Eur J Epidemiol (2014) 29:791–800
DOI 10.1007/s10654-014-9946-8

REVIEW

Subclinical thyroid dysfunction and the risk of stroke: a systematic review and meta-analysis

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Received: 8 April 2014 / Accepted: 13 August 2014 / Published online: 2 September 2014

Abstract Subclinical thyroid dysfunction has been associated with coronary heart disease, but the risk of stroke is unclear. Our aim is to combine the evidence on the association between subclinical thyroid dysfunction and the risk of stroke in prospective cohort studies. We searched Medline (OvidSP), Embase, Web-of-Science, Pubmed Publisher, Cochrane and Google Scholar from inception to November 2013 using a cohort filter, but without language restriction or other limitations. Reference lists of articles were searched. Two independent reviewers screened articles according to pre-specified criteria and selected prospective cohort studies with baseline thyroid function measurements and assessment of stroke outcomes. Data were derived using a standardized data extraction form. Quality was assessed according to previously defined quality indicators by two independent reviewers. We pooled the outcomes using a random-effects model. Of 2,274 articles screened, six cohort studies, including 11,309 participants with 665 stroke events, met the criteria. Four of six studies provided information on subclinical hyperthyroidism including a total of 6,029 participants and five on subclinical hypothyroidism (n = 10,118). The pooled hazard ratio (HR) was 1.08 (95 % CI 0.87–1.34) for subclinical hypothyroidism (I^2 of 0 %) and 1.17 (95 % CI 0.54–2.56) for subclinical hyperthyroidism (I^2 of 67 %) compared to euthyroidism. Subgroup analyses yielded similar results. Our systematic review provides no evidence supporting an increased risk for stroke associated with subclinical thyroid dysfunction. However, the available literature is insufficient and larger datasets are needed to perform extended analyses. Also, there were insufficient events to exclude clinically significant risk from subclinical hyperthyroidism, and more data are required for subgroup analyses.

Keywords Subclinical hypothyroidism · Subclinical hyperthyroidism · Stroke · Systematic review · Meta-analysis

Electronic supplementary material The online version of this article (doi:10.1007/s10654-014-9946-8) contains supplementary material, which is available to authorized users.

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Introduction

Thyroid disease has been associated with several metabolic disorders as well cardiovascular disease [1, 2] and cardiovascular mortality [3, 4]. The cardiovascular system is one

of the main targets of thyroid hormones, which decrease systemic vascular resistance [5], alter systolic and diastolic cardiac function [4] and directly increase cardiac contractility and heart rate [6]. They also have effects on several cardiovascular risk factors including changed lipid profile [7] and increased risk of atrial fibrillation and other supraventricular arrhythmias [8]. Many of these effects are also seen in subclinical thyroid dysfunction [9].

Subclinical thyroid dysfunction is defined by serum thyroid stimulating hormone (TSH) values outside the reference range, but with normal concentrations of free thyroxine (T4), as well as free triiodothyronine (T3) in the case of subclinical hyperthyroidism [10, 11]. The reference ranges depend on several factors including the thyroid function assay used [10] and iodine status of the population [12]. Thyroid dysfunction in the subclinical range is very common, with a prevalence of subclinical hypothyroidism varying between 4 and 14 % in adults [13–15] which increases with age [14]. Subclinical hyperthyroidism is less common in the general population with a prevalence ranging from 0.7 % [16] up to 10 % in women [17].

Two meta-analyses of individual participant data of prospective cohorts showed an increased risk of coronary heart disease in subclinical hypothyroidism [18], as well as subclinical hyperthyroidism [19]. Stroke, which is worldwide the second most common cause of death and one of the leading causes of disability [20], shares many of the same risk factors as other cardiovascular disease, including high blood pressure, high cholesterol, obesity and atrial fibrillation. The link between overt hyperthyroidism and atrial fibrillation [2] and ischemic stroke has been established, even in young adults [21]. The association between overt hypothyroidism, atrial fibrillation and cardioembolic stroke has been suggested, but is not established [2, 22]. While subclinical thyroid dysfunction influences several of the mentioned cardiovascular risk factors, there remains debate to what extent this actually affects stroke risk [9]. Prior studies assessing this association are few, with conflicting outcomes and have never been systematically analyzed. With this meta-analysis, we aim to determine whether subclinical thyroid dysfunction is associated with an increased risk of stroke in prospective cohort studies.

Materials and methods

Eligibility criteria

We searched for published studies of prospective cohorts that satisfy the following criteria: (1) measurement of thyroid function at baseline in subjects above the age 18, (2) assessment of stroke and/or transient ischemic attack (TIA) outcomes (3) inclusion of subclinical thyroid dysfunction group and a comparison group with euthyroidism and (4) evaluation of the association of altered thyroid function on stroke providing a measure of this association with either a risk ratio, odds ratio or hazard ratio. We excluded studies including participants with only overt thyroid disease or only participants taking thyroid-function altering medication, or with only stroke and/or TIA patients. We did include studies with a proportion of participants taking thyroid function altering medication. In prospective cohort studies this will probably not exceed 10 % of the studied population. We did however conduct a sensitivity analysis excluding those studies. Our outcome of interest was fatal and non-fatal stroke.

Study search and identification

We conducted a systematic literature search for studies on the association between subclinical thyroid dysfunction and stroke published between earliest inception and November 2013 in several databases (Supplemental Material). The databases searched were: Medline (OvidSP), Embase, Web-of-Science, Pubmed Publisher, Cochrane and Google Scholar. We used a cohort filter designed by BMJ Evidence Centre information specialists [23] to select prospective studies for both the Medline as well as the Embase database, but not for the other databases. Filters for observational studies have shown to perform well in Medline and Embase with a sensitivity of >99 % and reduce the amount of retrieved articles up to 30 % [24]. We did not use any other filters or restrictions including language restrictions. In addition, we searched in other sources including bibliographies of key articles in the field and those included in this review.

Study selection

Two reviewers (LC, CB) screened the abstracts and titles of the search results independently and in duplicate. Articles of prospective cohorts studying the association between subclinical thyroid dysfunction and stroke and/or TIA were included. When potentially eligible studies were retrieved, the full text publications were evaluated according to the eligibility criteria. The inter-reviewer agreement was calculated according to the kappa-statistic (κ), which was fair to good ($\kappa = 0.61$) for abstract and title, and excellent ($\kappa = 1.0$) for full-text screening. Disagreements were resolved by either consensus or discussion with a third independent reviewer (RP).

Subclinical hypothyroidism was defined as an elevated TSH and normal free T4 (FT4), subclinical hyperthyroidism as a decreased TSH and normal (F)T4/T3. We used TSH and (F) T4/T3 -cutoffs as reported by each cohort separately.

Table 1 Description, characteristics and results of included studies on the effect of subclinical thyroid dysfunction and the risk of stroke

First author, name of cohort, year of start	Description of population	Journal, year of publication	Age (mean)	Total no. of subjects	No. of euthyroid subjects (%)	No. of subclinical hyperthyroidism subjects (%)	No. of subclinical hypothyroidism subjects (%)	Women (%)	Exclusion of thyroid altering medication?
Schultz, Frederiksberg, 1998	General population in Copenhagen, >50 years, normal LVF. Denmark	Horm Metab Res, 2011	67.9	605	549 (90.7)	25 (4.1)	31 (5.1)	352 (58.2)	No
Rodondi, Health ABC, 1997	Community-dwelling adults aged 70–79 years from Medicare. USA	Arch Intern Med, 2005	74.7	2730	2,392 (87.6)	NA	338 (12.4)	1,392 (51.0)	No[a]
Imaizumi, Nagasaki, 1984	Atomic bomb survivors in Nagasaki. Japan	JCEM, 2004	58.5	2,550	2,293 (89.9)	NA	257 (10.1)	1,551 (60.8)	Yes
Parle, Birmingham, 1988	Community-dwelling patients ≥60 years old in Birmingham, England	Lancet, 2001	70.4	1,191	1,026 (86.1)	70 (5.9)	76 (6.4)	681 (57.2)	Yes
Cappola, CHS, 1989	Community-dwelling adults from Medicare aged ≥65 years. USA	JAMA, 2006	72.7	3,233	2,639 (81.6)	47 (1.5)	496 (15.3)	1,926 (59.6)	Yes
Drechsler, 4D study, 1998	RCT investigating atorvastatin in patients, aged 18–80 years, with DM II and hemodialysis <2 years. Germany	Am J Kidney Dis., 2013	65.6[b]	1,000	781 (78.1)	137 (13.7)	16 (1.6)	431 (43.1)	No

Name of cohort	Stroke events (no.)	Stroke mortality (no.)	Total mortality (no.)	Follow-up duration (years)	Reference range TSH (mIU/L)	Reference range (F)T4	Reference range (F)T3	T4/T3 measured in all?
Frederiksberg	28	NR	88	5 (median)	0.4–4.0	T4: 4.7–12.3 ng/dL[c]	T3:65–196 pg/dL[d]	Yes
Health ABC	153	NR	324	4[e]	0.1–4.5	FT4: 0.8–1.8 ng/dL	NA	No[f]
Nagasaki	44	12	152	6 (max)	0.6–5.0	FT4: 0.8–2.5 ng/dL	NA	Yes
Birmingham	NA	45	509	8.3 (mean)	0.5–5.0	FT4: 0.7–1.9 ng/dL[c]	FT3:130–519 pg/dL[d]	No[f]
CHS	320	NR	847	12.5 (mean)	0.45–4.5 [g]	FT4: 0.7–1.7 ng/dL	NA	No[f]
4 D study	75	NR	471	3.94 (mean)	0.30–4.0 [g]	FT4: 0.9–1.9 ng/dL[c]	FT3:175–494 pg/dL[d]	Yes

Name of Cohort	TSH mU/L, mean (SD)					HR (95 % CI)	
	Hypothyroidism	Subclinical hypothyroidism	Euthyroidism	Subclinical hyperthyroidism	Hyperthyroidism	Subclinical hyperthyroidism	Subclinical hypothyroidism
Frederiksberg[h]	NR	5.84 (4.49–7.35)	1.36 (0.93–1.95)	0.26 (0.12–0.34)	NR	3.39 (1.15–10.00)	0.74 (0.10–5.50)
Health ABC	NR	NR	NR	NR	NR	NA	1.37 (0.85–2.20)
Nagasaki	NR	6.79 (3.45)[i]	2.82 (1.01)[i]	NA	NA	NA	1.9 (0.5–7.3) [j]
Birmingham	NR	NR	NR	NR	NR	1.8 (0.7–4.7)[j]	NA
CHS	28.1 (15.7)	6.67 (2.54)	2.20 (0.99)	0.5 (0.13)	NA	0.70 (0.31–1.57)	1.01 (0.79–1.29)

Table 1 continued

Name of Cohort	TSH mU/L, mean (SD)					HR (95 % CI)	
	Hypothyroidism	Subclinical hypothyroidism	Euthyroidism	Subclinical hyperthyroidism	Hyperthyroidism	Subclinical hyperthyroidism	Subclinical hypothyroidism
4 D study	NR	5.9 (2.9)	1.2 (0.8)	0.14 (0.1)	NR	0.56 (0.27–1.23)	0.71 (0.10–5.27)

LVF left ventricular function, *RCT* randomized controlled trial, *DM II* type 2 diabetes, *NR* not reported, if information is part of the scope of the study, but not reported, *NA* not applicable, if information is not part of the scope of the study

[a] Excluded only 2 taking anti-thyroid drugs

[b] Calculated from provided mean ages per thyroid subgroup

[c] Conversion 1 pmol/L = 0.0777 ng/dL

[d] Conversion 1 pmol/L = 65 pg/dL

[e] Unclear descriptive

[f] T4 and or T3 only measured in higher and or lower levels of TSH

[g] Subclinical hypothyroidism groups defined as: CHS: TSH 4.5–20 mIU/L, 4D study: TSH 4.0–15 mIU/L

[h] Provided TSH and interquartile range

[i] Calculated by using provided data in the publication

[j] Only stroke mortality

Data collection and quality assessment process

Standardized data collection forms were used to extract data from the individual cohorts of the included studies concerning participant characteristics, used reference ranges for thyroid function measurements, including the minimally and maximally adjusted HR's for the outcome events of interest, types of analysis and covariates adjusted for (Table 1). The correctness of the abstracted information was confirmed by a second reviewer (RP) and corrected and/or completed where needed.

Two independent reviewers assessed study quality using previous criteria for the assessment of key indicators of cohort study quality [25]. The components assessed were: (1) whether the study was population based, (2) whether the study had a formal adjudication procedures for stroke defined as having clear criteria for the outcome that were reviewed by experts for each potential case, (3) which methods were used for stroke ascertainment, (4) which if any adjudication was performed without knowledge of thyroid status, (5) what was the loss of follow-up and (6) what were the adjustments for the multivariate analysis, if any. We also assessed study quality using the Newcastle Ottawa Scale (NOS) for cohort studies [26]. Two reviewers (LC, CB) rated all studies for quality and any disagreement was resolved by a third reviewer (OF).

Statistical analysis

We used the most adjusted HRs and 95 % confidence intervals (CI) available provided by the included studies as the primary analysis. We used the random-effects method by DerSimonian and Laird [27] to assess the pooled estimates and 95 % CIs of the risk of subclinical hypothyroidism and hyperthyroidism on stroke. In addition we also conducted a fixed-effect analysis for comparison. We used the Cochrane Q test and I^2 index with a conservative p value of 0.10 to evaluate heterogeneity across individual studies [28]. I^2 values of <25 % indicate low, 25 and 50 % moderate and >50 % high heterogeneity. We also evaluated publication bias visually through funnel plots and statistically with an Egger test [29]. For the analyses we used Review Manager (RevMan) Version 5.2. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012. To explore sources of heterogeneity, we planned sensitivity analyses to exclude non-population based studies, exclude studies including a proportion of levothyroxine users, including only studies with a adjudication procedure, including studies with (F)T4/T3 measured in all participants and a sensitivity analysis using only the minimally adjusted HRs. We also planned subgroup analyses stratifying for different age groups, gender, TSH levels.

Results

Study selection

We identified 3,095 reports, of which 2,274 remained after removing duplicates (Fig. 1). We excluded 2,258 based on the title and abstract as they were unrelated to the association between subclinical thyroid dysfunction and stroke. Of the remaining 16 articles, we excluded 10 articles because they did not meet inclusion criteria after full-text screening, leaving six reports that met the eligibility criteria and were included in further qualitative and quantitative analyses.

Study characteristics

The 6 studies selected for the analysis enrolled 11,309 participants in total (Table 1) and included 665 stroke events. The included studies were from Europe, Japan and the USA. Out of the six studies, five studies provided information on subclinical hypothyroidism analyzing a total of 10,118 participants with 620 stroke events, and four studies provided data on subclinical hyperthyroidism analyzing a total of 6,029 participants with 301 stroke events. The mean age ranged from 58.5 up to 74.7 years at baseline, while the overall mean age was 69 years. Out of the 6 cohorts, 3 excluded participants with thyroid-altering medication and three studies measured T4 (and/or T3) only in abnormal TSH values. None of the studies evaluated stroke as a primary outcome and none specified the type of stroke. The percentage of subclinical thyroid dysfunction varied across studies ranging from 1.5 % to 5.9 % for subclinical hyperthyroidism and from 5.1 to 15.3 % in subclinical hypothyroidism. The TSH cut-offs for subclinical hyperthyroidism ranged between 0.1 and 0.6 mIU/L and for subclinical hypothyroidism between 4.0 and 5.0 mIU/L. The follow-up duration varied from 4 years up to 12.5 years. All studies except for one [30] used a second or third generation TSH-assay. The first-generation TSH-assay used by this study is insufficiently sensitive to detect a TSH in the range of subclinical hyperthyroidism. However, the Nagasaki Study did not provide information on subclinical hyperthyroidism and was only included in the subclinical hypothyroidism analysis.

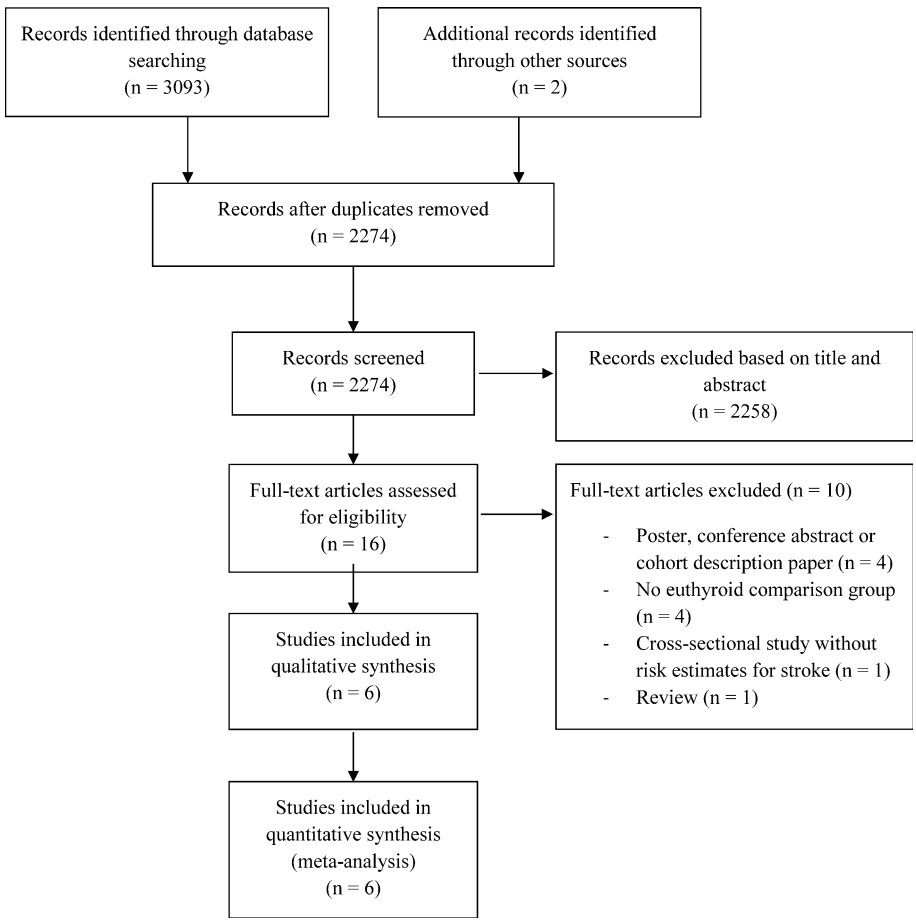

Fig. 1 Flow chart for study inclusion; adapted from PRISMA statement

Quality assessment

Five out of the six studies were population based and one study was a randomized clinical trial (Table 1). Three studies had formal adjudication procedure for stroke of which 2 studies also reported adjudication without knowledge of thyroid status. The studies with no formal adjudication procedure used the International Classification of Diseases (ICD) to ascertain stroke outcomes. None except for one cohort [31] reported loss to follow-up and all but one [31] reported HR adjusted for covariates (Supplemental Material Table S1). The studies showed similar scores on the NOS assessment scale overall, but scored differently on the separate quality item (Supplemental Material Table S2). As an overall quality check and in order to ensure transparent reporting of this systematic review and meta-analysis, the PRISMA guidelines were followed and the PRISMA checklist is provided (Supplemental Material Table S3).

Subclinical hyperthyroidism and stroke

Of the 6 included studies, 4 provided data on subclinical hyperthyroidism and the risk of stroke. Two studies included in this analysis [31, 32] showed an increased risk, with one study providing an adjusted HR reaching statistical significance with a HR 3.39 (95 % CI 1.15–10.00) [32]. The two other studies showed a statistically non-significant decreased risk for stroke associated with subclinical hyperthyroidism [33, 34] (Table 2). The overall pooled estimated HR using a random effects model showed no association of subclinical hyperthyroidism with stroke with a HR of 1.17 (95 % CI 0.54–2.56) and substantial heterogeneity (Q-statistic p value <0.05 and I^2 of 67 %,

Table 2 Stratified and sensitivity analyses of the association between subclinical thyroid disease and the risk of stroke

	Subclinical hyperthyroidism			Subclinical hypothyroidism		
	Pooled HR (95 % CI)	No. of studies	p for heterogeneity*	Pooled HR (95 % CI)	No. of studies	p for heterogeneity*
Eligible study model						
Random effects	1.17 (0.54–2.56)	4	0.03	1.08 (0.87–1.34)	5	0.70
Fixed effects	1.05 (0.67–1.63)	4	0.03	1.08 (0.87–1.34)	5	0.70
Definition of subclinical hyperthyroidism						
TSH cutoff <0.45 mIU/L	1.33 (0.23–7.69)	2	0.008	NA	NA	NA
Exclusion of studies with thyroxine users[a]	1.09 (0.43–2.74)	2	0.14	1.03 (0.81–1.31)	2	0.36
Measurement of T4 in all[b]	1.33 (0.23–7.69)	2	0.008	1.20 (0.45–3.19)	3	0.63
Stratified by mean age at inclusion in the cohorts**						
<65 years	NA	NA	NA	1.90 (0.50–7.29)	1	NA
≥65 years	1.17 (0.54–2.56)	4	0.03	1.07 (0.86–1.32)	4	0.67
<70 years	1.33 (0.23–7.69)	2	0.008	1.20 (0.45–3.19)	3	0.63
≥70 years	1.09 (0.43–2.74)	2	0.14	1.10 (0.84–1.43)	2	0.27
Adjustments						
Minimally adjusted results[c]	1.26 (0.65–2.47)	4	0.07	1.06 (0.86–1.31)	5	0.68
Characteristics of study quality						
Formal stroke adjudication procedures	0.63 (0.36–1.10)	2	0.71	1.09 (0.88–1.35)	4	0.56
Excluding studies						
One study that was not population based	1.54 (0.62, 3.83)	3	0.06	1.09 (0.88–1.35)	4	0.56
One study as an outlier in funnel plot	0.85 (0.44, 1.65)	3	0.16	1.09 (0.88–1.35)	4	0.56

NA not applicable

[a] Studies that excluded thyroid hormone recipients were included in this analysis

[b] these studies measure T4 or T3 only in higher and/or lower TSH levels

[c] Adjusted for the least amount of covariates per study

* $p > 0.10$, ratios are homogeneous; ** p for interaction: for age threshold 70 in subclinical hypothyroidism 0.25, in subclinical hyperthyroidism 0.88, age threshold 65 in subclinical hypothyroidism 0.23

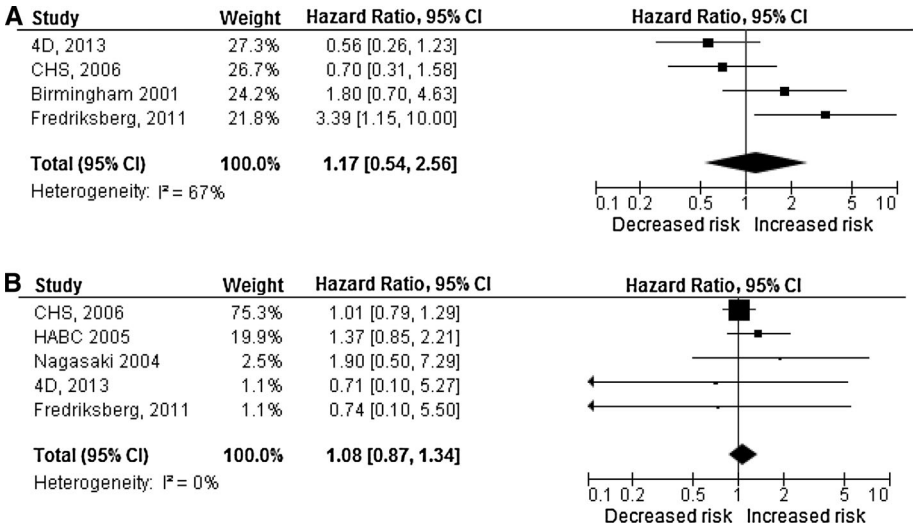

Fig. 2 Forest plots for subclinical thyroid disease and risk of stroke. **a** Subclinical hyperthyroidism and stroke. **b** Subclinical hypothyroidism and stroke. Overall hazard ratios are displayed as diamonds. The forest plots are ordered by study weight. 4D = Die Deutsche Diabetes Dialyse Studie, CHS = Cardiovascular Health Study, HABC = Health, Aging and Body Composition study

Fig. 2a). Sensitivity analyses excluding studies without formal stroke adjudication procedures, not population based or including participants on levothyroxine yielded similar results (Table 2).

Subclinical hypothyroidism and stroke

In the five studies that included results on the effect of subclinical hypothyroidism on the risk of stroke the pooled HR was 1.08 (95 % CI 0.87–1.34) without evidence for heterogeneity (p value of 0.70, I^2 of 0 %) (Fig. 2b). The results were mainly due to the large weight (75 %) of one particular study. Sensitivity analyses did not show any relevant difference in the results, except stratifying by age with a higher risk in the population aged <65 years (HR 1.90, 95 % CI 0.50–7.29), but with only one study contributing with participants with a mean age below 65 years old.

Subgroup and sensitivity analyses

Pre-specified subgroup analyses were performed on different age categories, different cut-off points for TSH levels as well as the inclusion of levothyroxine users in the study and showed no significant differences. Due to the lack of data, no subgroup analysis on gender could be performed (Table 2). Sensitivity analysis using only minimally adjusted HRs did not alter the risk estimates substantially (Table 2).

Evaluation of publication bias

Neither the visual assessment of the funnel plots (Supplemental Material Figure S1) nor the Egger test ($p = 0.76$) showed signs for publication bias for the association between subclinical hypothyroidism and the risk of stroke. However the Egger test did show significant publication bias for the analysis on subclinical hyperthyroidism ($p = 0.003$). Furthermore, the funnel plots for subclinical hyperthyroidism and risk of stroke also showed publication bias with the Frederiksberg study being a possible outlier. Excluding this study in a sensitivity analysis yielded different risk estimates for subclinical hyperthyroidism, slightly reducing statistical heterogeneity (Table 2). The results for subclinical hypothyroidism did not change by this additional analysis.

Discussion

In our systematic review and meta-analysis we did not find evidence supporting an increased risk of stroke in participants with subclinical thyroid dysfunction. This is in line with previous studies that found no association between subclinical hyperthyroidism and stroke [19, 35] or subclinical hypothyroidism and stroke [35, 36]. The number of studies retrieved was low and the study quality (assessed by scoring key indicator of quality and the NOS scale) was heterogeneous with few studies reporting adjudication of the outcome without prior knowledge of the thyroid status. Five studies adjusted for at least age and sex, but all studies included a different number of additional covariates for both minimal as maximal adjustment making them hard to compare. For example, only three out of the six studies corrected for smoking status [30, 33, 37], while smoking is associated with both stroke as with thyroid disease [38]. Smoking is negatively associated with hypothyroidism and positively associated with hyperthyroidism with current smokers having lower levels of TSH [38]. It has even been

suggested that smoking might mediate the associations found between thyroid function and BMI [39].

Stroke shares many of the same risk factors with other cardiovascular diseases. Subclinical hyperthyroidism significantly increases the risk of atrial fibrillation, as demonstrated in an individual participant level meta-analysis by Collet et al. [19]. In subclinical hypothyroidism, relevant changes in low-density lipoprotein cholesterol (LDL-cholesterol) were seen, mainly with a TSH higher than 10 mIU/L [40]. Although the association between subclinical thyroid dysfunction and various risk factors for stroke have been established, the risk of stroke in subclinical thyroid dysfunction remains unclear.

This is the first systematic review and meta-analysis on the association between subclinical thyroid dysfunction and the risk of stroke. We conducted an extensive literature search in several electronic databases with as little limitations as possible in order to retrieve the maximum amount of literature available on the topic. However, the number of retrieved papers was still small, revealing a scarcity of literature on this issue. Moreover almost all studies were conducted in populations of 65 years or older, limiting the generalizability to other populations. The only study with a younger population looking at subclinical hypothyroidism found an increased risk with a hazard ratio of 1.90, even though statistically not significant [30]. Looking at different age groups would be of special interest as previous studies evaluating the association between subclinical thyroid dysfunction, cardiovascular disease and mortality suggest an age dependent effect [25, 41]. Another important limitation is the lack of information on different TSH levels. Previous studies showed an association between different TSH levels and the risk of cardiovascular disease [18] and cardiovascular mortality [19]. Only one study [37] in our meta-analysis included different TSH-levels in the analysis, showing no clear dose–response relation. Only two [32, 33] out of the four studies included in the subclinical hyperthyroidism analysis provided information on atrial fibrillation, which did not allow for stratification. We were not able to explore age-related nor TSH level associated risks of stroke in subclinical thyroid dysfunction in our meta-analysis, due to limited data. Also, we were not able to stratify for follow-up time, in order to take into account the time between exposure and outcome, due to the difference in definition of follow-up time (Table 1). Furthermore, we were not able to take possible treatment during follow-up into account, neither did we have information on the progression of the thyroid function or thyroperoxidase (TPO) autoantibody status of participants. Finally, (Free)T3 was not measured or taken into account in all studies, allowing for possible misclassification of subclinical hyperthyroidism, which might have been the case in two studies [31, 33].

All included studies evaluated stroke as a secondary outcome next to other cardiovascular diseases and deaths or total mortality. This is reflected by the lack of subgroup analyses per cohort and the inability of our study to stratify for different possible risk populations, such as gender specific analyses. For the subclinical hyperthyroidism analysis we found statistically significant heterogeneity, complicating the interpretation of the meta-analysis results. Reference ranges differed substantially between the individual studies, especially for subclinical hyperthyroidism, with lower limits of TSH ranging from 0.1 to 0.6 mIU/L. This might be one of the reasons for heterogeneity. Another reason might be the underlying differences in populations ranging from healthy volunteers [32] to patients on hemodialysis [34] and from multiracial [33, 37] to a solely Asian population [30], leading to possible selection bias. In order to examine the issue of heterogeneity in the subclinical hyperthyroidism analysis, we conducted sensitivity and subgroup analyses, which led to a reduction in heterogeneity by excluding studies that included levothyroxine users, including studies with formal stroke adjudication procedures only and stratifying by age (e.g. cut-off at 70 years of age). However, these analyses included no more than 2 studies and none reached statistical significance for the outcome measure. Furthermore, the visual assessment of publication bias, showed no evidence for publication bias for the analysis on subclinical hypothyroidism but some for subclinical hyperthyroidism. This remains a concern in meta-analyses, especially when only a small number of studies are retrieved.

While we could not provide evidence for an effect of subclinical thyroid dysfunction on the risk of stroke, these results should be interpreted with caution. Thyroid dysfunction, even in the subclinical range gives rise to several cardiovascular risk factors. In subclinical hypothyroidism some seem to be reversible if treated with levothyroxine [42, 43]. Furthermore, restoring thyroid function with levothyroxine treatment in subclinical hypothyroid individuals showed a reduction of almost 10 % of the carotid artery mean intima media thickness (IMT) [44]. As IMT has shown to be a risk factor of cardiovascular disease and stroke [45], this decline in IMT might also result in a decreased risk of stroke. Also, the association between subclinical hyperthyroidism and atrial fibrillation has been clearly demonstrated [19] and therefore an association between subclinical hyperthyroidism and stroke could be presumed. However, we were not able to demonstrate this expected risk increase in our meta-analysis for subclinical hyper- nor for hypothyroidism. This might be due to the limited number of populations evaluated and gathered (hence the lack of power) by the included studies, not representing specific populations at risk. Treatment of subclinical thyroid dysfunction in relation to

cardiovascular disease is still controversial and highly debated. Consensus guidelines have advocated treatment of subclinical hyperthyroidism but only in the elderly or patients with cardiac risk factors, heart disease or osteoporosis [46]. Levothyroxine treatment has shown to improve several subclinical cardiovascular disease markers, e.g. IMT and endothelial dysfunction [43, 47, 48], in subclinical hypothyroidism, but no large controlled trials have been performed to evaluate the effect in preventing cardiovascular events. Moreover, there are concerns about the risk of overtreatment, as population-based studies reported that among patients treated with thyroid medication, only 60 % were within the normal biochemical range of TSH with more than one fifth having a TSH level that was suppressed below normal [15]. Randomized clinical trials, like the ongoing IEMO 80 + Thyroid Study and Thyroid Hormone Replacement for Subclinical Hypothyroidism (TRUST) trial (ClinicalTrials.gov Identifier: NCT01660126), are expected to give more insight into the benefit of treatment in the general population as well as specific subgroups.

In summary, we found no association between subclinical thyroid dysfunction and the risk of stroke. However, the available literature is insufficient and more research is needed. Future studies should focus on the association between subclinical thyroid dysfunction and the risk of stroke as a primary outcome and be adequately powered to conduct subgroup analyses including different age groups, TSH levels and gender differences.

Acknowledgments We would like to express our gratitude to Wichor M. Bramer from the medical library (Medical Library, Erasmus Medical Center, Rotterdam) for the important contribution to the literature search. Dr. R.P. Peeters is supported by a Zon-MW TOP grant (nr 91212044) and an Erasmus MCMRACE grant. Dr. A. Dehghan is supported by NWO grant (veni, 916.12.154) and the EUR Fellowship. Dr. C. Baumgartner is supported by a grant from the Swiss National Science Foundation (SNSF 320030-138267 and 320030-150025 to Prof. Rodondi). Prof. N. Rodondi's research is supported by a grant from the Swiss National Science Foundation (SNSF 320030-138267) and by a grant from the Swiss Heart Foundation. Prof. O. H. Franco works in ErasmusAGE, a center for aging research across the life course funded by Nestlé Nutrition (Nestec Ltd.), Metagenics Inc., and AXA. Nestlé Nutrition (Nestec Ltd.), Metagenics Inc., and AXA had no role in design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review or approval of the manuscript.

Conflict of interest The authors declare that they have no conflict of interest.

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