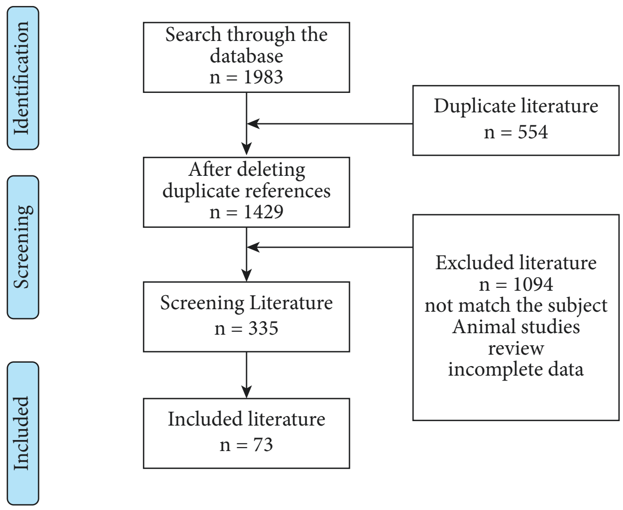


Figure 1: Literature screening process and results.

normal thyroid function, and the difference was statistically significant ($I^2 = 0\%$, $P = 0.50$, $Z = 2.09$, $P = 0.04$, OR = 1.16, 95% CI: 1.01–1.34, Figure 2(a)).

3.2.2. Relationship between SCH/SCHyper and Serum UA Levels. 68 studies involved the comparison of serum UA levels between patients with SCH and subjects with normal thyroid function. 7 studies involved the comparison of serum UA levels between patients with SCHyper and subjects with normal thyroid function. 6 studies involved the comparison of serum UA levels between patients with SCH and SCHyper. The results showed that serum UA levels were significantly higher in patients with SCH than in those of normal controls ($I^2 = 96\%$, $P < 0.01$, $Z = 9.04$, $P < 0.01$, SMD = 0.78, 95% CI: 0.61–0.95, Figure 3(a)). There was no statistical difference in the levels of UA between patients with SCHyper and normal controls ($I^2 = 97\%$, $P < 0.01$, $Z = 0.00$, $P = 1.00$, SMD = 0.00, 95% CI: −0.67–0.67, Figure 4(a)). In addition, levels of UA in patients with SCH were significantly higher than those with SCHyper ($I^2 = 95\%$, $P < 0.01$, $Z = 2.02$, $P = 0.04$, SMD = 0.63, 95% CI: 0.02–1.23, Figure 2(b)).

3.2.3. Meta-Regression. Meta-regression analysis showed that patient age ($P = 0.076$) and TSH level ($P = 0.608$) did not significantly impact the UA level in patients with SCH compared with those with normal thyroid function. However, area ($P = 0.004$) affected the pooled effect size.

3.2.4. Subgroup Analysis. Due to the heterogeneity of the studies included, in order to further increase the reliability of the study, a subgroup analysis of age, area, and comorbidities in patients was performed.

(1) Area: (a) SCH: according to the area, patients were divided into two subgroups: Chinese and non-Chinese. There were 60 studies involving 38247 subjects in Chinese ($I^2 = 96\%$, $P < 0.01$, $Z = 8.16$, $P < 0.01$, SMD = 0.66, 95% CI: 0.50–0.82), and 8 studies involving 1202 subjects elsewhere ($I^2 = 97\%$, $P < 0.01$, $Z = 2.50$, $P < 0.01$, SMD = 0.95, 95% CI: 0.20–1.69). These outcomes suggested the UA levels were higher in SCH patients, regardless of whether the patients were Chinese, and the difference was statistically significant (Figure 3(b)). (b) SCHyper: there were 5 studies involving 19146 subjects in Chinese ($I^2 = 98\%$, $P < 0.01$, $Z = 0.33$, $P = 0.74$, SMD = −0.14, 95% CI: −0.93–0.66), and 2 studies involving 228 subjects elsewhere ($I^2 = 0\%$, $P = 0.53$, $Z = 2.360$, $P = 0.02$, SMD = 0.42, 95% CI: 0.07–0.77). These outcomes suggested UA levels were higher in SCHyper patients only in those who were non-Chinese (Figure 4(b)).

(2) Age: according to the average age of patients with subclinical thyroid dysfunction, the subjects were divided into three subgroups: age < 45 years old, 45 ≤ age < 60 years old, and age ≥ 60 years old. (a) SCH: there were 16 studies involving 21535 subjects with an average age younger than 45 years old. The result of the heterogeneity test was $I^2 = 97\%$, $P < 0.01$, $Z = 4.84$, $P < 0.01$, SMD = 0.95, 95% CI: 0.57–1.34, and the difference was statistically significant. 35 studies involved 12957 subjects with an average age between 45 and 60 years old. The result of the heterogeneity test was $I^2 = 95\%$, $P < 0.01$, $Z = 6.67$, $P < 0.01$, SMD = 0.73, 95% CI: 0.52–0.95, and the difference was statistically significant. 17 studies involved 4957 subjects with an average older than 60 years old. The result of the heterogeneity test was $I^2 = 88\%$, $P < 0.01$, $Z = 3.71$, $P < 0.01$, SMD = 0.38, 95% CI: 0.18–0.58, and the difference was statistically significant. It was suggested that regardless of age, UA levels in patients with SCH were higher than those with normal thyroid function (Figure 3(c)). (b) SCHyper: there were 4 studies involving 18735 subjects with an average age younger than 45 years old, 2 studies involving 390 subjects with an average age between 45 and 60 years old, and 1 study involving 249 subjects with an average older than 60 years old. There were no significant differences among the ages in the levels of UA in SCHyper patients (Figure 4(c)).

(3) Comorbidities: of the 68 studies which compared levels of UA between patients with SCH and normal thyroid function subjects, only two involved a comparison of serum UA levels between chronic kidney disease patients with and without SCH, six involved cardiovascular diseases including coronary heart diseases and hypertension, eighteen pertained to metabolic syndromes (diabetes and dyslipidemia), four were focusing on severe preeclampsia, and the other three were on pregnancy. Furthermore, 35 studies involved a comparison of SCH-only patients and normal subjects. Serum UA levels were significantly higher in SCH patients combined with

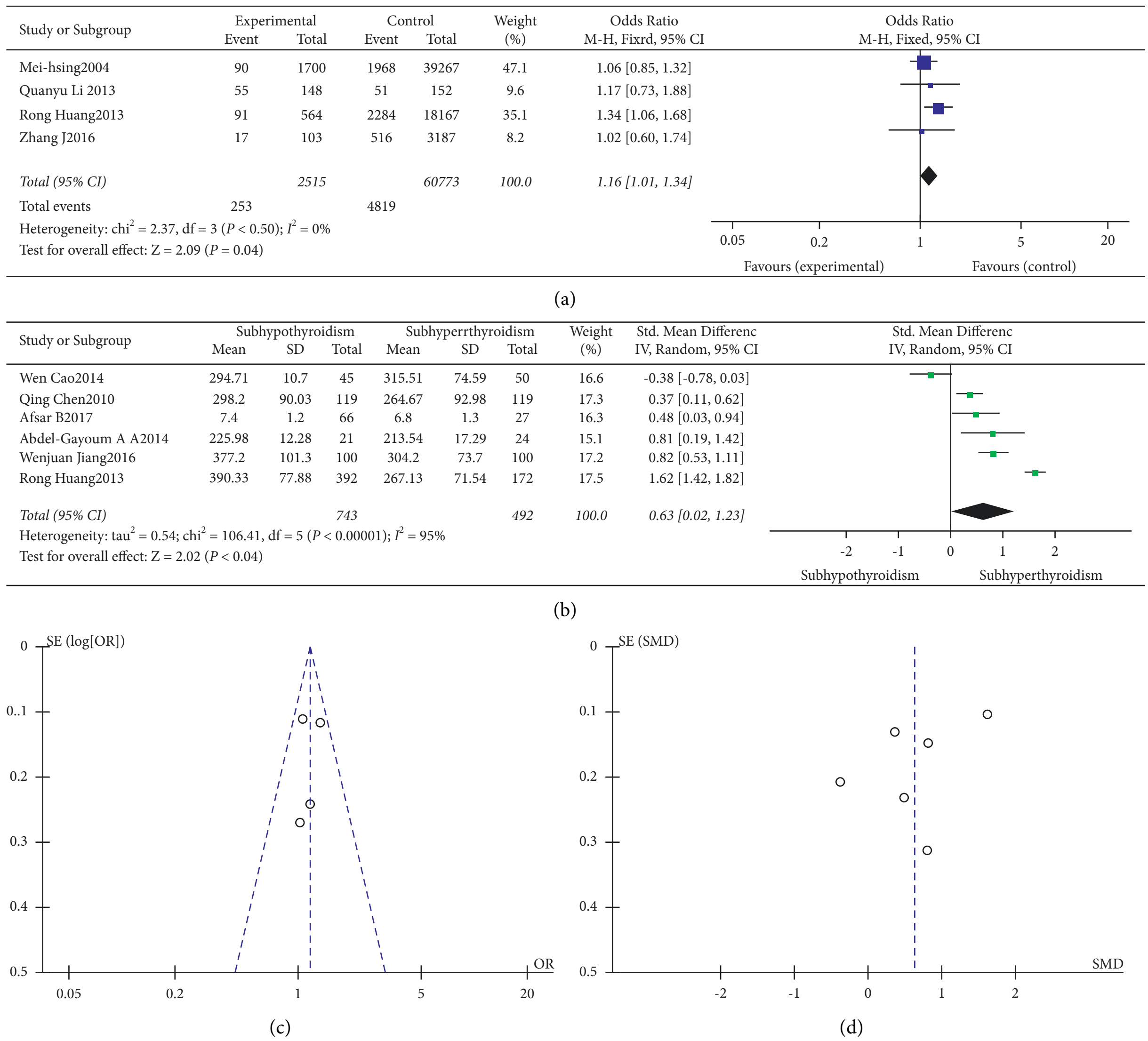


FIGURE 2: (a) Forest plot of subclinical thyroid dysfunction and hyperuricemia. (b) Forest plot of the comparison of subclinical hypothyroidism and subclinical hyperthyroidism. (c) Funnel plot of subclinical thyroid dysfunction and hyperuricemia. (d) Funnel plot of the comparison of subclinical hypothyroidism and subclinical hyperthyroidism.

metabolic syndrome or severe preeclampsia or pregnancy than those without SCH. No difference in the levels of serum UA was found between chronic kidney disease and cardiovascular diseases patients with or without SCH. The results are shown in Figure 3(d). Of the 7 studies which compared levels of UA between patients with SCHyper and normal thyroid function subjects, only one involved a comparison of serum UA levels between chronic kidney disease patients with and without SCHyper. The serum UA levels were significantly higher in patients with SCHyper with chronic kidney disease than in those with chronic kidney disease but without SCHyper. There was no statistically significant difference in the levels of serum UA between patients with or without SCHyper in six studies that included patients with SCHyper alone (Figure 4(d)).

3.2.5. Relationship between SCH and Serum UA Levels before and after Treatment. Four studies examined the level of UA in patients with SCH before and after treatment. The result showed that the level of UA reduced after treatment compared with before treatment ($I^2 = 87\%$, $P < 0.01$; $Z = 2.47$, $P < 0.05$, SMD $= -0.66$, 95% CI: -1.19 to -0.14, Figure 5(a)). The difference was statistically significant.

3.2.6. Publication Bias. The funnel plot is shown in Figures 2(c), 2(d), 3(e), 4(e), and 5(b). Egger's test ($P > 0.05$) suggested no obvious publication bias.

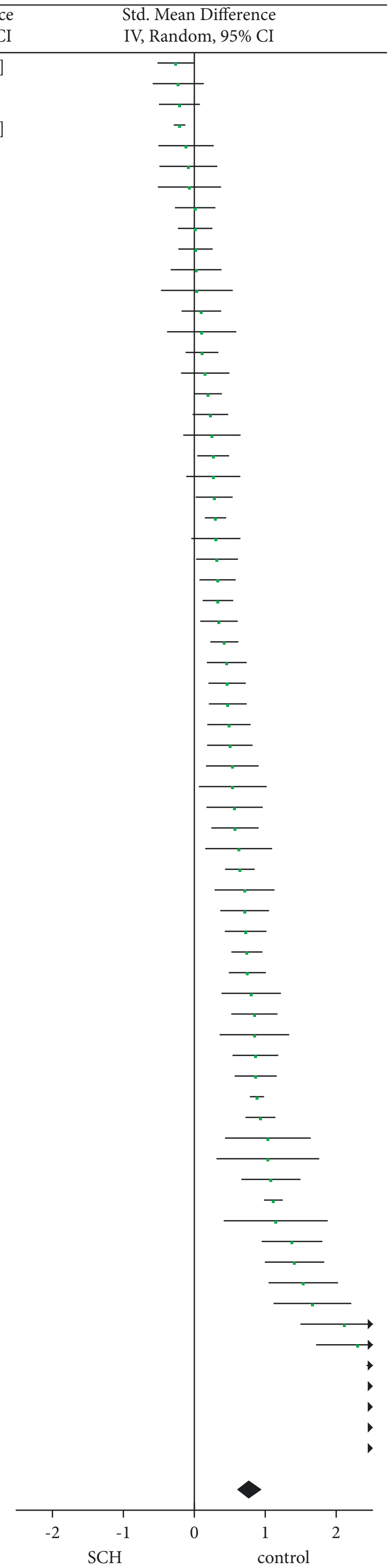
4. Discussion

The results of this analysis showed that hyperuricemia was more prevalent in subclinical thyroid dysfunction than in normal thyroid function subjects. The serum UA levels of

Study or Subgroup	SCH Mean	SCH SD	SCH Total	Control Mean	Control SD	Control Total	Weight (%)	Std. Mean Difference IV, Random, 95% CI
Man jin2016	334.3	98.18	95	357.97	84.53	153	1.5	-0.26 [-0.52, -0.01]
Jinyuan Ren2012	357.24	96.08	35	379.38	97.72	198	1.5	-0.23 [-0.59, 0.13]
Qiannan Du2018	289	92	55	311	107	287	1.5	-0.21 [-0.50, 0.08]
Zhang J2016	304.09	87.62	710	322.32	87.58	3187	1.6	-0.21 [-0.29, -0.13]
Rongrong Zhang2013	369.72	91.33	45	380.67	94.97	58	1.5	-0.12 [-0.51, 0.27]
Qian Jiang2020	302.2	75.34	25	309.81	91.63	299	1.5	-0.08 [-0.49, 0.32]
Juanjuan Sun2018	361.12	107.2	25	368.69	111.99	86	1.4	-0.07 [-0.51, 0.38]
Jingli Cheng2019	291.21	79.21	62	290.31	73.23	198	1.5	0.01 [-0.27, 0.30]
Yuelei Wu2020	339.256	124.032	129	337.866	106.047	131	1.5	0.01 [-0.23, 0.26]
Devika Tayal2009	5.93	4.95	98	5.87	2.53	198	1.5	0.02 [-0.23, 0.26]
Qiang Song2016	440.7	98.6	60	438.1	105.2	60	1.5	0.03 [-0.33, 0.38]
Yanhua Xi2013	272.13	87.03	30	268.97	85.72	30	1.4	0.04 [-0.47, 0.54]
Ping Dou2016	306.19	87.76	52	297.18	90.65	948	1.5	0.10 [-0.18, 0.38]
Mustafa Altay2017	4.3	1	35	4.2	0.9	30	1.4	0.10 [-0.38, 0.59]
Yuan Guo2018	306.53	83.88	108	297.44	83.5	216	1.5	0.11 [-0.12, 0.34]
AoLiu2018	311.75	74.84	66	300.2	74.18	67	1.5	0.15 [-0.19, 0.49]
Jiadan Wang2016	333	86	202	317	79	202	1.6	0.19 [-0.00, 0.39]
Ruoxi Tang2016	329	78	73	309	90	371	1.5	0.23 [-0.02, 0.48]
Tianfang Fu2016	408.58	87.44	45	385.41	97.29	50	1.5	0.25 [-0.16, 0.65]
Wei Wei2019	252.7	22.5	114	246.4	24.2	235	1.5	0.27 [0.04, 0.49]
Sayari Saba2018	4.24	1.2	56	3.94	1.01	51	1.5	0.27 [-0.11, 0.65]
Liping Xiao2018	335.35	91	114	310.12	88.69	114	1.5	0.28 [0.02, 0.54]
Libo Liang2013	327.06	86.7	356	302.86	74.1	331	1.6	0.30 [0.15, 0.45]
Jiaren Zhou2014	411	92	46	378	114	109	1.5	0.30 [-0.04, 0.65]
Wei Liu2015	386	94	78	357	87	105	1.5	0.32 [0.03, 0.62]
Torkian P2020	5.1	1.4	118	4.6	1.63	121	1.5	0.33 [0.07, 0.58]
Xiaolei Chen2018	370.85	118.62	154	335.88	91.93	183	1.6	0.33 [0.12, 0.55]
Yahui liu2019	338.41	70.13	112	312.34	78.81	112	1.5	0.35 [0.08, 0.61]
Weina Xu2015	308.75	81.71	107	277.13	74.12	1348	1.6	0.42 [0.23, 0.62]
Wenjuan Jiang2016	377.2	101.3	100	333.2	90.1	100	1.5	0.46 [0.18, 0.74]
Yingchuan Liu2017	368.52	135.94	67	320.87	95.38	352	1.5	0.46 [0.20, 0.73]
Hua Zhong2014	380.1	82.6	63	341.5	81.6	418	1.5	0.47 [0.20, 0.74]
Xiaoyan Guo2019	284.58	76.2	85	248.79	69.77	85	1.5	0.49 [0.18, 0.79]
Wenping Li2020	429.46	90.61	57	385.04	87.24	118	1.5	0.50 [0.18, 0.82]
Shunyou Deng 2008	358.5	138.48	60	289.4	116.11	56	1.5	0.54 [0.16, 0.91]
Song Bo2010	359.5	138.48	35	289.5	116.23	35	1.4	0.54 [0.06, 1.02]
Junzheng Chen2012	349.8	127.56	54	279.9	115.73	48	1.5	0.57 [0.17, 0.96]
Chungrong Wang2019	357.83	125.19	74	288.97	113.28	70	1.5	0.57 [0.24, 0.91]
Zhangxia Cui2016	477.9	87.5	42	391.8	90.5	32	1.4	0.63 [0.15, 1.10]
Cong Chen2017	371	95.4	102	312	91.4	770	1.6	0.64 [0.43, 0.85]
Jue Wang2014	366	123.45	47	286.96	95.51	45	1.4	0.71 [0.29, 1.13]
Gao F2017	277.9	78.07	95	229.94	41.46	54	1.5	0.71 [0.37, 1.05]
Qing Chen2010	298.2	90.03	119	230.07	99.26	79	1.5	0.72 [0.43, 1.02]
Fei Li2014	316.82	73.42	118	262.3	73.42	298	1.6	0.74 [0.52, 0.96]
Leyin Xia2015	351.58	83.3	355	286.51	103.47	70	1.5	0.75 [0.49, 1.01]
Chunjiang Yang2011	312.81	61.03	45	268.47	48.65	50	1.5	0.80 [0.38, 1.22]
Jianting Zhong2009	398.2	136.26	80	289.6	118.21	78	1.5	0.85 [0.52, 1.17]
Zhiling Hao2012	389.2	89.41	31	323.71	64.71	40	1.4	0.85 [0.36, 1.34]
Min Guo2015	328.6	77.02	54	266.11	70.54	150	1.5	0.86 [0.54, 1.18]
Afsar B2017	7.4	1.2	66	5.9	1.9	163	1.5	0.86 [0.57, 1.16]
Rong Huang2013	390.33	77.88	392	340.26	56.12	18167	1.6	0.88 [0.78, 0.98]
Yin Li2016	356.56	80.69	155	275.16	90.95	250	1.6	0.93 [0.72, 1.14]
Yuhong Chen2015	356.05	86.26	30	274.29	62.2	20	1.3	1.04 [0.43, 1.64]
Abdel-Gayoum A A2014	225.98	12.28	21	209.04	20.37	14	1.2	1.04 [0.31, 1.76]
Xueqin Wang2019	326.31	37.92	51	287.82	32.65	51	1.5	1.08 [0.66, 1.50]
Yanbin Zhang2017	352.72	54.26	424	284.33	65.79	613	1.6	1.11 [0.98, 1.25]
Krysiak R2014	405	50	16	345	52	18	1.2	1.15 [0.41, 1.88]
Xuelian Jiang2017	375	81	50	269	72	55	1.4	1.38 [0.95, 1.80]
Mingling Deng2016	297.68	30.54	39	257.44	27.25	85	1.5	1.41 [0.99, 1.83]
Yuqin Yuan2016	367	65	42	270	60	42	1.4	1.54 [1.05, 2.03]
Wenzhu Yu2015	386	80	35	261	68	35	1.4	1.67 [1.12, 2.21]
Guoqing Chen2013	258.8	33.6	32	198.6	21.3	32	1.3	2.11 [1.50, 2.73]
Yating Zhang2012	258.33	33.21	25	199.54	21.26	60	1.3	2.30 [1.72, 2.89]
Daijiajia Yin2015	295.02	33.24	40	220.61	21.26	100	1.4	2.93 [2.43, 3.44]
Wenhui He2016	390.23	18.82	115	320.61	17.63	110	1.4	3.80 [3.36, 4.24]
Saini V2012	6.03	0.27	77	4.9	0.3	120	1.4	3.90 [3.42, 4.38]
Chuang Zhang2019	294.9	31.3	80	220.2	4.6	200	1.4	4.35 [3.90, 4.79]
Wen Cao2014	294.71	10.7	45	225.66	6.7	50	0.9	7.76 [6.57, 8.96]
Total (95% CI)			*6623*			*32611*	*100.0*	*0.78 [0.61, 0.95]*

Heterogeneity: $tau^2 = 0.47$; $chi^2 = 1760.13$, df = 67 ($P < 0.00001$); $I^2 = 96\%$

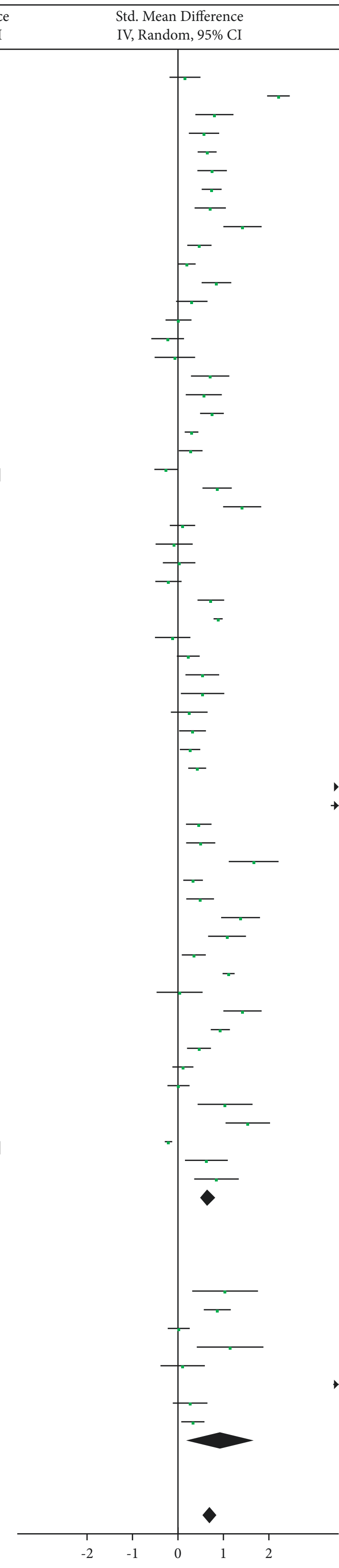
Test for overall effect: Z = 9.04 ($P < 0.00001$)



(a)

Figure 3: Continued.

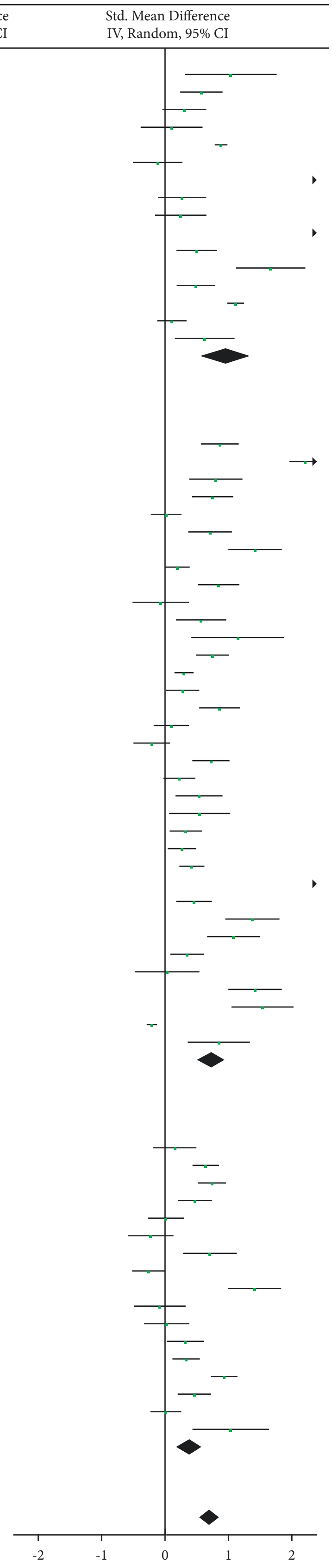
Study or Subgroup	SCH Mean	SCH SD	SCH Total	Control Mean	Control SD	Control Total	Weight (%)	Std. Mean Difference IV, Random, 95 CI
17.1.1 Chinese								
Ao Liu2018	311.75	74.84	66	300.2	74.18	67	1.5	0.15 [-0.19, 0.49]
Chuang Zhang2019	275.94	35.3	200	220.2	4.6	200	1.5	2.21 [1.96, 2.46]
Chunjiang Yang2011	312.81	61.03	45	268.47	48.65	50	1.4	0.80 [0.38, 1.22]
Chunrong Wang2019	357.83	125.19	74	288.97	113.28	70	1.5	0.57 [0.24, 0.91]
Cong Chen2017	371	95.4	102	312	91.4	770	1.6	0.64 [0.43, 0.85]
Daijiajia Yin2015	242.65	38.47	64	220.61	21.26	100	1.5	0.75 [0.43, 1.08]
Fei Li2014	316.82	73.42	118	262.3	73.42	298	1.6	0.74 [0.52, 0.96]
Gao F2017	277.9	78.07	95	229.94	41.46	54	1.5	0.71 [0.37, 1.05]
Guoqing Chen2013	242.27	37.75	50	199.54	21.26	60	1.4	1.42 [1.00, 1.84]
Hua Zhong2014	380.1	82.6	63	341.5	81.6	418	1.5	0.47 [0.20, 0.74]
Jiadan Wang2016	333	86	202	317	79	202	1.6	0.19 [-0.00, 0.39]
Jianting Zhong2009	398.2	136.26	80	289.6	118.21	78	1.5	0.85 [0.52, 1.17]
Jiaren Zhou2014	411	92	46	378	114	109	1.5	0.30 [-0.04, 0.65]
Jingli Cheng2019	291.21	79.21	62	290.31	73.23	198	1.5	0.01 [-0.27, 0.30]
Jinyuan Ren2012	357.24	96.08	35	379.38	97.72	198	1.5	-0.23 [-0.59, 0.13]
Juanjuan Sun2018	361.12	107.2	25	368.69	111.99	86	1.4	-0.07 [-0.51, 0.38]
Jue Wang2014	366	366	47	286.96	95.51	45	1.4	0.71 [0.29, 1.13]
Junzheng Chen2012	349.8	123.56	54	279.9	115.73	48	1.5	0.57 [0.17, 0.96]
Leyin Xia2015	351.58	83.3	355	286.51	103.47	70	1.5	0.75 [0.49, 1.01]
Libo Liang2013	327.06	86.7	356	302.86	74.1	331	1.6	0.30 [0.15, 0.45]
Liping Xiao2018	335.35	91	114	310.12	88.69	114	1.5	0.28 [0.02, 0.54]
Man Jin2016	334.3	98.18	95	357.97	84.53	153	1.5	-0.26 [-0.52, -0.01]
Min Guo2015	328.6	77.02	54	266.11	70.54	150	1.5	0.86 [0.54, 1.18]
Mingling Deng2016	297.68	30.54	39	257.44	27.25	85	1.4	1.41 [0.99, 1.83]
Ping Dou2016	306.19	87.76	52	297.18	90.65	948	1.5	0.10 [-0.18, 0.38]
Qian Jiang2020	302.2	75.34	25	309.81	91.63	299	1.4	-0.08 [-0.49, 0.32]
Qiang Song2016	440.7	98.6	60	438.1	105.2	60	1.5	0.03 [-0.33, 0.38]
Qiannan Du2018	289	92	55	311	107	287	1.5	-0.21 [-0.50, 0.08]
Qing Chen2010	298.2	90.03	119	230.07	99.26	79	1.5	0.72 [0.43, 1.02]
Rong Huang2013	390.33	77.88	392	340.26	56.12	18167	1.6	0.88 [0.78, 0.98]
Rongrong Zhang2013	369.72	91.33	45	380.67	94.97	58	1.5	-0.12 [-0.51, 0.27]
Ruoxi Tang2016	329	78	73	309	90	371	1.5	0.23 [-0.02, 0.48]
Shunyou Deng 2008	358.5	138.48	60	289.4	116.11	56	1.5	0.54 [0.16, 0.91]
Song Bo2010	359.5	138.48	35	289.5	116.23	35	1.4	0.54 [0.06, 1.02]
Tianfang Fu2016	408.58	87.44	45	385.41	97.29	50	1.4	0.25 [-0.16, 0.65]
Wei Kiu2015	386	94	78	357	87	105	1.5	0.32 [0.03, 0.62]
Wei Wei2019	252.7	22.5	114	246.4	24.2	235	1.6	0.27 [0.04, 0.49]
Weina Xu2015	308.75	81.71	107	277.13	74.12	1348	1.6	0.42 [0.23, 0.62]
Wen Cao2014	294.71	10.7	45	225.66	6.7	50	0.8	7.76 [6.57, 8.96]
Wenhui He2016	390.23	18.82	115	320.61	17.63	110	1.4	3.80 [3.36, 4.24]
Wenjuan Jiang2016	377.2	101.3	100	333.2	90.1	100	1.5	0.46 [0.18, 0.74]
Wenlang Li2009	429.46	90.61	57	385.04	87.24	118	1.5	0.50 [0.18, 0.82]
Wenzhu Yu2015	386	80	35	261	68	35	1.3	1.67 [1.12, 2.21]
Xiaolei Chen2018	370.85	118.62	154	335.88	91.93	183	1.6	0.33 [0.12, 0.55]
Xiaoyan Guo2019	284.58	76.2	85	248.79	69.77	85	1.5	0.49 [0.18, 0.79]
Xuelian Jiang2017	375	81	50	269	72	55	1.4	1.38 [0.95, 1.80]
Xueqin Wang2019	326.31	37.92	51	287.82	32.65	51	1.4	1.08 [0.66, 1.50]
Yahui Liu2019	338.41	70.13	112	312.34	78.81	112	1.5	0.35 [0.08, 0.61]
Yanbin Zhang2017	352.72	54.26	424	284.33	65.79	613	1.6	1.11 [0.98, 1.25]
Yanhua Xi2013	272.13	87.03	30	268.97	85.72	30	1.4	0.04 [-0.47, 0.54]
Yating Zhang2012	242.27	37.75	50	199.54	21.26	60	1.4	1.42 [1.00, 1.84]
Yin Li2016	356.56	80.69	155	275.16	90.95	250	1.6	0.93 [0.72, 1.14
YingChuan Liu2017	368.52	135.94	67	320.87	95.38	352	1.5	0.46 [0.20, 0.73]
Yuan Guo2018	306.53	83.88	108	297.44	83.5	216	1.5	0.11 [-0.12, 0.34]
Yuelei Wu2020	339.26	124.03	129	337.87	106.05	131	1.5	0.01 [-23, 0.26]
Yuhong Chen2015	356.05	86.26	30	274.29	62.2	20	1.3	1.04 [0.43, 1.64]
Yuqin Yuan2016	367	65	42	270	60	42	1.4	1.54 [1.05, 2.03]
Zhang J2016	304.09	87.62	710	322.32	87.58	3187	1.6	-0.21 [-0.29, -0.13]
Zhangxia Cui2016	447.9	87.5	42	391.8	90.5	32	1.4	0.63 [0.15, 1.10]
Zhiling Hao2012	389.2	89.41	31	323.71	64.71	40	1.4	0.85 [0.36, 1.34]
Subtotal (95 CI)			*6323*			*31924*	*88.8*	*0.66 [0.50, 0.82]*
Heterogeneity: $tau^2 = 0.37$; $chi^2 = 1319.24$, df = 59 ($P < 0.00001$); $I^2 = 96\%$								
Test for overall effect: Z = 8.16 ($P < 0.00001$)								
17.1.2 non-Chinese								
Abdel-Gayouum A A2014	225.98	12.28	21	209.04	20.37	14	1.2	1.04 [0.31, 1.76]
Afsar B2017	7.4	1.2	66	5.9	1.9	163	1.5	0.86 [0.57, 1.16]
Devika Tayal2009	5.93	4.95	98	5.87	2.53	198	1.5	0.02 [-0.23, 0.26]
Krysiak R2014	405	50	16	345	52	18	1.2	1.15 [0.41, 1.88]
Mustafa Altay2017	4.3	1	35	4.2	0.9	30	1.4	0.10 [-0.38, 0.59]
Saini V2012	6.03	0.27	77	4.9	0.3	120	1.4	3.90 [3.42, 4.38]
Sayari Saba2018	4.24	1.2	56	3.94	1.01	51	1.5	0.27 [-0.11, 0.65]
Torkian P2020	5.1	1.4	118	4.6	1.63	121	1.5	0.33 [0.07, 0.58]
Subtotal (95 CI)			*487*			*715*	*11.2*	*0.95 [0.20, 1.69]*
Heterogeneity: $tau^2 = 1.08$; $chi^2 = 219.47$, df = 7 ($P < 0.00001$); $I^2 = 97\%$								
Test for overall effect: Z = 2.50 ($P < 0.01$)								
Total (95% CI)			*6810*			*32639*	*100.0*	*0.70 [0.54, 0.85]*
Heterogeneity: $tau^2 = 0.40$; $chi^2 = 1542.75$, df = 67 ($P < 0.00001$); $I^2 = 96\%$								
Test for overall effect: Z = 8.72 ($P < 0.00001$)								
Test for subgroup differences: $chi^2 = 0.53$; DF = 1 ($P < 0.47$); $I^2 = 0$								



(b)

Figure 3: Continued.

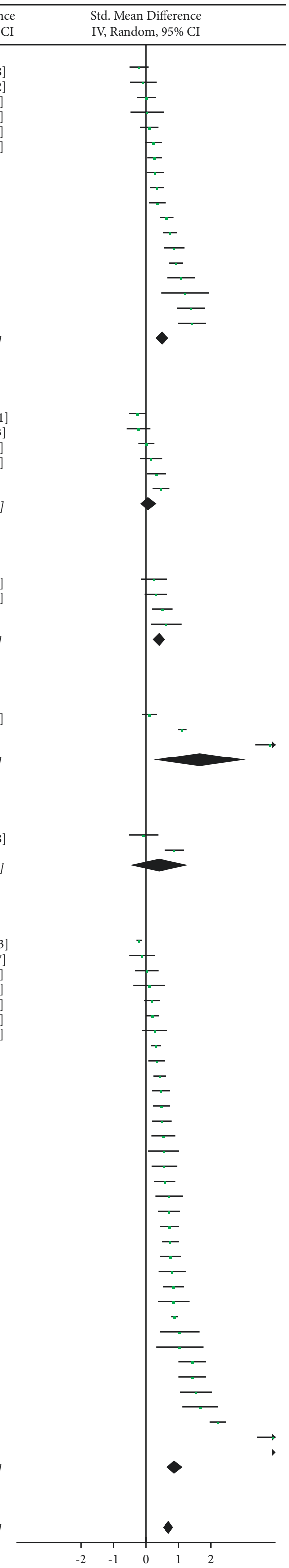
Study or Subgroup	SCH Mean	SCH SD	SCH Total	Control Mean	Control SD	Control Total	Weight (%)	Std. Mean Difference IV, Random, 95% CI
19.1.1 Age<45 years old								
Abdel-Gayoum A A2014	225.98	12.28	21	209.04	20.37	14	1.2	1.04 [0.31, 1.76]
Chunrong Wang2019	357.83	125.19	74	288.97	113.28	70	1.5	0.57 [0.24, 0.91]
Jiaren Zhou2014	411	92	46	378	114	109	1.5	0.30 [-0.04, 0.65]
Mustafa Altay2017	4.3	1	35	4.2	0.9	30	1.4	0.10 [-0.38, 0.59]
Rong Huang2013	390.33	77.88	392	340.26	56.12	18167	1.6	0.88 [0.78, 0.98]
Rongrong Zhang20133	369.72	91.33	45	380.67	94.97	58	1.5	-0.12 [-0.51, 0.27]
Saini V2012	6.03	0.27	77	4.9	0.3	120	1.4	0.90 [3.42, 4.38]
Sayari Saba2018	4.24	1.2	56	3.94	1.01	51	1.5	0.27 [-0.11, 0.65]
Tianfang Fu2016	408.58	87.44	45	385.41	97.29	50	1.4	0.25 [-0.16, 0.65]
Wenhui He2016	390.23	18.82	115	320.61	17.63	110	1.4	3.80 [3.36, 4.24]
Wenping Li2020	429.46	90.61	57	385.04	87.24	118	1.5	0.50 [0.18, 0.82]
Wenzhu Yu2015	386	80	35	261	68	35	1.3	1.67 [1.12, 2.21]
Xiaoyan Guo2019	284.58	76.2	85	248.79	69.77	85	1.5	0.49 [0.18, 0.79]
Yanbin Zhang2017	352.72	54.26	424	284.33	65.79	613	1.6	1.11 [0.98, 1.25]
Yuan Guo2018	306.53	83.88	108	297.44	83.5	216	1.5	0.11 [-0.12, 0.34]
Zhangxia Cui2016	447.9	87.5	42	391.8	90.5	32	1.4	0.63 [0.15, 1.10]
Subtotal (95% CI)			*1657*			*19878*	*23.2*	*0.95 [0.57, 1.34]*
Heterogeneity: $Tau^2 = 0.58$; $Chi^2 = 462.75$, df = 15 ($P < 0.00001$); $I^2 = 97\%$								
Test for overall effect: $Z = 4.84$ ($P < 0.00001$)								
19.1.2 45<Age<60 years old								
Afsar B2017	7.4	1.2	66	5.9	1..9	163	1.5	0.86 [0.57, 1.16]
Chuang Zhang2019	275.94	35.3	200	220.2	4.6	200	1.5	2.21 [1.96, 2.46]
Chunjiang Yang2011	312.81	61.03	45	268.47	48.65	50	1.4	0.80 [0.38, 1.22]
Daijiajia Yin2015	242.65	38.47	64	220.61	21.26	100	1.5	0.75 [0.43, 1.08]
Devika Tayal2009	5.93	4.95	98	5.87	2.53	198	1.5	0.02 [-0.23, 0.26]
Gao F2017	277.9	78.07	95	229.94	41.46	54	1.5	0.71 [0.37, 1.05]
Guoqing Chen2013	242.27	37.75	50	199.54	21.26	60	1.4	1.42 [1.00, 1.84]
Jiadan Wang2016	333	86	202	317	79	202	1.6	0.19 [-0.00, 0.39]
Jianting Zhong2009	398.2	136.26	80	289.6	118.21	78	1.5	0.85 [0.52, 1.17]
Juanjuan Sun2018	361.12	107.2	25	368.69	111.99	86	1.4	-0.07 [-0.51, 0.38]
Junzheng Chen2012	349.8	127.56	54	279.9	115.73	48	1.5	0.57 [0.17, 0.96]
Krysiak R2014	405	50	16	345	52	18	1.2	1.15 [0.41, 1.88]
Leyin Xia2015	351.58	83.3	355	286.51	103.47	70	1.5	0.75 [0.49, 1.01]
Liba Liang2013	327.06	86.7	356	302.86	74.1	331	1.6	0.30 [0.15, 0.45]
Liping Xiao2018	335.35	91	114	310.12	88.69	114	1.5	0.28 [0.02, 0.54]
Min Guo2015	328.6	77.02	54	266.11	70.54	150	1.5	0.86 [0.54, 1.18]
Ping Dou2016	306.19	87.76	52	297.18	90.65	948	1.5	0.10 [-0.18, 0.38]
Qiannan Du2018	289	92	55	311	107	287	1.5	-0.21 [-0.50, 0.08]
Qing Chen2010	298.5	90.03	119	230.07	99.26	79	1.5	0.72 [0.43, 1.02]
Ruoxi Tang2016	329	78	73	309	90	371	1.5	0.23 [-0.02, 0.48]
Shunyou Deng 2008	358.2	138.48	60	289.4	116.11	56	1.5	0.54 [0.16, 0.91]
Song Bo2010	359.5	138.48	35	289.5	116.23	35	1.4	0.54 [0.06, 1.02]
Torkian P2020	5.1	1.4	118	4.6	1.63	121	1.5	0.33 [0.07, 0.58]
Wei wei2019	252.7	22.5	114	246.4	24.2	235	1.6	0.27 [ ]0.004, 0.49]
Weina Xu2015	308.75	81.71	107	277.13	74.12	1348	1.6	0.42 [0.23, 0.62]
Wen Cao2014	294.71	10.7	45	225.66	6.7	50	0.8	7.76 [6.57, 8.96]
Wenjuan jiang2016	377.2	101.3	100	333.2	90.1	100	1.5	0.46 [0.18, 0.74]
Xuelian jiang2017	375	81	50	269	72	55	1.4	1.38 [0.95, 1.80]
Xueqin Wang2019	326.31	37.92	51	287.82	32.65	51	1.4	1.08 [0.66, 1.50]
Yahui Liu2019	338.41	70.13	112	312.34	78.81	112	1.5	0.35 [0.08, 0.61]
Yanhua Xi2013	272.13	87.03	30	268.97	85.72	30	1.4	0.04 [-0.47, 0.54]
Yating Zhang2012	242.27	37.75	50	199.54	21.26	60	1.4	1.42 [1.00, 1.84]
Yuqin Yuan2016	367	65	42	270	60	42	1.4	1.54 [1.05, -0.13]
Zhang J2016	304.09	87.62	710	322.32	87.58	3187	1.6	-0.21 [-0.29, -0.13]
Zhiling Hao2012	389.2	89.41	31	323.71	64.71	40	1.4	0.85 [0.36, 1.34]
Subtotal (95% CI)			*3828*			*9129*	*51.3*	*0.73 [0.52, 0.95]*
Heterogeneity: $Tau^2 = 0.39$; $Chi^2 = 753.76$, df = 34 ($P < 0.00001$); $I^2 = 95\%$								
Test for overall effect: $Z = 6.67$ ($P < 0.00001$)								
19.1.3 Age>60 years old								
Ao Liu2018	311.75	74.84	66	300.2	74.18	67	1.5	0.15 [-0.19, 0.49]
Cong Chen2017	371	95.4	102	312	91..4	770	1.6	0.64 [0.43, 0.85]
Fei Li2014	316.82	73.42	118	262.3	73.42	298	1.6	0.74 [0.52, 0.96]
Hua Zhong2014	380.1	82.6	63	341.5	81.6	418	1.5	0.47 [0.20, 0.74]
Jingli Cheng2019	291.21	79.21	62	290.31	73.23	198	1.5	0.01 [-0.27, 0.30]
Jinyuan Ren2012	357.24	96..08	35	379.38	97.72	198	1.5	-0.23 [-0.59, 0.13]
Jue Wang2014	366	123.45	47	286.96	95.51	45	1.4	0.71 [0.29, 1.13]
Man Jin2016	334.3	98.18	95	357.97	84.53	153	1.5	-0.26 [-0.52, -0.01]
Mingling Deng2016	297.68	30.54	39	257.44	27.25	85	1.4	1.41 [0.99, 1.83]
Qian Jiang2020	302.2	75.34	25	309.81	91.63	299	1.4	-0.08 [-0.49, 0.32]
Qiang Song2016	440.7	98.6	60	438.1	105.2	60	1.5	0.03 [-0.33, 0.38]
Wei Liu2015	386	94	78	357	87	105	1.5	0.32 [0.03, 0.62]
Xiaolei Chen2018	370.85	118.62	154	335.88	91.93	183	1.6	0.33 [0.12, 0.55]
Yin Li2016	356.56	80.69	155	275.16	90.95	250	1.6	0.93 [0.72, 1.14]
Yingchuan Liu2017	368.52	135.94	67	320.87	95.38	352	1.5	0.46 [0.20, 0.73]
Yuelei Wu2020	339.256	124.032	129	337.866	106.047	131	1.5	0.01 [-0.23, 0.26]
Yuhong Chen2015	356.05	86.26	30	274.29	62.2	20	1.3	1.04 [0.43, 1.64]
Subtotal (95% CI)			*1325*			*3632*	*25.5*	*0.38 [0.18, 0.58]*
Heterogeneity: $Tau^2 = 0.15$; $Chi^2 = 134.51$, df = 16 ($P < 0.00001$); $I^2 = 88\%$								
Test for overall effect: $Z = 3.71$ ($P = 0.0002$)								
Total (95% CI)			*6810*			*32639*	*100.0*	*0.70 [0.54, 0.85]*
Heterogeneity: $Tau^2 = 0.40$; $Chi^2 = 1542.75$, df = 67 ($P < 0.00001$); $I^2 = 96\%$								
Test for overall effect: $Z = 8.72$ ($P < 0.00001$)								
Test for subgroup differences: $Chi^2 = 9.19$; DF = 2 ($P = 0.01$); $I^2 = 78.2\%$								



(c)

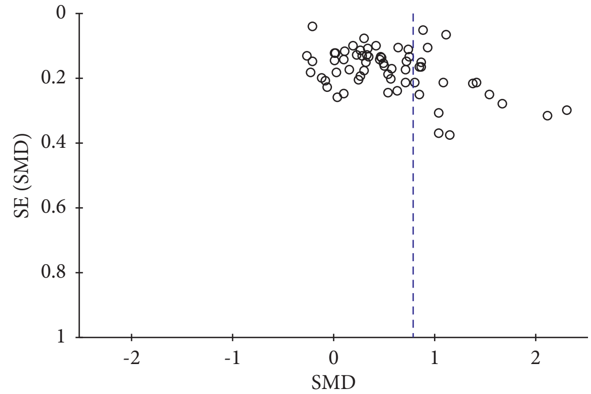
Figure 3: Continued.

Study or Subgroup	SCH Mean	SCH SD	SCH Total	Control Mean	Control SD	Control Total	Weight (%)	Std. Mean Difference IV, Random, 95% CI
5.1.1 MS								
Qiannan Du2018	289	92	55	311	107	287	1.5	-0.21 [-0.50, 0.08]
Qian Jiang2020	302.2	75.34	25	309.81	91.63	299	1.4	-0.08 [-0.49, 0.32]
Jingli Cheng2019	291.21	79.21	62	291.31	73.23	198	1.5	0.01 [-0.27, 0.30]
Yanhua Xi2013	272.13	87.03	30	268.97	85.72	30	1.4	0.04 [-0.47, 0.54]
Ping Dou2016	306.19	87.76	52	297.18	90.65	948	1.5	0.10 [-0.18, 0.38]
Ruoxi Tang2016	329	78	73	309	90	371	1.5	0.23 [-0.02, 0.48]
Wei Wei2019	252.7	22.5	114	246.4	24.2	235	1.6	0.27 [0.04, 0.49]
Liping Xiao2018	335.35	91	114	310.12	88.69	114	1.5	0.28 [0.02, 0.54]
Xiaolei Chen2018	370.85	118.62	154	335.88	91.93	183	1.6	0.33 [0.12, 0.55]
Yahui Liu2019	338.41	70.13	112	312.34	78.81	112	1.5	0.35 [0.08, 0.61]
Cong Chen2017	371	95.4	102	312	91.4	770	1.6	0.64 [0.43, 0.85]
Fei Li2014	316.82	73.42	118	262.3	73.42	298	1.6	0.74 [0.52, 0.96]
Min Guo2015	328.6	77.02	54	266.11	70.54	150	1.5	0.86 [0.54, 1.18]
Yin Li2016	356.56	80.69	155	275.16	90.95	250	1.6	0.93 [0.72, 1.14]
Xueqin Wang2019	326.31	37.92	54	287.82	32.65	51	1.4	1.08 [0.66, 1.50]
Krysiak R2014	405	50	16	342	52	18	1.2	1.20 [0.47, 1.94]
Xuelian Jiang2017	375	81	50	269	72	55	1.4	1.38 [0.95, 1.80]
Mingling Deng2016	297.68	30.54	39	257.44	27.25	85	1.4	1.41 [0.99, 1.83]
Subtotal (95% CI)			*1376*			*4454*	*26.8*	*0.51 [0.31, 0.70]*
Heterogeneity: $Tau^2 = 0.15$; $Chi^2 = 140.42$, $df = 17$ ($P < 0.00001$); $I^2 = 88\%$								
Test for overall effect: $Z = 5.06$ ($P < 0.00001$)								
5.1.2 Cardiovascular disease								
Man Jin2016	334.3	98.18	95	357.97	84.53	153	1.5	-0.26 [-0.52, -0.01]
JinYuan Ren2012	357.24	96.08	35	379.38	97.72	198	1.5	-0.23 [-0.59, 0.13]
Yuelei Wu2020	339.256	124.032	129	337.866	106.047	131	1.5	0.01 [-0.23, 0.26]
Ao Liu2018	311.75	74.84	66	300.2	74.18	67	1.5	0.15 [-0.19, 0.49]
Wei Liu2015	386	94	78	357	87	105	1.5	0.32 [0.03, 0.62]
Yingchuan Liu217	368.52	135.94	67	320.87	95.38	352	1.5	0.46 [0.20, 0.73]
Subtotal (95% CI)			*470*			*1006*	*9.1*	*0.08 [-0.16, 0.32]*
Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 20.74$, $df = 5$ ($P = 0.0009$); $I^2 = 76\%$								
Test for overall effect: $Z = 0.66$ ($P = 0.51$)								
5.1.3 Severe preeclampsia								
Tianfang Fu2016	408.58	87.44	45	385.41	97.29	50	1.4	0.25 [-0.16, 0.65]
Jiaren Zhou2014	411	92	46	378	114	109	1.5	0.30 [-0.04, 0.65]
Wenping Li2020	429.46	90.61	57	385.04	87.24	118	1.5	0.50 [0.18, 0.82]
Zhangxia Cui2016	447.9	87.5	42	391.8	90.5	32	1.4	0.63 [0.15, 1.10]
Subtotal (95% CI)			*190*			*309*	*5.8*	*0.41 [0.22, 0.60]*
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.08$, $df = 3$ ($P < 0.56$); $I^2 = 0\%$								
Test for overall effect: $Z = 4.29$ ($P < 0.0001$)								
5.1.5 pregnancy								
Yuan Guo2018	306.53	83.88	108	297.44	83.5	216	1.5	0.11 [-0.12, 0.34]
Yanbin Zhang2017	352.72	54.26	424	284.33	65.79	613	1.6	1.11 [0.98, 1.25]
Wenhui He2016	390.23	18.82	115	320.61	17.63	110	1.4	3.80 [3.36, 4.24]
Subtotal (95% CI)			*647*			*939*	*4.6*	*1.66 [0.24, 3.07]*
Heterogeneity: $Tau^2 = 1.54$; $Chi^2 = 214.68$, $df = 2$ ($P < 0.00001$); $I^2 = 99\%$								
Test for overall effect: $Z = 2.30$ ($P = 0.02$)								
5.1.6 Chronic kidney disease								
Juanjuan Sun2018	361.12	107.2	25	368.69	111.99	86	1.4	-0.07 [-0.51, 0.38]
Afsar B2017	7.4	1.2	66	5.9	1.9	163	1.5	0.86 [0.57, 1.16]
Subtotal (95% CI)			*91*			*249*	*2.9*	*0.41 [-0.50, 1.33]*
Heterogeneity: $Tau^2 = 0.40$; $Chi^2 = 11.66$, $df = 1$ ($P < 0.0006$); $I^2 = 91\%$								
Test for overall effect: $Z = 0.89$ ($P = 0.37$)								
5.1.7 normal								
Zhang J2016	304.086	87.62	710	322.323	87.58	3187	1.6	-0.21 [-0.29, -0.13]
Rongrong Zhang2013	369.72	91.33	45	380.67	94.97	58	1.5	-0.12 [-0.51, 0.27]
Qiang Song2016	440.7	98.6	60	105.2	105.2	60	1.5	0.03 [-0.33, 0.38]
Mustafa Alltay2017	4.3	1	35	4.2	0.9	30	1.4	0.10 [-0.38, 0.59]
Devika Tayal2009	5.93	0.5	98	5.87	0.18	198	1.5	0.19 [-0.06, 0.43]
Jiadan Wang2016	333	86	202	317	79	202	1.6	0.19 [-0.00, 0.39]
Sayari Saba2018	4.24	1.2	56	3.94	1.01	51	1.5	0.27 [-0.11, 0.65]
Libo Liang2013	327.06	86.7	356	302.86	74.1	331	1.6	0.30 [0.15, 0.45]
Torkian P2020	5.1	1.4	118	4.6	1.63	121	1.5	0.33 [0.07, 0.58]
Weina Xu2015	308.75	81.71	107	277.13	74.12	1348	1.6	0.42 [0.23, 0.62]
Wenjuan Jiang2016	377.2	101.3	100	333.2	90.1	100	1.5	0.46 [0.18, 0.74]
Hua Zhong2014	380.1	82.6	63	341.5	81.6	418	1.5	0.47 [0.20, 0.74]
Xiaoyan Guo2019	284.58	76.2	85	248.79	69.77	85	1.5	0.49 [0.18, 0.79]
Shunyou Deng 2008	358.5	138.48	60	289.4	116.11	56	1.5	0.54 [0.16, 0.91]
Song Bo2010	359.5	138.48	35	289.5	116.23	35	1.4	0.54 [0.06, 1.02]
Junzheng Chen2012	349.8	127.56	45	279.9	115.73	48	1.5	0.57 [0.17, 0.96]
Chungrong Wang2019	357.83	125.19	74	288.97	113.28	70	1.5	0.57 [0.24, 0.91]
Jue Wang2014	366	123.45	47	286.96	95.51	45	1.4	0.71 [0.29, 1.13]
Gao F2017	277.9	78.07	95	229.94	41.46	54	1.5	0.71 [0.37, 1.05]
Qing Chen2010	298.2	90.03	119	230.07	99.26	79	1.5	0.72 [0.43, 1.02]
Leyin Xia2015	351.58	83.3	355	286.51	103.47	70	1.5	0.75 [0.49, 1.01]
Daijiajia Yin2015	242.65	38.47	64	220.61	21.26	100	1.5	0.75 [0.43, 1.08]
Chungjiang Yang2011	312.81	61.03	45	268.47	48.65	50	1.4	0.80 [0.38, 1.22]
Jianting Zhong2009	398.2	136.26	80	289.6	118.21	78	1.5	0.85 [0.52, 1.17]
Zhiling Hao2012	389.2	89.41	31	323.71	64.71	40	1.4	0.85 [0.36, 1.34]
Rong Huang2013	390.33	77.88	392	340.26	56.12	18167	1.6	0.88 [0.78, 0.98]
Yuhong Chen2015	356.05	86.26	30	274.29	62.2	20	1.3	1.04 [0.43, 1.64]
Abdel-Gayoum A A2014	255.98	12.28	21	209.04	20.37	14	1.2	1.04 [0.31, 1.76]
Guoqing Chen2013	242.27	37.75	50	199.54	21.26	60	1.4	1.42 [1.00, 1.84]
Yating Zhang2012	242.27	37.75	50	199.54	21.26	60	1.4	1.42 [1.00, 1.84]
Yuqin Yuan2016	367	65	42	270	60	42	1.4	1.54 [1.05, 2.03]
Wenzhu Yu2015	386	80	35	261	68	35	1.3	1.67 [1.12, 2.21]
Chuang Zhang2019	275.94	35.3	200	220.2	4.6	200	1.5	2.21 [1.96, 2.46]
Saini V2012	6.03	0.27	77	4.9	0.3	120	1.4	3.90 [3.42, 4.38]
Wen Cao2014	294.71	10.7	45	225.66	6.7	50	0.8	7.76 [6.57, 8.96]
Subtotal (95% CI)			*4036*			*25682*	*50.8*	*0.89 [0.64, 1.13]*
Heterogeneity: $Tau^2 = 0.49$; $Chi^2 = 997.25$, $df = 34$ ($P < 0.00001$); $I^2 = 97\%$								
Test for overall effect: $Z = 7.21$ ($P < 0.00001$)								
Total (95% CI)			*6810*			*32639*	*100.0*	*0.70 [0.54, 0.86]*
Heterogeneity: $Tau^2 = 0.40$; $Chi^2 = 1534.84$, $df = 67$ ($P < 0.00001$); $I^2 = 96\%$								
Test for overall effect: $Z = 8.78$ ($P < 0.00001$)								
Test for subgroup differences: $Chi^2 = 24.90$, $df = 5$ ($P = 0.0001$); $I^2 = 79.9\%$								



(d)

Figure 3: Continued.

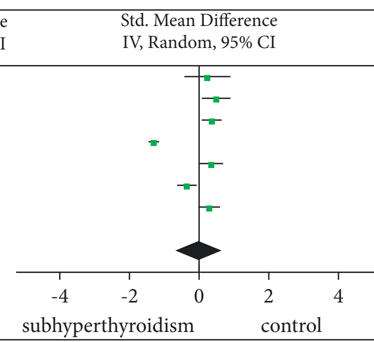


(e)

Figure 3: (a) Forest plot of subclinical hypothyroidism and uric acid. (b) Subgroup analysis of subclinical hypothyroidism, grouped by area. (c) Subgroup analysis of subclinical hypothyroidism, grouped by age. (d) Subgroup analysis of subclinical hypothyroidism, grouped by basic diseases. (e) Funnel plot of subclinical hypothyroidism.

Study or Subgroup	subhyperthyroidism			Control			Weight	Std. Mean Difference
	Mean	SD	Total	Mean	SD	Total	(%)	IV, Random, 95% CI
Abdel-Gayoum A A2014	213.54	17.29	24	209.04	20.37	14	13.1	0.24 [-0.42, 0.90]
Afsar B2017	6.8	1.3	27	5.9	1.9	163	14.2	0.49 [0.08, 0.90]
Qing Chen2010	264.67	92.98	119	230.07	99.26	79	14.5	0.36 [0.07, 0.65]
Rong Huang2013	267.13	71.54	172	340.26	56.12	18167	114.8	-1.30 [-1.45, -1.15]
Wen Cao2014	315.51	74.59	50	292.07	62.32	110	14.4	0.35 [0.01, 0.69]
Wenjian Jiang2016	304.2	73.7	100	333.2	90.1	100	14.6	-0.35 [-0.63, -0.07]
Zhengxia Di2019	308.04	84.01	49	280.93	95.74	200	14.5	0.29 [-0.02, 0.60]
Total (95% CI)			*541*			*18833*	*100.0*	*0.00 [-0.67, 0.67]*

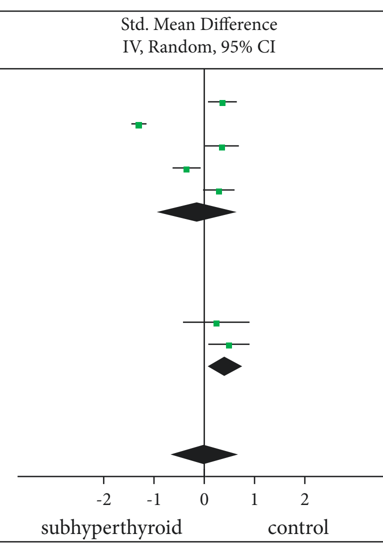
Heterogeneity: $tau^2 = 0.79$; $chi^2 = 219.80$, df = 6 ($P < 0.00001$); $I^2 = 97\%$
Test for overall effect: $Z = 0.00$ ($P = 1.00$)



(a)

Study or Subgroup	subhyperthyroid			Control			Weight	Std. Mean Difference
	Mean	SD	Total	Mean	SD	Total	(%)	IV, Random, 95% CI
18.1.1 Chinese								
Qing Chen2010	264.67	92.98	119	230.07	99.26	79	14.5	0.36 [0.07, 0.65]
Rong Huang2013	267.13	71.54	172	340.26	56.12	18167	14.8	-1.30 [-1.45, -1.15]
Wen Cao2014	315.51	74.59	50	292.07	62.32	110	14.4	0.35 [0.01, 0.69]
Wenjuan jiang2016	304.2	73.7	100	333.2	90.1	100	14.6	-0.35 [-0.63, -0.07]
Zhengxia Di2019	308.04	84.01	49	280.93	95.74	200	14.5	0.29 [-0.02, 0.60]
Subtotal (95% CI)			*490*			*18656*	*72.8*	*-0.14 [-0.93, 0.66]*
Heterogeneity: $tau^2 = 0.80$; $chi^2 = 190.35$, df = 4 ($P < 0.00001$); $I^2 = 98\%$								
Test for overall effect: $Z = 0.33$ ($P = 0.74$)								
18.1.2 non-chinese								
Abdel-Gayoum A A2014	213.54	17.29	24	209.04	20.37	14	13.1	0.24 [-0.42, 0.90]
Afsar B2017	6.8	1.3	27	5.9	1.9	163	14.2	0.49 [0.08, 0.90]
Subtotal (95% CI)			*51*			*177*	*27.2*	*0.42 [0.07, 0.77]*
Heterogeneity: $tau^2 = 0.00$; $chi^2 = 0.40$, df = 1 ($P = 0.53$); $I^2 = 0\%$								
Test for overall effect: $Z = 2.36$ ($P = 0.02$)								
Total (95% CI)			*541*			*18833*	*100.0*	*0.00 [-0.67, 0.67]*

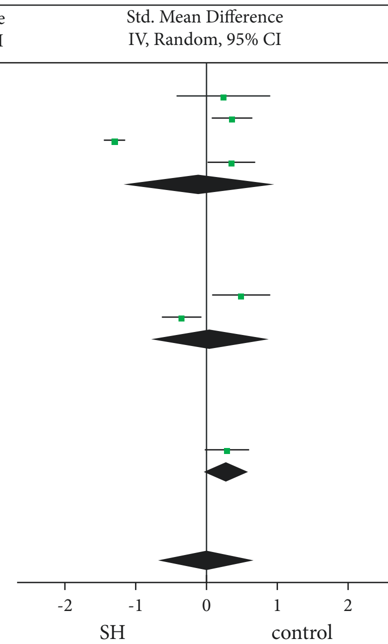
Heterogeneity: $tau^2 = 0.79$; $chi^2 = 219.80$, df = 6 ($P < 0.00001$); $I^2 = 97\%$
Test for overall effect: $Z = 0.00$ ($P = 1.00$)
Test for subgroup differences: $chi^2 = 1.57$, df = 1 ($P = 0.21$); $I^2 = 36.5\%$



(b)

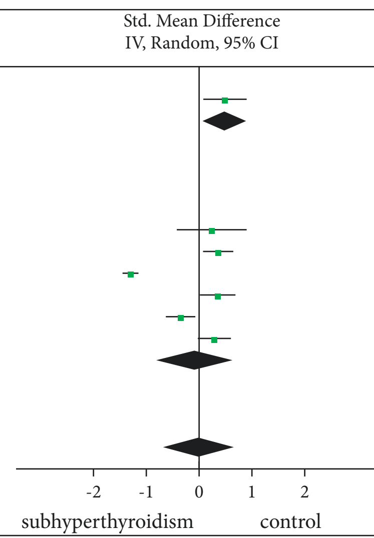
Figure 4: Continued.

Study or Subgroup	SH Mean	SH SD	SH Total	Control Mean	Control SD	Control Total	Weight (%)	Std. Mean Difference IV, Random, 95% CI
20.1.1 Age <45 years old								
Abdel-Gayoum A A2014	213.54	17.29	24	209.04	20.37	14	13.1	0.24 [-0.42, 0.90]
Qing Chen2010	264.67	92.98	119	230.07	99.26	79	14.5	0.36 [0.07, 0.65]
Rong Huang2013	267.13	71.54	172	340.26	56.12	18167	14.8	-1.30 [-1.45, -1.15]
Wen Cao2014	315.51	74.59	50	292.07	62.32	110	14.4	0.35 [0.01, 0.69]
Subtotal (95% CI)			*365*			*18370*	*56.8*	*-0.10 [-1.17, 0.97]*
Heterogeneity: $Tau^2 = 1.15$; $Chi^2 = 158.30$, df = 3 ($P < 0.00001$); $I^2 = 98\%$								
Test for overall effect: $Z = 0.18$ ($P = 0.86$)								
20.1.2 45<Age <60 years old								
Afsar B2017	6.8	1.3	27	5.9	1.9	163	14.2	0.49 [0.08, 0.90]
Wenjuan jiang2016	304.2	73.7	100	333.2	90.1	100	14.6	-0.35 [-0.63, -0.07]
Subtotal (95% CI)			*127*			*263*	*28.7*	*0.06 [-0.77, 0.88]*
Heterogeneity: $Tau^2 = 0.32$; $Chi^2 = 11.03$, df = 1 ($P < 0.0009$); $I^2 = 91\%$								
Test for overall effect: $Z = 0.13$ ($P = 0.89$)								
20.1.3 Age >60 years old								
Subtotal (95% CI)			*49*			*200*	*14.5*	*0.29 [-0.02, 0.60]*
Heterogeneity: Not applicable								
Test for overall effect: $Z = 1.81$ ($P = 0.07$)								
Total (95% CI)			*541*			*18833*	*100.0*	*0.00 [-0.67, 0.67]*
Heterogeneity: $Tau^2 = 0.79$; $Chi^2 = 219.80$, df = 6 ($P < 0.00001$); $I^2 = 97\%$								
Test for overall effect: $Z = 0.00$ ($P = 1.00$)								
Test for subgroup differences: $Chi^2 = 0.64$, df = 2 ($P = 0.72$); $I^2 = 0\%$								

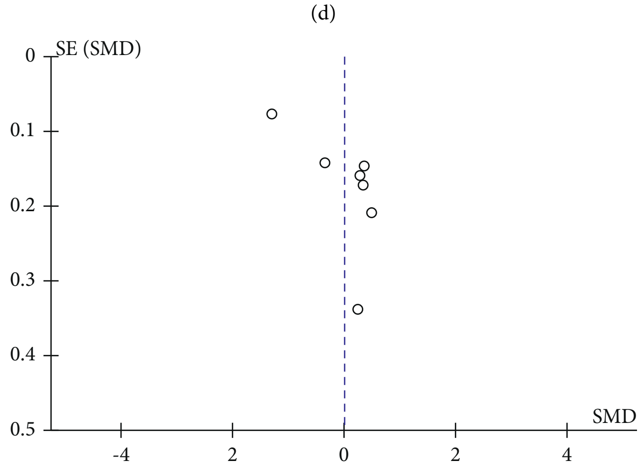


(c)

Study or Subgroup	subhyperthyroidism Mean	subhyperthyroidism SD	subhyperthyroidism Total	Control Mean	Control SD	Control Total	Weight (%)	Std. Mean Difference IV, Random, 95% CI
14.1.1 CKD								
Afsar B2017	6.8	1.3	27	5.9	1.9	163	14.2	0.49 [0.08, 0.90]
Subtotal (95% CI)			*27*			*163*	*14.2*	*0.49 [0.08, 0.90]*
Heterogeneity: Not applicable								
Test for overall effect: $Z = 2.34$ ($P = 0.02$)								
14.1.2 normal								
Abdel-Gayoum A A2014	213.54	17.29	24	209.04	20.37	14	13.1	0.24 [-0.42, 0.90]
Qing Chen2010	264.67	92.98	119	230.07	99.26	79	14.5	0.36 [0.07, 0.65]
Rong Huang2013	267.13	71.54	172	340.26	56.12	18167	14.8	-1.30 [-1.45, -1.15]
Wen Cao2014	315.51	74.59	50	292.07	62.32	110	14.4	0.35 [0.01, 0.69]
Wenjuan jiang2016	304.2	73.7	100	333.2	90.1	100	14.6	-0.35 [-0.63, -0.07]
Zhengxia Di2019	308.04	84.01	49	280.93	95.74	200	14.5	0.29 [-0.02, 0.60]
Subtotal (95% CI)			*514*			*18670*	*85.8*	*-0.08 [-0.80, 0.65]*
Heterogeneity: $tau^2 = 0.79$; $chi^2 = 196.11$, df = 5 ($P < 0.00001$); $I^2 = 97\%$								
Test for overall effect: $Z = 0.21$ ($P = 0.83$)								
Total (95% CI)			*541*			*18833*	*100.0*	*0.00 [-0.67, 0.67]*
Heterogeneity: $tau^2 = 0.79$; $chi^2 = 219.80$, df = 6 ($P < 0.18$); $I^2 = 44.2\%$								
Test for overall effect: $Z = 0.00$ ($P = 1.00$)								
Test for subgroup differences: $chi^2 = 1.79$, df = 1 ($P = 0.18$; $I^2 = 44.2\%$								



(d)

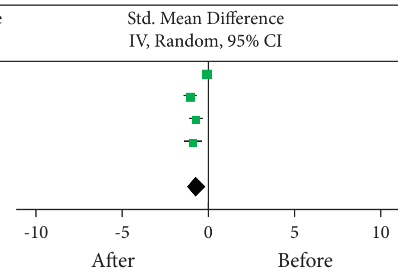


(e)

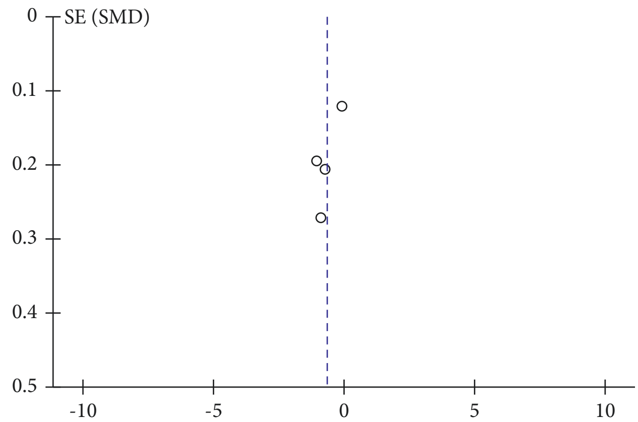
Figure 4: (a) Forest plot of subclinical hyperthyroidism and uric acid. (b) Subgroup analysis of subclinical hyperthyroidism, grouped by area. (c) Subgroup analysis of subclinical hyperthyroidism, grouped by age. (d) Subgroup analysis of subclinical hyperthyroidism, grouped by basic diseases. (e) Funnel plot of subclinical hyperthyroidism.

Study or Subgroup	After Mean	After SD	After Total	Before Mean	Before SD	Before Total	Weight (%)	Std. Mean Difference IV, Random, 95% CI
Liu Peng2015	352	44	136	355	46	136	27.5	-0.07 [-0.30, 0.17]
Qiang Song2016	342.5	85.4	60	440.7	98.6	60	25.2	-1.06 [-1.44, -0.68]
Xin Wang2014	336.18	161	50	433.45	101.93	50	24.8	-0.72 [-1.12, -0.31]
Yuhong Chen2015	287.8	63.72	30	356.05	86.26	30	22.4	-0.89 [-1.42, -0.36]
Total (95% CI)			*276*			*276*	*100.0*	*-0.66 [-1.19, -0.14]*

Heterogeneity: $tau^2 = 0.25$; $chi^2 = 23.92$, df = 3 ($P < 0.0001$); $I^2 = 87\%$
Test for overall effect: $Z = 2.47$ ($P = 0.01$)



(a)



(b)

Figure 5: Relationship between SCH and serum UA levels before and after treatment. (a) Forest plot. (b) Funnel plot.

patients with SCH were significantly higher than that of patients with SCHyper and were higher than that of normal thyroid function subjects, with the difference being statistically significant.

Thyroid diseases include both hypo and hyperthyroidism with types of overt and subclinical [30].The relationship between overt thyroid dysfunction (hyperthyroidism and hypothyroidism) and UA has received considerable attention. Giordano et al. reported the prevalence of hyperuricemia was significantly higher among patients with hyperthyroidism and hypothyroidism compared with the general population [31]. Ford HC et al. also indicated that hyperthyroidism can cause hyperuricemia by increasing UA production or decreasing renal excretion [32]. The association between hypothyroidism and hyperuricemia was first proposed by Kuzell et al. in 1955 [33]; subsequent studies confirmed this association. A previous study showed that hyperthyroidism resulted in elevated levels of UA, but the increase was less than in hypothyroidism [31], which were similar to our results.

UA is the end product of the endogenous and dietary purine metabolism, which may be influenced by the thyroid hormones. It was reported that increased levels of UA were associated with reduced glomerular filtration rate (GFR) and renal plasma flow in hypothyroidism patients [25, 26, 34–38]. Furthermore, SCH could reduce cardiac contractility, and the GFR can decrease by 20–30% to below normal levels, thereby, changing reabsorption and secretion in the tubular, which simultaneously increases the level of uric acid, which results in a decrease in UA excretion [28]. The study by Desideri G et al. suggested that serum UA levels were significantly lower after replacement therapy with LT-4 in patients with iatrogenic SCH who had undergone thyroidectomy. Furthermore, it seemed that changes of UA levels are directly associated with changes of HOMA-IR. These observations further suggested that the effect of the UA metabolism in patients with recent-onset SCH was mediated by insulin sensitivity [27]. Several reports suggested that hyperuricemia could occur among hyperthyroidism participants. This could be due to the acceleration of the purine nucleotide metabolism during UA production [31, 39, 40].

In conclusion, this study provided a systemic analysis of the association between subclinical thyroid dysfunctions. Moreover, as most of the included studies are from China, our results may be more applicable to Chinese subjects. A limitation of the study is the retrospective data collection. One of the limitations of our study is the lack of a brief description of the purine content of foods with known effects on thyroid function. Inclusion and exclusion criteria for included studies are given in Table S2 in Supplementary Materials. Therefore, prospective longitudinal studies are needed to further confirm these results.

5. Conclusion

Subclinical thyroid dysfunction was associated with the higher prevalence of hyperuricemia. The levels of serum UA had significantly increased in SCH compared to SCHyper patients or normal controls. The level of UA decreased after treatment in patients with SCH.

Data Availability

The data used to support this study are included within this article.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

YX retrieved literature, extracted data, developed quality evaluation standard, and wrote articles. YL and LJ retrieved literature and extracted data. MH selected topic and guided writing of the article.

Supplementary Materials

Table S1. Basic characteristics of included studies. Table S2. Inclusion and exclusion criteria and TSH level in patients with SCH/SCHyper of included studies. (*Supplementary Materials*)

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