



The Association of Overt and Subclinical Hyperthyroidism with the Risk of Cardiovascular Events and Cardiovascular Mortality: Meta-Analysis and Systematic Review of Cohort Studies

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Background: Whether hyperthyroidism is an independent risk factor for cardiovascular events remains controversial. We aimed to evaluate the association of overt and subclinical hyperthyroidism with the risk of ischemic heart disease (IHD), stroke, heart failure, and cardiovascular mortality.

Methods: Studies regarding the association between hyperthyroidism and cardiovascular events were searched on PubMed and Embase databases. The cardiovascular disease (CVD) risk was classified as high and low, based on pre-existing diseases, including history of coronary, cerebral, or peripheral artery disease; heart failure; atrial fibrillation; diabetes mellitus; or chronic kidney disease.

Results: Thirty-seven cohort studies were included in this meta-analysis. The pooled hazard ratio for subjects with overt hyperthyroidism compared with the control group was 1.11 (95% confidence interval [CI], 1.03 to 1.19) for IHD, 1.35 (95% CI, 1.03 to 1.75) for stroke, and 1.20 (95% CI, 1.00 to 1.46) for cardiovascular mortality. For subjects with subclinical hyperthyroidism, the pooled hazard ratio was 1.24 (95% CI, 1.07 to 1.45) for IHD, when compared with the control group. Subgroup analysis by CVD risk showed that the risk of stroke in overt hyperthyroidism was increased in the low CVD risk group; however, these association was not observed in the high CVD risk group. Similarly, the risk of IHD in subjects with subclinical hyperthyroidism was significantly increased in the low CVD risk group.

Conclusion: Overt hyperthyroidism is associated with increased risk of IHD, stroke, and cardiovascular mortality, and subclinical hyperthyroidism is associated with increased risk of IHD. These associations were particularly observed in the low risk CVD group without underlying CVD.

Keywords: Hyperthyroidism; Myocardial infarction; Stroke; Heart failure; Mortality; Meta-analysis

INTRODUCTION

Hyperthyroidism is a common endocrine disease, with a reported prevalence of 0.3% to 3%, depending on the age, sex,

and iodine intake [1]. Hyperthyroidism is known to have an impact on the cardiovascular (CV) system, such as increased heart rate, contractility, systolic hypertension, changes in peripheral vascular resistance, atrial fibrillation (AF), and hypercoagulabil-

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ity [2,3]. As a milder form of hyperthyroidism, subclinical hyperthyroidism is also associated with systolic hypertension, AF, and diastolic dysfunction, especially when the thyroid stimulating hormone (TSH) level is less than 0.1 mIU/L [2,4]. Although both overt hyperthyroidism and subclinical hyperthyroidism are associated with various CV risk factors, whether they are independent risk factors for CV events or CV mortality remains controversial [2,3,5-46].

Several meta-analyses, including individual participant data meta-analyses, investigating the relationship of hyperthyroidism with CV events and/or CV mortality have been published; however, most of them have been limited because they were restricted to patients with subclinical hyperthyroidism and provided conflicting results [12,14,19]. Furthermore, it remains unclear whether the risk of cardiovascular disease (CVD) in hyperthyroidism varies by age and individual CVD risk. Many additional cohort studies have been published recently [9,17,20,21,25-29, 32,33,42]. Therefore, an updated comprehensive meta-analysis is warranted to clarify the association of hyperthyroidism with CV events.

METHODS

We conducted meta-analysis and the systematic review based on a predefined protocol (Appendix 1) and reported the results based on the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement (Supplemental Table S1).

Search strategy

A literature search was performed on the PubMed and Embase databases from their inception (January 1, 1990) to February 28, 2020. The reference list of recent reviews, related articles, and meta-analyses were also reviewed. The search strategy was conducted by medical subject headings (“hyperthyroidism,” “thyroid diseases,” “thyroid hormones,” “myocardial ischemia,” “heart failure,” “stroke,” “brain ischemia,” “mortality,” and “cardiovascular disease”) and with text words (“subclinical thyroid,” “thyroid diseases,” “coronary heart disease,” and “ischemic heart disease”). We also searched for grey literature from the website of OpenGrey [47]. The specific searching strategy is described in the Appendix 1. Only articles published in English were considered.

Study selection

Two independent reviewers (S.Y.S. and E.L.) initially screened the titles and abstracts. From this, studies that were clearly irrel-

evant were excluded. Any disagreements were resolved by a third reviewer (M.K.L.).

A second screening was based on full-text reviews. Studies were included if they met the following criteria: (1) the study design was a cohort study; (2) the outcome of interest was considered as ischemic heart disease (IHD), stroke, heart failure, or CV mortality; (3) the study compared the endogenous hyperthyroidism between the euthyroid control group and the general population without hyperthyroidism; and (4) the effect measure was reported as hazard ratio (HR) with 95% confidence interval (CI). The following studies were excluded: (1) the study design was not a cohort study; (2) the outcome of interest was not related to a CVD; (3) the study included duplicated datasets; (4) the study investigated the effect of exogenous hyperthyroidism; and (5) the study had insufficient data.

Data extraction and quality assessment

Two reviewers independently extracted the data using a standardized data collection form. The following data were extracted from the included articles: first author’s name, publication year, country, number of study participants, characteristics of study participants, mean age, and CV outcome explored.

The Newcastle-Ottawa Scale—a validated tool for non-randomized studies in meta-analysis—was used to evaluate the methodological quality of the included studies. Reviewers independently assessed the selection of studies, comparability, and their outcomes using a rating system—low, moderate, and high risk—depending on the scoring for each section as presented in Newcastle-Ottawa Scale assessment. Any disagreements were resolved by a third investigator.

Statistical analyses

The study-specific maximally adjusted HR was used to compute a summary HR and its 95% CI. Heterogeneity was graded using the I^2 statistics, with I^2 of less than 25%, in between 25% and 50%, and greater than 50% representing low, moderated and high heterogeneity, respectively. The Higgins’ I^2 statistic was used to test for heterogeneity. When I^2 was $\leq 50\%$, the included studies were considered to have little heterogeneity, and a fixed-effects model was used. When I^2 was $> 50\%$, the included studies were considered to have significant heterogeneity, and a random effects model was used.

We performed sensitivity and subgroup analyses to explore and interpret the sources of high heterogeneity. We explored the relationship between hyperthyroidism and CV outcomes by age (< 65 or ≥ 65 years), pre-existing CVD and regional iodine in-

take status (sufficient areas vs. deficient areas) [48]. The high CVD risk group was defined as those with any underlying disease that could increase the risk of CVD, including history of coronary, cerebral, or peripheral artery disease; dilated cardiomyopathy; heart failure; AF; diabetes mellitus; or chronic kidney disease. The low CVD risk group was defined as those without diseases that would increase the risk of CVD. All statistical analyses were performed using Review Manager version 5.3 (<https://training.cochrane.org>).

Ethical approval

This article does not contain examinations performed on human participants in that ethical approval is not necessary.

RESULTS

Characteristics of included studies

A study selection flow chart is presented in Fig. 1. A total of 15,118 studies were initially identified, and 13,075 remained after excluding duplicate citations. Of these, most studies were excluded after the first screening based on the abstracts or titles, mainly because they were reviews, case reports, conference abstracts, meta-analyses or different topic of interest. After a full text review of 143 studies, 106 studies were further excluded,

and 37 studies [5-11,13,15-17,20-44,46] were finally included for analysis. No additional studies which met the inclusion criteria were found on OpenGrey (<http://www.opengrey.eu>).

Characteristics of the studies are presented in Table 1. In total, 1,626,005 participants were enrolled, and 113,393 had hyperthyroidism. Sample sizes of these studies ranged from 269 to 1,239,441 participants. Among them, 22 studies showed a mean age of <65 years, and 15 had a mean age of ≥ 65 years. A total of 11 studies were defined as involving participants at high CVD risk based on pre-existing diseases. Twenty-six studies were population-based studies with participants from a general population. They were classified as low CVD risk. All included studies were judged as being of relatively high quality according to the Newcastle-Ottawa Scale assessment tool, with scores ranging from 6 to 9 (Supplemental Table S2).

Hyperthyroidism and Ischemic heart disease

Four eligible studies on the association between overt hyperthyroidism and IHD were pooled (Fig. 2A). We found that overt hyperthyroidism was related to IHD (HR, 1.11; 95% CI, 1.03 to 1.19) with evidence of low heterogeneity ($I^2=0\%$, $P=0.70$). Because, all eligible studies included patients with age younger than 65 years and low CVD risk, subgroup analysis by age and CVD risk was not available (Table 2). In the subgroup analysis

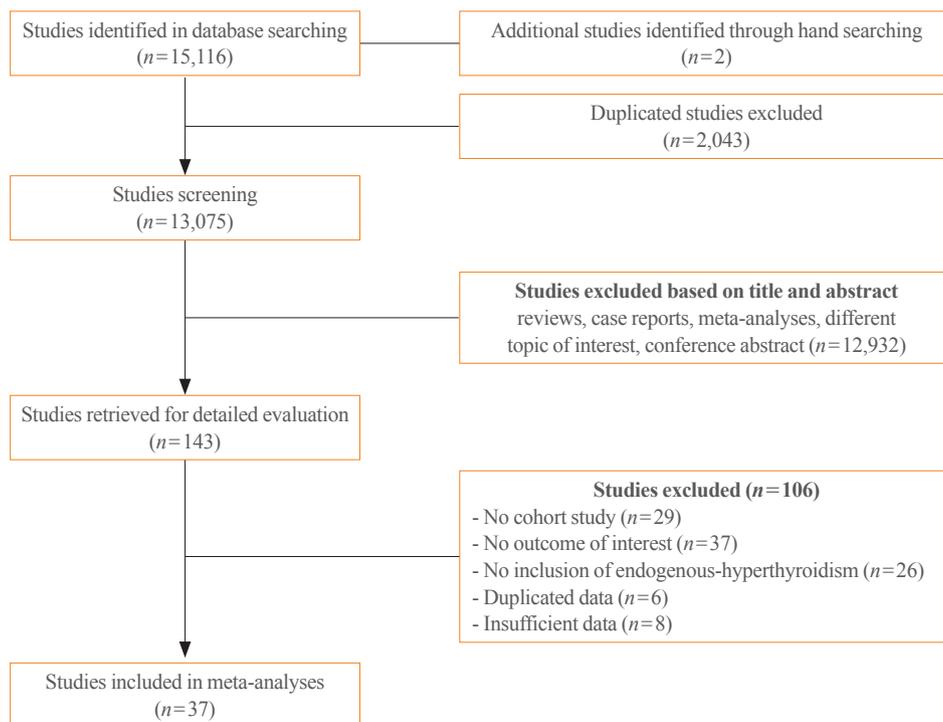


Fig. 1. Flowchart of study screening and selection.

Table 1. Baseline Characteristics of Cohort Studies Included in the Present Meta-Analysis

Study	Country	Study population	Classification of hyperthyroidism	Mean or median age	No. of total subjects	No. of hyperthyroid subjects	CV outcome
Kim et al. (2020) [26]	Korea	Community dwelling	Overt	Overt: 48.5 Control: 48.5	1,239,441	59,021	IHD and stroke
Okosieme et al. (2019) [32]	England	Community dwelling	Overt	Overt: 48±16 Control: 48±16	20,945	4,189	IHD, stroke, and HF
Langen et al. (2018) [28]	Finland	Community dwelling	Subclinical	Subclinical: 56.8±16.5 Control: 50.5±13.8	5,211	108	IHD and stroke
Ryodi et al. (2018) [17]	Finland	Community dwelling	Overt	49 (35–63)	24,580	6,148	IHD, stroke, HF, and CV mortality
Journy et al. (2017) [25]	United States	Community dwelling	Overt	Overt: <60 years Control: <60 years	75,076	1,501	CV mortality
Giesecke et al. (2017) [21]	Sweden	Community dwelling	Overt	Overt: 61.3 Control: 49.1	15,924	12,239	CV mortality
Martin et al. (2017) [29]	United States	Community dwelling	Overt, subclinical	Overt: 56.7±5.8 Subclinical: 56.2±5.7 Control: 56.5±5.7	11,359	Overt: 206 Subclinical: 378	IHD and stroke
Pearce et al. (2016) [33]	United Kingdom	Community dwelling	Subclinical	85.5±0.4	643	19	CV mortality
Bruere et al. (2015) [9]	France	High CVD risk (A-fib patients)	Overt	Overt: 71±14 Control: 68±13	8,962	141	Stroke
Geng et al. (2015) [20]	China	High CVD risk (type 2 diabetes)	Subclinical	Subclinical: 57.5±14.7 Control: 58.8±13.5	1,115	74	IHD
la Cour et al. (2015) [27]	Denmark	Community dwelling	Overt	Overt: 61.9±14.3 Control: 61.0±14.2	25,562	4,000	Stroke
Yang et al. (2015) [42]	Taiwan	Community dwelling	Overt	Overt: 40.9±14.3 Control: 41.3±14.5	68,462	16,808	Stroke
Chen et al. (2014) [13]	China	High CVD risk (A-fib patients)	Overt	Overt: 55.1±1.7 Control: 59.4±1.1	269	62	Stroke
Drechsler et al. (2014) [16]	Germany	High CVD risk (diabetic hemodialysis)	Subclinical	Subclinical: 66.9±7.9 Control: 65.3±8.5	1,000	137	IHD and stroke
Perez et al. (2014) [34]	Europe, multicenter	High CVD risk (heart failure)	Subclinical	Subclinical: 72.9±6.2 Control: 72.6±7.1	4,987	175	HF and CV mortality
Brandt et al. (2013) [8]	Denmark	Community dwelling	Overt	Graves' disease: 55 (18–96) Toxic nodular goiter: 62 (18–96)	10,760	2,152	CV mortality
Ceresini et al. (2013) [11]	Italy	Community dwelling	Subclinical	>65 years	951	83	CV mortality
Asvold et al. (2012) [5]	Norway	Community dwelling	Subclinical	Male: 53 (46–65) Female: 54 (47–67)	26,707	524	IHD and HF
Nanchen et al. (2012) [31]	Europe, multicenter	High CVD risk (CVD patients)	Subclinical	Subclinical: 75.3±3.1 Control: 75.3±3.4	5,316	71	IHD, HF, and CV mortality
Waring et al. (2012) [41]	United States	Community dwelling	Subclinical	Subclinical: 74.1 Control: 73.6	1,587	41	CV mortality
Molinario et al. (2012) [30]	Italy	High CVD risk	Subclinical	Subclinical: 69.3 (65–73) Control: 65 (64–66)	1,026	23	CV mortality

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Table 1. Continued

Study	Country	Study population	Classification of hyperthyroidism	Mean or median age	No. of total subjects	No. of hyperthyroid subjects	CV outcome
de Jongh et al. (2011) [15]	Netherland	Community dwelling	Subclinical	Subclinical: 77.7±7.0 Control: 75.5±6.5	1,219	34	CV mortality
Schultz et al. (2011) [36]	Denmark	High CVD risk (type 2 diabetes)	Subclinical	Subclinical: 74±10 Control: 67.5±10.5	609	25	Stroke and CV mortality
Boekholdt et al. (2010) [7]	United Kingdom	Community dwelling	Subclinical	Subclinical: 59±10 Control: 58±9	11,554	216	IHD
Ittermann et al. (2010) [24]	German	Community dwelling	Overt, subclinical	Subclinical: 61 (48–69) Overt: NA Control: 48 (35–62)	3,651	Subclinical: 243 Overt: 27	CV mortality
Sheu et al. (2010) [38]	Taiwan	Community dwelling	Overt	Overt: 32.1±7.4 Control: 32.1±7.5	28,584	3,176	Stroke
Sgarbi et al. (2010) [37]	Brazil	Community dwelling	Subclinical	Subclinical: 61.4±12.5 Control: 56.4±12.4	1,110	69	CV mortality
Siu et al. (2009) [39]	Hong Kong	High CVD risk (A-fib patients)	Overt	Overt: 64.7±1.3 Control: 64.7±1.1	480	160	Stroke
Volzke et al. (2009) [40]	Germany	High CVD risk (IHD patients)	Subclinical	Subclinical: 62.0±7.9 Control: 61.0±8.0	942	118	CV mortality
Rodondi et al. (2008) [35]	United States	Community dwelling	Subclinical	Subclinical: 73.8±6.9 Control: 72.5±5.5	3,044	44	HF
Bauer et al. (2007) [6]	United States	Community dwelling	Overt	Overt: 72.3±5.6 Control: 71.6±5.3	9,449	891	CV mortality
Iervasi et al. (2007) [23]	Italy	High CVD (IHD patients)	Subclinical	Subclinical: 60.5 (59–62) Control: 59.9 (59–60)	3,121	98	CV mortality, IHD
Cappola et al. (2006) [10]	United States	Community dwelling	Subclinical	Subclinical: 73.9±6.8 Control: 72.6±5.6	3,233	31	IHD, stroke, and CV mortality
Qureshi et al. (2006) [44]	United States	Community dwelling	Overt	48±14	5,269	34	Stroke
Walsh et al. (2005) [46]	Australia	Community dwelling	Subclinical	Subclinical: 51.3±14.9 Control: 49.2±17.0	2,108	37	IHD and CV mortality
Gussekkloo et al. (2004) [22]	Netherland	Community dwelling	Subclinical	>85 years	558	19	CV mortality, IHD
Parle et al. (2001) [43]	United Kingdom	Community dwelling	Subclinical	Male 70.1 (69.6–70.6) Female 70.7 (70.2–71.4)	1,191	71	CV mortality

CV, cardiovascular; IHD, ischemic heart disease; HF, heart failure; CVD, cardiovascular disease; NA, not available; A-fib, atrial fibrillation.

by iodine intake status, increased risk of IHD was observed in iodine sufficient areas (Supplemental Table S3).

For subclinical hyperthyroidism, 11 eligible studies were pooled to calculate the overall HR for IHD (Fig. 2B). Compared with euthyroid subjects, patients with subclinical hyperthyroidism was associated with IHD (HR, 1.24; 95% CI, 1.07 to 1.45) and the heterogeneity was low ($I^2=0\%$, $P=0.79$). In the subgroup analysis by age (<65 or ≥65 years) and CVD risk, increased risk of IHD was found among subjects aged less than 65 years

(HR, 1.27; 95% CI, 1.06 to 1.53) and in those with low CVD risk (HR, 1.22; 95% CI, 1.02 to 1.45) (Table 3).

Hyperthyroidism and stroke

Eleven studies demonstrated the relationship between overt hyperthyroidism and stroke (Fig. 3A). The result of meta-analysis showed a significant association (HR, 1.35; 95% CI, 1.03 to 1.75) with moderate heterogeneity ($I^2=51\%$, $P=0.02$). In the subgroup analysis by age and CVD risk, significant association

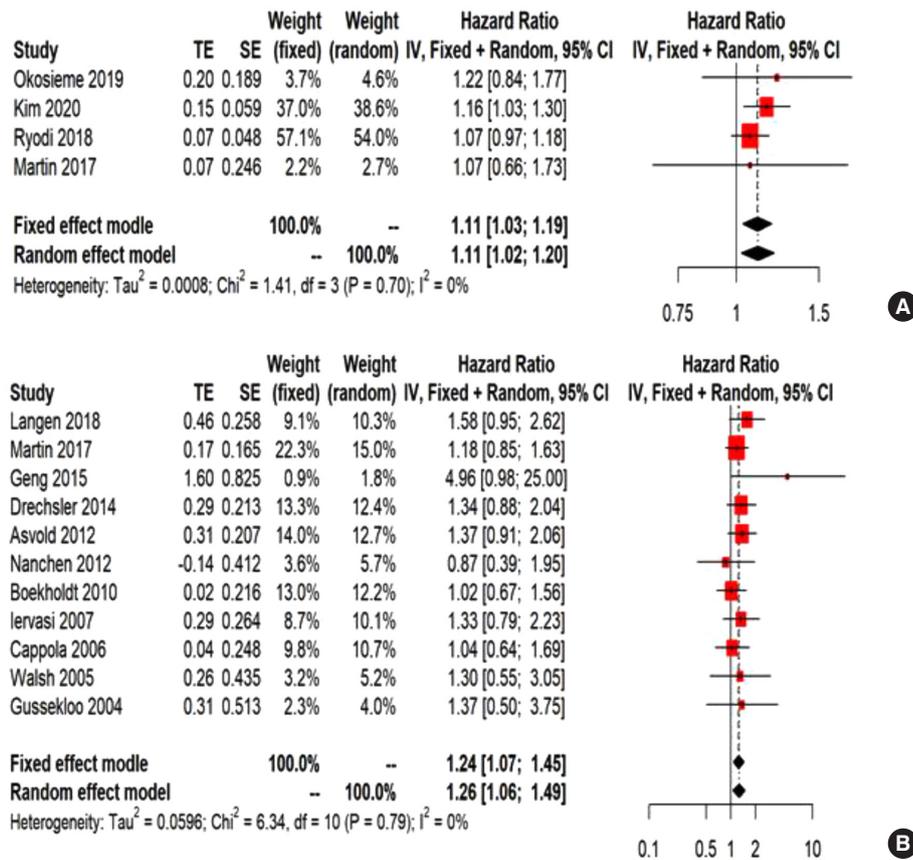


Fig. 2. Forest plots for hyperthyroidism and risk of ischemic heart disease (IHD). (A) Overt hyperthyroidism and IHD. (B) Subclinical hyperthyroidism and IHD. TE, total effect; SE, standard error; IV, inverse variance; CI, confidence interval.

between overt hyperthyroidism and stroke was particularly observed in subjects aged younger than 65 years (HR, 1.38; 95% CI, 1.06 to 1.78) and in those without AF (HR, 1.19; 95% CI, 1.13 to 1.25) (Table 2). Increased risk of stroke was consistently observed in both iodine-sufficient and -deficient areas (Supplemental Table S3).

Five studies which showed the association between subclinical hyperthyroidism and stroke were pooled (Fig. 3B). No statistically significant association was found between subclinical hyperthyroidism and stroke (HR, 1.17; 95% CI, 0.90 to 1.52). Subgroup analyses did not show any relevant difference in the results (Table 2, Supplemental Table S4).

Hyperthyroidism and heart failure

Two eligible studies reported a relationship between overt hyperthyroidism and heart failure. The pooled HR for heart failure was 1.42 (95% CI, 0.93 to 2.16), with high heterogeneity ($I^2=91\%$, $P<0.01$) (Fig. 4A).

Based on the four studies, we found no significant association

between subclinical hyperthyroidism and heart failure (HR, 1.41; 95% CI, 0.60 to 3.30) with moderated heterogeneity ($I^2=66\%$, $P=0.03$) (Fig. 4B).

Hyperthyroidism and CV mortality

Seven studies showed that overt hyperthyroidism is associated with increased CV mortality (HR, 1.2; 95% CI, 1.00 to 1.46) with high heterogeneity ($I^2=76\%$, $P<0.01$) (Fig. 5A). Increased risk of CV mortality was further observed in iodine sufficient areas by the subgroup analysis (Supplemental Table S3).

For subclinical hyperthyroidism, fourteen eligible studies were pooled to estimate the overall HR for CV mortality (Fig. 5B). No statistically significant association was found between subclinical hyperthyroidism and CV mortality (HR, 1.21; 95% CI, 0.88 to 1.67) with moderated heterogeneity ($I^2=51\%$, $P=0.01$). Subgroup analyses did not show any relevant difference in the results (Table 3, Supplemental Table S4).

Table 2. Subgroup Analysis of the Association between Overt Hyperthyroidism and the Risk of Cardiovascular Events

Subgroup	Pooled HR (95% CI)	I ² , %	No. of studies
Ischemic heart disease			
Age group			
<65 yr	1.11 (1.03–1.19)	0	4
≥65 yr	NA	-	-
CVD risk group			
High	NA	-	-
Low	1.11 (1.03–1.19)	0	4
Stroke			
Age group			
<65 yr	1.38 (1.06–1.78)	54.2	10
≥65 yr	0.64 (0.18–2.26)	-	1
CVD risk			
High (with A-fib)	2.05 (0.21–20.29)	60.7	3
Low	1.19 (1.13–1.25)	35.5	8
Heart failure			
Age group			
<65 yr	1.42 (0.93–2.16)	90.6	2
≥65 yr	NA	-	-
CVD risk group			
High	NA	-	-
Low	1.42 (0.93–2.16)	90.6	2
CV mortality			
Age group			
<65 yr	1.16 (0.93–1.45)	76.4	6
≥65 yr	1.46 (1.20–1.77)	-	1
CVD risk group			
High	-	-	-
Low	1.20 (1.00–1.46)	76.3	7

HR, hazard ratio; CI, confidence interval; NA, not available; CVD, cardiovascular disease; A-fib, atrial fibrillation.

Table 3. Subgroup Analysis of the Association between Subclinical Hyperthyroidism and the Risk of Cardiovascular Events

Subgroup	Pooled HR (95% CI)	I ² , %	No. of studies
Ischemic heart disease			
Age group			
<65 yr	1.27 (1.06–1.53)	0	7
≥65 yr	1.17 (0.88–1.55)	0	4
CVD risk group			
High	1.32 (0.98–1.77)	16.7	4
Low	1.22 (1.02–1.45)	0	7
Stroke			
Age group			
<65 yr	1.25 (0.92–1.70)	0	2
≥65 yr	1.12 (0.13–9.93)	68.6	3
CVD risk			
High	1.48 (0.32–6.84)	81	2
Low	1.16 (0.87–1.55)	0	3
Heart failure			
Age group			
<65 yr	1.52 (0.86–2.69)	-	1
≥65 yr	1.40 (0.27–7.34)	75.2	3
CVD risk group			
High	1.73 (0.56–5.36)	86.9	2
Low	1.24 (0.81–1.92)	12.9	2
CV mortality			
Age group			
<65 yr	1.34 (0.61–2.94)	67	6
≥65 yr	0.99 (0.79–1.25)	18.7	9
CVD risk group			
High	1.26 (0.40–3.91)	74.7	5
Low	1.26 (1.00–1.59)	14.1	10

HR, hazard ratio; CI, confidence interval; NA, not available; CVD, cardiovascular disease.

DISCUSSION

In the present meta-analysis, we investigated the association of hyperthyroidism with IHD, stroke, heart failure, and CV mortality by pooling 37 cohort studies. We found that overt hyperthyroidism was associated with increased risk of IHD, stroke, and CV mortality, while subclinical hyperthyroidism was associated with increased risk of IHD.

In this study, overt hyperthyroidism seems to be associated with increased risk of CV mortality by 20% compared with the

euthyroid control or general population, and increased IHD and stroke risk appear to be the cause of CV mortality. To the best of our knowledge, this is the first meta-analysis evaluating the association of overt hyperthyroidism with IHD and stroke. There are several plausible mechanisms that could explain the increased risk of atherosclerotic event in hyperthyroid patients. Excess thyroid hormone is known to be associated with endothelial damage and increased procoagulant proteins, including von Willebrand factor, fibrinogen, and factors VIII and IX [49]. Recently, Bano et al. [3] also suggested that free thyroxine levels may be

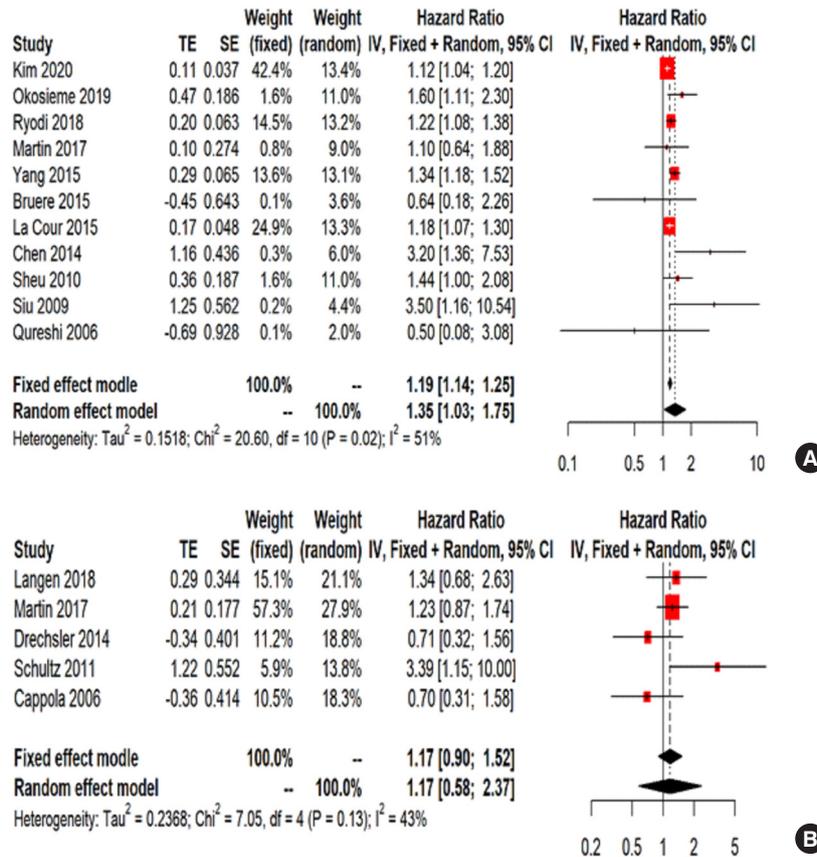


Fig. 3. Forest plots for hyperthyroidism with the risk of stroke. (A) Overt hyperthyroidism and stroke. (B) Subclinical hyperthyroidism and stroke. TE, total effect; SE, standard error; IV, inverse variance; CI, confidence interval.

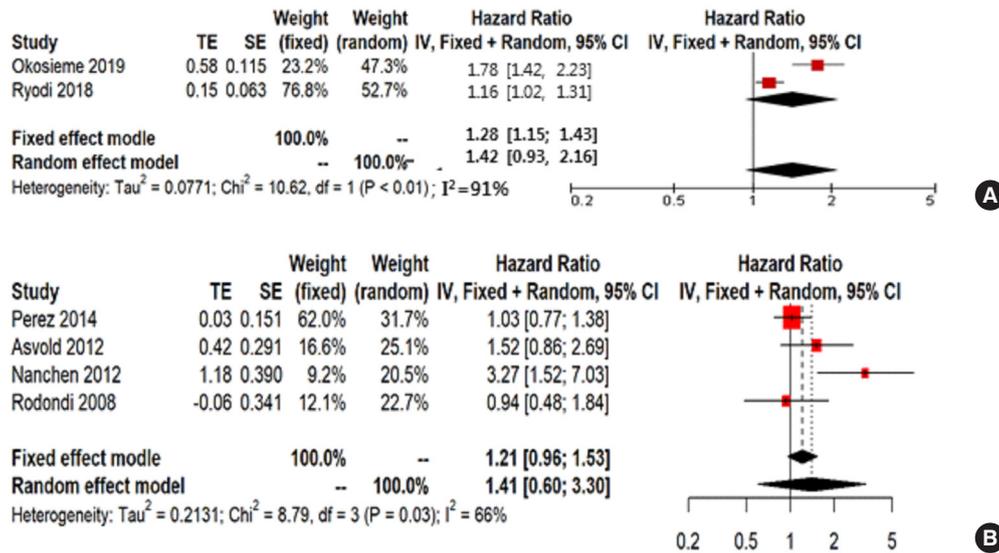


Fig. 4. Forest plots for hyperthyroidism with the risk of heart failure. (A) Overt hyperthyroidism and heart failure. (B) Subclinical hyperthyroidism and heart failure. TE, total effect; SE, standard error; IV, inverse variance; CI, confidence interval.

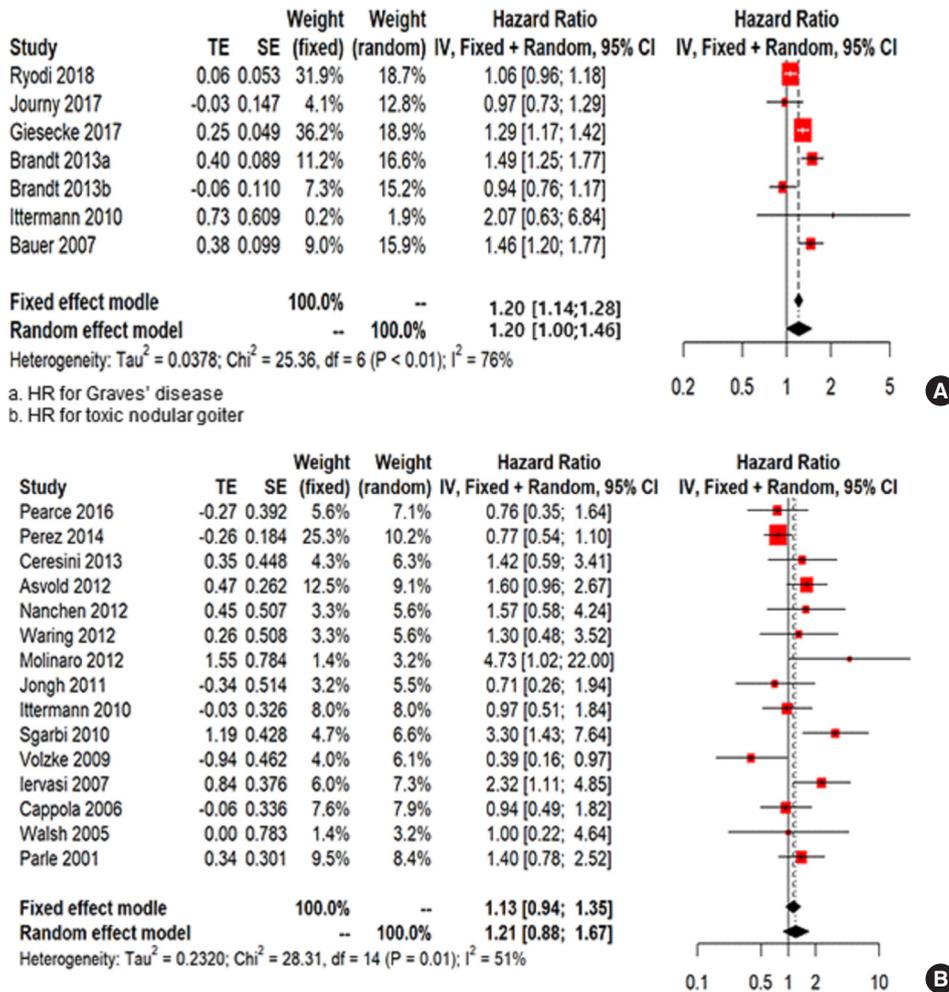


Fig. 5. Forest plots for hyperthyroidism with the risk of cardiovascular (CV) mortality. (A) Overt hyperthyroidism and CV mortality. (B) Subclinical hyperthyroidism and CV mortality. TE, total effect; SE, standard error; IV, inverse variance; CI, confidence interval.

positively associated with atherosclerotic events, independent of conventional CV risk factors. Regarding the association between hyperthyroidism and stroke, some studies have suggested that AF induced by hyperthyroidism may increase the risk of thromboembolic events, such as ischemic stroke [13]. In our subgroup analyses by CVD risk, significant association between overt hyperthyroidism and stroke was only observed in subjects without AF. Therefore, it seems unlikely that the increased risk of stroke in overt hyperthyroidism is mediated by AF; however, additional prospective cohort studies are required to confirm this finding. In the subgroup analysis by age group, increased risk of stroke was observed in hyperthyroid patients aged <65 years. However, a small number of studies were conducted on the hyperthyroid patients older than 65 years, it was not possible to conclude whether age-related risks were different.

Hyperthyroidism is commonly associated with hyperdynamic circulation characterized by decreased peripheral vascular resistance and increased total blood volume, heart rate, and contractility [2]. Previous studies found significant echocardiographic abnormalities, such as increased left ventricle mass, systolic, and diastolic dysfunction in hyperthyroid patients [50]. In the current meta-analysis, we did not find any association between hyperthyroidism and heart failure; however, our finding should be interpreted with caution. Because we included only cohort studies that investigated the incidence of hospitalization for heart failure in hyperthyroid patients, only a small number of studies met such criteria. Moreover, the incidence rate of reported heart failure events was likely underestimated in cohort studies since some may have developed heart failure without hospitalization.

With respect to the association between subclinical hyperthy-

roidism and CV events, we found an increased risk of IHD in patients with subclinical hyperthyroidism compared to those with euthyroid control, findings are consistent with previous meta-analyses [14,45]. As shown in our subgroup analysis, a significant association between subclinical hyperthyroidism and IHD was only observed in those with low CVD risk. This finding suggests that subclinical hyperthyroidism may be an independent risk factor for IHD in subjects without CVD. In age stratified analysis, increased risk of IHD was found among subjects aged less than 65 years. This result is similar with recent meta-analysis by Sun et al. [45]; they showed that the risk of coronary heart disease mortality was higher in those aged less than 65 years. According to the current guideline, treatment for subclinical hyperthyroidism is recommended in all individuals over the age of 65 years, as well as in patients with heart disease, symptoms of hyperthyroidism or osteoporosis when TSH is persistently less than 0.1 mIU/L [51]. This recommendation was based primarily on the studies showing an increased rate of AF and CV mortality and altered skeletal health in younger as well as older patients with a suppressed TSH level [14,52]. Although, there is no subgroup analysis according to the TSH level in this meta-analysis, our findings suggest that a careful follow-up strategy for CVD is warranted in subjects with subclinical hyperthyroidism, even if they are less than the age of 65 years or have no underlying CVD. Large prospective studies are needed to clarify the benefit of treating low risk younger patients with subclinical hyperthyroidism.

In the current meta-analysis, we did not find any association between subclinical hyperthyroidism and stroke, which is in line with a previous meta-analysis [12]. Although subclinical hyperthyroidism significantly increases the risk of AF, as demonstrated in a large cohort study [4], the risk of stroke in subclinical hyperthyroidism remains unclear based on current evidence. We also found no significant association between subclinical hyperthyroidism and heart failure/CV mortality. This result is different from previous meta-analysis, which reported increased risk of heart failure and CV mortality, especially when TSH level is lower than 0.1 mIU/L [14,19]. First, this might be due to the lack of subgroup analyses based on different TSH levels in this meta-analysis. Only one study in our meta-analysis analyzed the association between risk of heart failure incidence and degree of subclinical hyperthyroidism. Second, the difference may be due to the recent cohort studies added in the current analysis [5,31,33,41].

In the subgroup analyses by regional iodine intake status, an increased risk of IHD, stroke and CV mortality in patients with

overt hyperthyroidism was generally observed in iodine-sufficient areas. Since Graves' disease is the most prevalent cause of hyperthyroidism in iodine-sufficient areas, this finding suggested that thyroid autoimmunity might be associated with an increased risk of CVD. Further studies based on individual participant data are needed to confirm this finding.

There are several strengths in our study. First, we analyzed the association of both overt and subclinical hyperthyroidism with specific CV events, including IHD, stroke, HF, and CV mortality, instead of combining these events into a single combined CV event. Second, we included many cohort studies with a large population and conducted subgroup analyses for various outcome measures. However, our study also has some limitations. First, this study lacked results of individual thyroid function tests, and thus, we were unable to perform a subgroup analysis according to different TSH levels. Second, although previous study has suggested that radioiodine treatment might be associated with increased CV risk in hyperthyroid patients [27], association with treatment method was not evaluated in this meta-analysis because very few studies included this parameter. Third, for the association of overt hyperthyroidism with IHD and heart failure, subgroup analysis according to age and CVD risk could not be performed since only a small number of studies met the inclusion criteria.

In conclusion, our meta-analysis showed that overt hyperthyroidism is associated with increased risk of IHD, stroke, and CV mortality, while subclinical hyperthyroidism is associated with increased risk of IHD. The associations outlined in the present study were more likely to be significant in subjects without underlying CVD. Future studies based on individual participant data are needed to better determine the association between hyperthyroidism and risk of CV events.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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AUTHOR CONTRIBUTIONS

Conception or design: S.Y.S., M.K.L. Acquisition, analysis, or

interpretation of data: S.Y.S., E.L. Drafting the work or revising: S.Y.S., E.L. Final approval of the manuscript: S.Y.S., J.H.L.

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Appendix 1. Study protocol

1. **Title:** The association of overt and subclinical hyperthyroidism with the risk of cardiovascular events and cardiovascular mortality: Meta-analysis and systematic review of cohort studies.
2. **Objectives:** This study is conducted to evaluate the association of overt and subclinical hyperthyroidism with the risk of ischemic heart disease (IHD), stroke, heart failure, and cardiovascular mortality.
3. **Protocol and registration:** Methods of database search, study selection, data extraction, assessment of study quality and risk of bias, and statistical analysis are predefined in the protocol at the beginning of the study.
4. **Reporting:** This meta-analysis and systematic review was reported according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement.
5. **Eligible criteria**
 - 1) Study characteristics
 - (1) Population: patients with hyperthyroidism
 - (2) Intervention: none
 - (3) Comparison: euthyroid population or general population without hyperthyroidism
 - (4) Outcomes of interests
 - ① IHDs
 - ② Stroke
 - ③ Hospitalization for heart failure
 - ④ Cardiovascular mortality
 - (5) Study design: prospective or retrospective cohort studies
 - 2) Report characteristics
 - (1) Years considered: published from inception to February 2020
 - (2) Language: English
 - (3) Publication status: full-text articles without limitation of publication status
 - 3) Inclusion and exclusion criteria
 - (1) We only included cohort studies investigating the relationship of hyperthyroidism with cardiovascular events.
 - (2) We included cohort studies reporting at least one cardiovascular outcome including ischemic heart disease, stroke, heart failure, and cardiovascular mortality.
 - (3) We included cohort studies reporting cardiovascular outcome as hazard ratio (HR) with 95% confidence interval (CI).
 - (4) We included cohort studies comparing the endogenous hyperthyroidism between euthyroid control group and the general population without hyperthyroidism.
 - (5) In case of duplicates or extensions, we only included a study with the longer duration or more information.
 - (6) We included full-text articles with no restriction of publication status.
 - (7) We excluded studies evaluating the effect of exogenous hyperthyroidism
6. **Information sources:** We searched electronic databases of MEDLINE, Embase, and the website of OpenGrey.
7. **Search strategy:** Cohort studies regarding the association between hyperthyroidism and cardiovascular events were searched using following criteria.
 - 1) MEDLINE
 - #1. “Thyroid diseases” OR “hyperthyroidism” OR “thyroid function tests” OR “thyrotropin” OR “thyroid hormones”
 - #2. “Myocardial ischemia” OR “heart failure” OR “stroke” OR “brain ischemia” OR “mortality” OR “death”
 - #3. #1 AND #2
 - #4. “Hyperthyroidism” OR “thyroid dysfunction” OR “thyrotoxicosis” OR “Graves’ disease” OR “thyroid function” OR “thyroid diseases”
 - #5. “Ischemic heart disease” OR “coronary heart disease” OR “coronary disease” OR “myocardial infarction” OR “stroke” OR “heart failure” OR “death” OR “mortality” OR “cardiovascular”

#6. #4 AND #5

2) EMBASE

#1. 'Hyperthyroidism' OR 'thyroid dysfunction' OR 'thyrotoxicosis' OR 'Graves' disease' OR 'thyroid function' OR 'thyroid diseases'

#2. 'Ischemic heart disease' OR 'coronary heart disease' OR 'coronary disease' OR 'myocardial infarction' OR 'stroke' OR 'heart failure' OR 'death' OR 'mortality' OR 'cardiovascular'

#3. #1 AND #2

3) Website of OpenGrey

#1. "Hyperthyroidism" OR "thyroid dysfunction" OR "thyrotoxicosis" OR "thyroid function" OR "thyroid diseases"

#2. "Ischemic heart disease" OR "coronary heart disease" OR "coronary disease" OR "myocardial infarction" OR "stroke" OR "heart failure" OR "death" OR "mortality" OR "cardiovascular"

#3. #1 AND #2

8. Study selection: All identified records were evaluated for eligibility by two reviewers independently. We reviewed titles, abstracts, and full texts of the studies thoroughly. Any disagreements were resolved by a third reviewer.

9. Data extraction: Standardized data extraction was performed by two reviewers independently as follows. Any disagreements were resolved by a third reviewer.

1) First author

2) Publication year

3) Country

4) Number of study participants

5) Characteristics of study participants: mean or median age, classification of hyperthyroidism, underlying comorbidity including history of coronary, cerebral, or peripheral artery disease; heart failure; atrial fibrillation; diabetes mellitus; or chronic kidney disease and regional iodine intake (sufficient area vs. deficient area)

6) Cardiovascular outcome explored

7) HRs for each cardiovascular outcome

10. Assessment of study quality and risk bias: We assessed quality and risk of bias of included studies using the Newcastle-Ottawa Scale. Two reviewers independently evaluated each study based on following aspects of trials:

1) Selection: representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of hyperthyroidism, demonstration that outcome of interest was not present at start of study

2) Comparability: comparability of cohorts based on the design or analysis

3) Outcome: assessment of outcome, adequacy of follow-up of cohorts

11. Data synthesis

1) Statistical analysis: We calculated pooled HRs with 95% CI for each cardiovascular outcome. We used both fixed and random-effects model to evaluate pooled HR.

2) Subgroup analysis: We performed subgroup analyses by age (<65 years, ≥65 years), CVD risk and regional iodine intake status (sufficient area vs. deficient area).

3) Identifying and measuring statistical heterogeneity: We used I^2 statistic for measuring the degree of heterogeneity.