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Subclinical Thyroid Dysfunction and the Risk of Heart Failure Events: An Individual Participant Data Analysis from Six Prospective Cohorts

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Abstract

Background—ACC/AHA Guidelines for the Diagnosis and Management of Heart Failure (HF) recommend investigating exacerbating conditions, such as thyroid dysfunction, but without specifying impact of different TSH levels. Limited prospective data exist regarding the association between subclinical thyroid dysfunction and HF events.

Methods and Results—We performed a pooled analysis of individual participant data using all available prospective cohorts with thyroid function tests and subsequent follow-up of HF events. Individual data on 25,390 participants with 216,248 person-years of follow-up were supplied from 6 prospective cohorts in the United States and Europe. Euthyroidism was defined as TSH 0.45–4.49 mIU/L, subclinical hypothyroidism as TSH 4.5–19.9 mIU/L and subclinical hyperthyroidism as TSH <0.45 mIU/L, both with normal free thyroxine levels. Among 25,390 participants, 2068 had subclinical hypothyroidism (8.1%) and 648 subclinical hyperthyroidism (2.6%). In age- and gender-adjusted analyses, risks of HF events were increased with both higher and lower TSH levels (P for quadratic pattern <0.01): hazard ratio (HR) was 1.01 (95% confidence interval [CI] 0.81–1.26) for TSH 4.5–6.9 mIU/L, 1.65 (CI 0.84–3.23) for TSH 7.0–9.9 mIU/L, 1.86 (CI 1.27–2.72) for TSH 10.0–19.9 mIUL/L (P for trend <0.01), and was 1.31 (CI 0.88–1.95) for TSH 0.10–

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0.44 mIU/L and 1.94 (CI 1.01–3.72) for TSH <0.10 mIU/L (P for trend = 0.047). Risks remained similar after adjustment for cardiovascular risk factors.

Conclusions—Risks of HF events were increased with both higher and lower TSH levels, particularly for TSH 10 mIU/L and for TSH <0.10 mIU/L.

Keywords

cohort study; epidemiology; heart failure; meta-analysis; thyroid

Background

Heart failure (HF) is a frequent cause of hospitalization in persons older than 65 years with an increasing trend in the number of patients living with heart failure.[1, 2] Given that HF constitutes a major public health problem within the context of an aging and growing population,[1, 3–5] recognizing modifiable risk factors for HF events is essential to target subjects who are at risk for developing this condition.[6, 7] The ACC/AHA Guidelines for the Diagnosis and Management of HF in Adults recommend measurement of thyroid function to investigate conditions that might exacerbate HF, such as hypothyroidism or hyperthyroidism, but without specifying the potential impact of different Thyroid Stimulating Hormone (TSH) levels.[8]

Subclinical thyroid dysfunction is common, particularly in older individuals, with a prevalence of subclinical hypothyroidism up to 10% and subclinical hyperthyroidism between 0.7%–3.2%.[9] Subclinical hypothyroidism is defined as a serum TSH concentration above the upper limit of the reference range with serum free thyroxine (FT4) concentration within its reference range. Subclinical hyperthyroidism is defined as a serum TSH concentration below the lower limit of the reference range with serum FT4 and free tri-iodothyronine (FT3) concentrations within their reference ranges.[10, 11] Subclinical hypothyroidism and subclinical hyperthyroidism have been associated with an increased risk of coronary heart disease (CHD) events and mortality,[12–14] but few prospective data are available concerning the association of subclinical thyroid dysfunction and the risk of HF events and the strengths of associations varied.[15–18] Subclinical thyroid dysfunction has been associated with systolic and diastolic cardiac dysfunction.[16,19] Small studies have shown that thyroxine replacement improved measurements of cardiac function in subjects with subclinical hypothyroidism.[20] However, no randomized controlled trials have been performed to evaluate the therapy effect among individuals with subclinical thyroid dysfunction with clinical HF outcomes. Currently the evidence for screening and treating subclinical thyroid dysfunction is limited.[10, 21, 22]

To clarify the association between subclinical thyroid dysfunction and HF events, we performed a pooled analysis of individual participant data using all available prospective cohorts. Analysis of individual participant data from large cohort studies may reconcile heterogeneity between studies by allowing a common TSH cutoff for subclinical thyroid dysfunction and further adjustment of similar confounding factors. Individual participant data analysis is the best method for assessing the impact of the degree of subclinical thyroid dysfunction (measured by TSH level) and of preexisting HF or cardiovascular disease (CVD) in subgroups analyses, and reduces potential bias from subgroup analyses derived from study-level meta-analyses.[23, 24]

Methods

Study selection

We updated our previous systematic review[13] of articles in any language published from 1950 to June 30 2011, in MEDLINE and EMBASE databases on the association between subclinical thyroid dysfunction and cardiovascular outcomes, searched bibliographies for key articles and contacted experts in this field (Supplemental Methods). For this analysis, we followed predefined inclusion criteria considering only full-text, published longitudinal cohort studies that fulfilled the following conditions: (1) measurement of TSH levels and FT4 levels at baseline in adults, (2) systematic follow-up over time, (3) assessment of HF events, and (4) a control euthyroid group. We excluded studies that only considered persons taking thyroid medications (antithyroid drug or thyroxine replacement) or with overt thyroid dysfunction (defined by abnormal TSH and FT4 levels). The updated search for additional studies until 30 June 30 2011, was independently assessed by 2 authors (BG and PB); any discrepancy between the authors was resolved by discussion with a third author (NR). The agreement rate between the 2 reviewers was 99.9% for the first screen (titles and abstracts, kappa=0.66, confidence interval [CI] 0.62–0.72) and 100% for the full-text screen (kappa=1.00). The assessment of the methodological quality of included studies was performed according to previously described criteria.[14] Two authors (NR, JG) rated all studies for quality: methods of outcome adjudication, evaluation of confounders and the completeness of follow-up. All studies were approved by institutional review boards and all participants gave written informed consent.

Investigators from eligible studies were contacted to join the Thyroid Studies Collaboration. We requested data about the baseline thyroid function (TSH and FT4, FT3 if available), HF outcome data, demographic characteristics (age, gender, race), cardiovascular risk factors (total cholesterol, diabetes, blood pressure, cigarette smoking), preexisting CVD, preexisting HF, medication (lipid-lowering, antihypertensive drugs, thyroxine replacement and antithyroid medication) and other potential confounding variables for HF such as body mass index (BMI), creatinine and atrial fibrillation (AF).

Definition of Subclinical Thyroid Dysfunction

To maximize comparability of the studies, we used a common definition of subclinical thyroid dysfunction based on expert reviews,[10, 21] definition used in the Cardiovascular Health Study,[16, 25] and a consensus meeting of our Collaboration (International Thyroid Conference, Paris, 2010). Euthyroidism was defined as a TSH level of 0.45–4.49 mIU/L, subclinical hypothyroidism as a TSH level of 4.5–19.9 mIU/L and subclinical hyperthyroidism as a TSH level <0.45 mIU/L, both with normal FT4 levels. Based on previously described TSH cutoffs[13, 16] and expert reviews,[10, 21] subclinical hypothyroidism was subdivided into three groups: TSH 4.5–6.9 mIU/L, 7.0–9.9 mIU/L and 10.0–19.9 mIU/L, and subclinical hyperthyroidism into two groups: TSH 0.10–0.44 mIU/L and <0.10 mIU/L. For FT4, we used study-specific cutoffs (Supplemental Table 1),[13] because FT4 measurements show greater inter-method variation than TSH assays. As done in a previous study,[13] participants with missing FT4 values were included in the primary analyses and excluded in the sensitivity analyses, as the vast majority of adults with an abnormal TSH have subclinical and not overt thyroid dysfunction.[26] FT3 was measured in two studies (Supplemental Table 1)[17, 27] and was added to the definition of subclinical hyperthyroidism in sensitivity analyses. As done in previous studies,[12,13,15,27] we performed sensitivity analyses excluding participants using thyroid medication (thyroxine, antithyroid drug) at baseline and during follow-up.

Definition of HF events

To limit outcome heterogeneity, HF events were defined by any acute HF events diagnosed by a physician, hospitalization and deaths related to HF events, based on all available documents (symptoms, signs, therapy, chest radiographs) within each cohort (Supplemental Table 1). The blindness of HF outcomes assessment to baseline thyroid status was evaluated in each cohort and sensitivity analyses were performed according to HF outcomes adjudication process by experts. Participants with preexisting HF were included in the primary analyses, as performed in our previous individual participant data analysis evaluating CHD outcome,[12, 13] and were separately analyzed in stratified analyses to explore the association between subclinical thyroid dysfunction and incident HF events, as well as for recurrent HF events.

Potential confounders

Primary analyses were adjusted for age and gender, then for traditional cardiovascular risk factors (systolic blood pressure, total cholesterol, smoking status, diabetes) that were available in all cohorts. We further adjusted the multivariable models for other potential confounding factors, such as creatinine, body mass index, preexisting AF at baseline and cardiovascular medications (lipid-lowering and antihypertensive treatment).

To explore heterogeneity, we performed predefined stratified analyses according to age, gender, race, TSH levels, preexisting CVD and preexisting HF. We also performed sensitivity analyses excluding participants with AF at baseline, a common cause of HF events.

Statistical analyses

For statistical analyses, we performed 2-stage individual participant data analyses as recommended[24, 28] and used in a recent publication.[12, 13] Briefly, we performed separate Cox proportional hazards models to assess the association of subclinical thyroid dysfunction with HF events for each cohort (SAS 9.2, SAS Institute Inc, Cary, NC; Stata 12.1, StataCorp, College Station, TX). The pooled estimates were calculated using random-effects models based on inverse variance model and summarized with forest plots (Review Manager 5.1.2, Nordic Cochrane Centre, Copenhagen, Denmark). We tested for linear trend across TSH and age categories and for interaction according to gender, race, preexisting CVD and preexisting HF. In *post-hoc* analysis, we also tested for quadratic patterns across TSH categories. All tests were 2-sided. We did not perform formal adjustments for multiple comparisons, which can be conservative for correlated outcomes. However, we recognize the potential for inflation of the type-I error rate, and interpret nominally significant ($P<0.05$) results cautiously, and in context. To assess heterogeneity across studies, we used the I^2 statistic, estimating the proportion of the variance across studies attributed to heterogeneity rather than chance.[29] The proportional hazard assumption was assessed using graphical methods and Schoenfeld tests (all $P > 0.05$). We used age- and gender-adjusted funnel plots to assess for publication bias and the Egger test.[30] In some subgroups analyses, some strata had participants with no HF event and we used penalized likelihood methods to obtain HRs and CI,[31] as in our previous individual participant data analyses.[12, 13]

Results

Among 5413 identified publications, 6 prospective studies met eligibility criteria and reported HF events (Supplemental Figure 1); all agreed to provide individual participant data (Table 1). The final sample consisted of 25,390 participants: 22,674 were euthyroid (89.3%), 2068 had subclinical hypothyroidism (8.1%) and 648 subclinical hyperthyroidism (2.6%). The median follow-up was 10.4 years, with a total follow-up of 216,248 person-

years. During follow-up, 2069 participants had HF events. The quality assessment of these studies showed that all studies had a loss of follow-up 5% and all outcome adjudicators were blinded for thyroid status. A formal adjudication was done in 3 studies, [15, 16, 18 18]while other cohorts relied on hospital discharge[17, 32] or general practitioners' medical records [27] (Supplemental Table 1).

In age- and gender-adjusted analyses, the risk of HF increased in participants with both higher and lower TSH levels (Figure 1) with a significant test for parabolic function across TSH categories (P for quadratic pattern < 0.01). For subclinical hypothyroidism compared to euthyroidism, HR was 1.01 (CI, 0.81–1.26) for TSH 4.5–6.9 mIU/L, 1.65 (CI, 0.84–3.23) for TSH 7.0–9.9 mIU/L and 1.86 (CI, 1.27–2.72) for TSH 10.0–19.9 mIUL/L (P for trend across higher TSH categories < 0.01). For subclinical hyperthyroidism compared to euthyroidism, HR was 1.31 (CI 0.88–1.95) for TSH 0.1–0.44 mIU/L and 1.94 (CI 1.01–3.72) for TSH <0.10 mIU/L (P for trend across lower TSH categories = 0.047).

Among all participants with subclinical hypothyroidism (Table 2), HR for HF events was 1.26 (95% CI, 0.91–1.74) in age- and gender-adjusted analyses with heterogeneity (I^2=77%) across studies (Supplemental Figure 2). The risk seemed to be higher in younger participants, but the number of events was small and therefore results were possibly not significant. Among older participants (80 years old), HF events were not increased and the interaction test across age categories was not significant (P value > 0.10). We found slightly higher risks in men and Caucasians but without significant interaction test (P value > 0.10), as well as for preexisting CVD or preexisting HF. Risks were similar after further adjustment for cardiovascular risk factors, although the strength of the association was attenuated, with HR remaining significant among those with TSH levels 10.0 mIU/L (HR 1.59, CI 1.15–2.19). Sensitivity analyses (Table 3) yielded similar results. After excluding participants using thyroid medication at baseline and during follow-up, the association was stronger among those with TSH between 10.0 and 19.9 mIU/L (HR 2.37, CI 1.59–3.54). Risks remained elevated among those with TSH 10.0 mIU/L after excluding those with missing FT4 values, after further adjustment for additional HF risk factors (creatinine, body mass index and preexisting AF) and after excluding those with preexisting AF. After excluding the Bari study (all with preexisting HF), [17] HR decreased to 1.62 (CI 1.15–2.29) with a low heterogeneity (I^2=0%). [29] Risks were lower after limiting the analyses to cohorts with formal adjudication procedures by experts; this analysis was only possible for three studies of older adults (Supplemental Table 1).

Among all participants with subclinical hyperthyroidism (Table 4), HR for HF events in age- and gender-adjusted analyses was 1.46 (CI 0.94–2.27) compared to euthyroidism with heterogeneity (I^2=61%) across studies (Supplemental Figure 3). In contrast to subclinical hypothyroidism, the risk was significantly increased among participants 80 years (HR 2.34, CI 1.27–4.31), but there was not significant trend across age categories (P=0.98). We found higher risks among women and Caucasians, but the interaction test was not significant (P >0.30), as well as for preexisting CVD or preexisting HF. Risks were similar after further adjustment for cardiovascular risk factors.

Among participants with TSH < 0.10 mIU/L, HR for HF events was 1.94 (CI 1.01–3.72) in age- and gender-adjusted analyses. In sensitivity analysis (Supplemental Table 2), excluding those with thyroid medication at baseline, HR was 1.80 mIU/L (CI 1.04–3.13). Risks were similar after further adjustments for HF potential confounding risk factors (body mass index, creatinine and AF), after excluding those with missing FT4 or abnormal FT3, and after excluding those with preexisting HF or preexisting AF.

We found limited evidence of publication bias with visual assessment of age- and gender adjusted funnel plots, although the Bari study might be an outlier with no corresponding negative study of similar size, and with Egger test for subclinical hypothyroidism (P=0.23) and for subclinical hyperthyroidism (P=0.60), although such analyses were limited by the small number of included studies.

Discussion

In this individual data analysis of 25,390 participants from 6 prospective cohorts, risks of HF events were increased with higher and lower TSH levels than normal range, with statistically significant increased risks among those with TSH ≥ 10.0 mIU/L (HR 1.86, CI 1.27–2.72) and those with TSH <0.10 mIU/L (HR 1.94, CI 1.01–3.72). The HF risks were mainly explained by the degree of thyroid dysfunction, with an observed parabolic association between TSH levels and risk of HF events (P for quadratic pattern < 0.01). The increased risk of HF in adults for TSH ≥ 10.0 mIU/L persisted after excluding those with preexisting HF or preexisting AF. Further adjustment for cardiovascular risk factors and other available HF confounding risk factors did not change significantly the association with HF events, although part of the risk seemed to be mediated by cardiovascular risk factors as point estimates were decreased in multivariate models. Excluding participants using thyroid medications (mainly thyroxine replacement) at baseline and during follow-up further increased the risks.

To our knowledge, this is the first individual participant data analysis of large cohorts examining the association between subclinical thyroid dysfunction and HF events. Our findings are consistent with previous observational studies[15, 16, 18] that reported a higher incidence and recurrent risks of HF among participants with higher TSH levels in comparison with euthyroid participants; our individual participant data analysis assessed this risk across a larger age range and several subgroups. The Health, Aging and Body Composition Study previously reported an increased risk of HF events among subjects with TSH ≥ 7.0 mIU/L (HR 2.58, CI 1.19–5.60 for TSH 7.0–9.9 mIU/L and HR 3.26, CI 1.37–7.77 for TSH ≥ 10.0 mIU/L) over 4-year follow-up, with a higher risk for recurrent HF events among those with preexisting HF (HR 7.62, CI 2.25–25.77);[15] these data were updated with 8-year follow-up in the current analysis. The Cardiovascular Health Study reported [16] an increased risk of HF events among subjects with TSH ≥ 10.0 mIU/L (HR 1.88; CI 1.05–3.34) over 12-year follow-up; these data were updated with 14-year follow-up in the present data. The Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) study[18] recently reported an increased risk of HF hospitalization among subjects with TSH ≥ 10.0 mIU/L (HR 3.01, CI 1.12–8.11) and among those with suppressed TSH <0.10 mIU/L (HR 4.61, CI 1.71–12.47). The Bari study that examined only patients with preexisting HF[17] reported an increased risk of recurrent HF events among participants with subclinical hypothyroidism (HR 2.03, CI 1.16–3.55), but without a categorization of TSH levels. We previously found similar pattern with an increased risk of CHD mortality among participants with subclinical hypothyroidism and subclinical hyperthyroidism, particularly in those with more severe thyroid dysfunction.[12, 13] The present data and these previous studies suggest that clinical thyroid dysfunction varies over the spectrum of TSH level and the risk of HF was proportional to the degree of TSH elevation and suppression.

Thyroid hormones play an important function in the homeostasis of the cardiovascular system with an impact on cardiac output, cardiac contractility, vascular resistance and blood pressure. [9] Subclinical hypothyroidism has been associated with left ventricular diastolic dysfunction at rest and during exertion and impaired left ventricular systolic function on exercise. Higher TSH levels among participants with subclinical hypothyroidism have been correlated with a decrease stroke volume of left ventricular, a decrease in the cardiac index

and an increase in systemic vascular resistance.[19] Isolated ventricular diastolic dysfunction is associated with the clinical manifestation of HF,[33] and might explained the associated risk of HF events reported in our study with higher TSH levels in subclinical hypothyroidism. The increased risk of CHD events with subclinical hypothyroidism[13] might also contribute to the development of HF, as CHD is a common etiology of HF.[34, 35] Restoration of a euthyroid state in patients with subclinical hypothyroidism has been associated with normalization of some structural cardiac parameters [36, 37] and one randomized controlled trial found that thyroxine therapy in patients with subclinical hypothyroidism reduced the preejection period-left ventricular ejection time ratio,[38] but no large RCT of the impact of thyroxine therapy on HF events has been conducted yet. Only few studies, in contrast with overt hyperthyroidism, reported an effect of endogenous subclinical hyperthyroidism on cardiac parameters: an increased average heart rate, a higher left ventricular mass and an impaired diastolic function.[20] Two longitudinal studies reported higher rates of atrial fibrillation with subclinical hyperthyroidism,[25, 39] which might predispose to the development of heart failure. Recently, an individual participant analysis has reported an increased risk of atrial fibrillation among participants with subclinical hyperthyroidism with greater risks in those with TSH < 0.10 mIU/L.[12]

Among the strengths of our study, our individual participant data analysis included all available cohorts with data on subclinical thyroid dysfunction and HF, and this design is considered the optimal method to perform time-to-event analyses, to avoid biases associated with subgroups analysis (ecology fallacy) and standardize definitions of predictors, outcomes, and adjustment for potential confounders.[13, 24, 28]

Our study had several limitations. First, thyroid function was measured at baseline, and the possible progression from subclinical to overt dysfunction was unknown, which is a limitation of all published observational studies.[15, 25, 27] In addition, FT3 was measured in only two cohorts, and thus was not included in the definition of subclinical hyperthyroidism in main analyses; sensitivity analyses excluding those with abnormal FT3 yielded similar results. Second, HF events were mainly related to hospitalizations, which might lower rates of HF events. Because some patients might develop heart failure without hospitalization, the rate of recorded HF event is likely underestimated.[15, 40] Although we considered a homogeneous definition of HF, possible misclassification of HF events might have occurred, because HF is difficult to define and adjudication might vary across large-population studies,[41] such misclassification was probably non-differential, as all HF outcome adjudication were blinded to thyroid status; non-differential misclassification would lower any potential associations. Even with the large number of individual participants, some subgroup analyses, particularly among those younger than 50 years and those with preexisting HF had limited power because of the limited number of participants with HF events. We cannot exclude that some interaction or trend tests might not be significant due to lack of power. Particularly a possible effect of gender and race might be explored in future larger studies. Finally, the studied population had limited data on young adults and non-white populations, which limits the generalization of our results to the entire population.

In conclusion, the combination of all available large prospective cohorts with 25,378 participants suggests that the risk of HF increased both with lower and higher TSH levels, particularly in those with TSH levels 10.0 mIU/L and in those with TSH <0.10 mIU/L. For the majority of participants with minimal TSH disturbances (TSH levels between 4.50–6.99 mIU/L and TSH levels between 0.10–0.44 mIU/L), the risk of HF was not increased compared to euthyroid participants. Similar to previous studies,[13] we found that subclinical thyroid dysfunction is a heterogeneous entity with varying risks of cardiovascular disease according to TSH levels. The ACC/AHA Guidelines for the Diagnosis and Management of HF in Adults recommend the measuring thyroid function to investigate conditions that might

exacerbate HF but without specifying the potential impact of different TSH levels. [88] Our findings contribute to a better interpretation of TSH levels in the prevention and investigation of HF. Pending results from RCTs, the findings of our study might be useful to define the TSH threshold for thyroid medication among participants with subclinical thyroid dysfunction, although clinical decision based only on observational studies should be used with great caution, as they are subject to limitations. No clinical trial has assessed yet whether treating subclinical hypothyroidism improved HF outcome. Given the high prevalence of subclinical hypothyroidism and HF in the elderly, thyroxine replacement should be investigated with appropriately powered randomized controlled trials with clinical HF outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Clinical perspective

Analysis of individual participant data from all available prospective cohorts suggests that the risk of heart failure (HF) is increased both with higher and lower levels of Thyroid Stimulating Hormone (TSH) compared to normal range, particularly in those with TSH levels   10.0 mIU/L or < 0.10 mIU/L. These findings might lead to a better interpretation of TSH levels, as the latest ACC/AHA guidelines for the Diagnosis and Management of HF in Adults recommend measurement of thyroid function to investigate conditions that might exacerbate HF without specifying the clinical impact of different TSH levels. In the absence of randomized controlled trials that would give definitive evidence about the impact of treatment on HF, our findings might be useful to define TSH threshold for thyroid medication, although clinical decision only based on observational studies should be used with great caution. To definitively clarify this issue, a randomized controlled trial (TRUST trial, www.trustthyroidtrial.com) has just been started in Europe among elderly with subclinical hypothyroidism to assess the impact of thyroxine replacement therapy on cardiovascular outcomes, including HF events
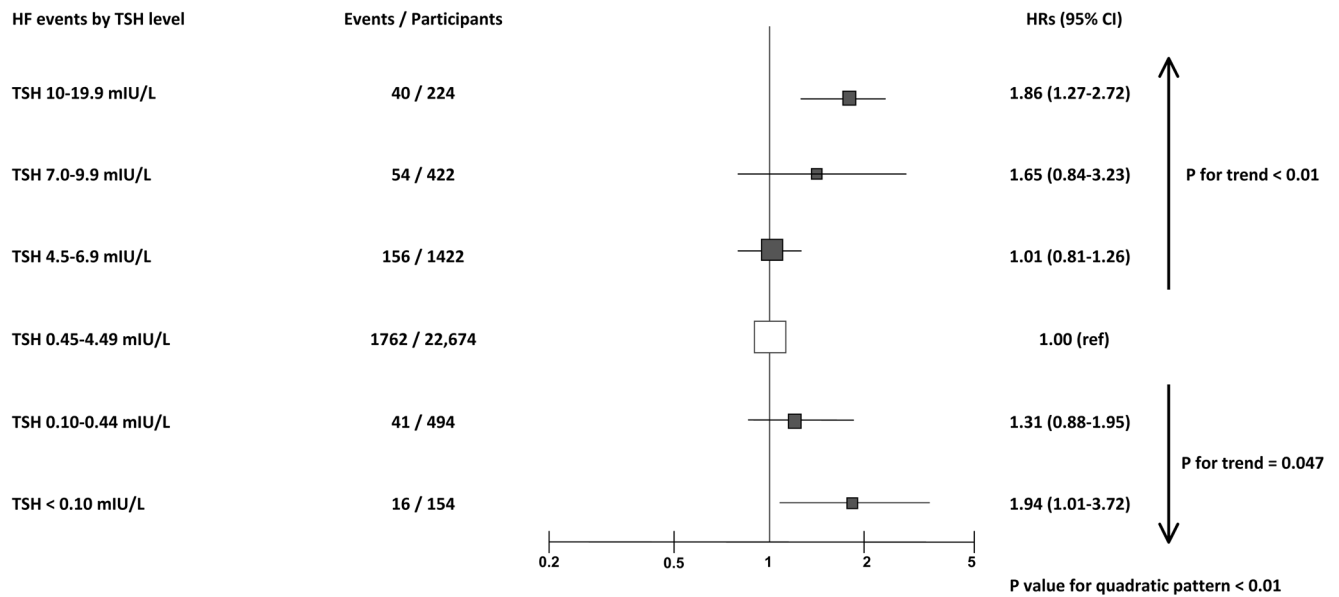
Figure 1.
Hazard Ratios for Heart Failure Events According to Thyroid-Stimulating Hormone Levels. Abbreviations: CI: Confidence Interval; HF: Heart Failure; HR: Hazard Ratio; TSH: Thyroid-Stimulating Hormone. Age- and gender-adjusted HRs and their 95% CI are represented by squares. Squares to the right of the solid lines indicate increased risk of HF events. Sized of data markers are proportional to the inverse of the variance of the HRs.

Table 1

characteristics of individuals in included studies (N = 25,390)

	Description of study sample	No	Age, median (range), years	Women, no (%)	Subclinical hypothyroidism, no (%)	Subclinical hyperthyroidism, no (%)*	Thyroid medication users, no (%)†			Start	Follow-up‡	Person-years
							At baseline	During follow-up	At anytime		Duration, median (Q1–Q3)	
tes												
cular Health Study	Community-dwelling adults with Medicare eligibility in 4 US communities	3064	71 (64–100)	1840 (60.1%)	495 (16.2%)	43 (1.4%)	0 (0.0%)	158 (5.2%)	158 (5.2%)	1989–1990	12.3 (7.0–16.3)	34'531
ging and Body ...ion Study	Community-dwelling adults with Medicare eligibility in 2 US communities	2762	74 (69–81)	1407 (50.9%)	335 (12.1%)	82 (3.0%)	267 (9.7%)	383 (13.9%)	392 (14.2%)	1997	7.1 (6.1–8.2)	17'869
folk Study	Adults living in Norfolk, England	13,066	58 (40–78)	7104 (54.4%)	720 (5.5%)	360 (2.8%)	0 (0.0%)	NA	0 (0.0%)	1995–1998	11.4 (10.7–12.3)	143'694
-plus Study	Adults aged 85 years living in Leiden, the Netherlands	514	85	336 (65.4%)	35 (6.8%)	23 (4.5%)	17 (3.3%)	20 (3.9%)	26 (5.1%)	1997–1999	4.8 (2.0–5.0)	1'861
...t	Outpatients with HF followed by Cardiology Department in Bari, Italy	335	66 (21–92)	77 (23.0%)	39 (11.6%)	7 (2.1%)	22 (6.6%)	61 (18.2%)	61 (18.2%)	2006–2008	1.1 (0.5–1.7)	370
...e Study of ...n in the Elderly at	Older community-dwelling adults at high-cardiovascular risk in the Netherlands, Ireland and Scotland	5649	75 (69–83)	2884 (51.0%)	444 (7.9%)	133 (2.3%)	207 (3.7%)	NA	207 (3.7%)	1997–1999	3.3 (3.0–3.5)	17'923
6 studies		**25,390**	**70 (21–100)**	**13,648 (53.8%)**	**2068 (8.1%)**	**648 (2.6%)**	**513 (2.0%)**	**622 (2.4%)**	**844 (3.3%)**	**1989–2008**	**10.4 (3.7–12.0)**	**216'248**

Abbreviations: HF, Heart failure; NA, data not available; Q1, first quartile; Q3, third quartile.

*
We used a common definition of subclinical hypothyroidism and hyperthyroidism, whereas TSH cutoff values varied among the previous reports from each cohort, resulting in different numbers of subclinical hypothyroidism and hyperthyroidism from previous reports.

†
Data on thyroid medication use were not available for 1 participant in CHS and 8 participants in the Health ABC Study at baseline, and for all participants during follow-up in EPIC-Norfolk.

‡
For all cohorts, we used the maximal follow-up data that were available, which might differ from previous reports for some cohorts.

Table 2

Stratified analyses for the association between subclinical hypothyroidism and Heart Failure (HF) Events

	Euthyroidism		Subclinical Hypothyroidism		HF Events	
	Events	Participants	Events	Participants	HR (95% CI) age/gender-adjusted	HR (95% CI) multivariate model*
Total population	1762	22,674	250	2068	1.26 (0.91, 1.74)	1.22 (0.93, 1.59)
Gender [†]						
Men	977	10,793	120	730	1.33 (0.91, 1.94)	1.28 (0.93, 1.76)
Women	785	11,881	130	1338	1.03 (0.85, 1.24)	1.07 (0.84, 1.36)
P for interaction					0.24	0.38
Age [‡] *(years)*						
18–49§	15	2756	2	107	4.56 (0.57, 36.30)	5.52 (0.66, 46.25)
50–64 ∥	128	5798	10	373	1.39 (0.62, 3.08)	1.79 (0.47, 6.80)
65–79	1370	12,666	205	1428	1.31 (0.92, 1.87)	1.30 (0.93, 1.82)
80	249	1454	33	160	1.01 (0.69, 1.46)	0.98 (0.66, 1.44)
P for trend					0.16	0.10
Race						
Caucasian	1573	21,541	230	1960	1.30 (0.92, 1.82)	1.25 (0.93, 1.67)
Black	189	1133	20	108	1.04 (0.66, 1.67)	1.03 (0.64, 1.67)
P for interaction					0.44	0.50
TSH (mIU/L)						
0.45–4.49	1762	22,674			1 (ref)	1 (ref)
4.5–6.9			156	1422	1.01 (0.81, 1.26)	1.01 (0.81, 1.25)
7.0–9.9			54	422	1.65 (0.84, 3.23)	1.78 (0.94, 3.38)
10.0–19.9			40	224	1.86 (1.27, 2.72)	1.59 (1.15, 2.19)
P for trend					<0.01	<0.01
Preexisting CVD [#]						
None	1091	18,448	162	1611	1.36 (0.93, 2.01)	1.33 (0.96, 1.84)
Yes	669	4214	88	456	1.19 (0.77, 1.85)	1.16 (0.77, 1.76)
P for interaction					0.65	0.61

	Euthyroidism		Subclinical Hypothyroidism		HF Events	
	Events	Participants	Events	Participants	HR (95% CI) age/gender-adjusted	HR (95% CI) multivariate model*
*Preexisting HF***						
None	1205	10,247	180	1285	0.95 (0.81, 1.11)	0.95 (0.81–1.12)
Yes	132	440	33	63	1.73 (0.81, 3.69)	1.66 (0.86, 3.23)
P for interaction					0.13	0.11

Abbreviations: CI, Confidence Interval; CVD, Cardiovascular Disease; HF, Heart Failure; HR, Hazard Ratio; NA, data not applicable; TSH, Thyroid-Stimulating Hormone.

*
Adjusted for age, sex, systolic blood pressure, current and former smoking, total cholesterol and prevalent diabetes at baseline.

†
These HRs were not adjusted for gender.

‡
These HRs were adjusted for gender and age as a continuous variable to avoid residual confounding within age strata.

§
Bari was excluded from this stratum because of only one participant with subclinical hypothyroidism leading to unstable estimates.

//
CHS was excluded from this stratum because of zero participant with subclinical hypothyroidism.

#
Data on previous CVD were not available for 11 participants in EPIC and for 2 participants in Leiden-study.

**
No data available in EPIC (only preexisting overall CVD assessed), 1 missing value in Leiden and, by inclusion criteria, all participants had HF at baseline in Bari study. No participants in PROSPER had preexisting HF. CHS was not included for the multivariable in those with pre-existent HF, as the model was unstable (1 event/ 2 participants).

Table 3

Sensitivity analyses of the effect of subclinical hypothyroidism on the risk of Heart Failure (HF) Events

| | Euthyroidism | | Subclinical Hypothyroidism | | | | | |
| | | | TSH 4.5–19.9 mIU/L | | | TSH 10–19.9 mIU/L | | |
	Events	Participants	Events	Participants	HR (95% CI)	Events	Participants	HR (95% CI)
All eligible studies								
Random-effects model	1762	22,674	40	2068	1.26 (0.91, 1.74)	40	224	1.86 (1.27, 2.72)
Fixed-effects model	1762	22,674	40	2068	1.10 (0.96, 1.26)	40	224	1.81 (1.32, 2.49)
Excluding those with thyroid medication use *								
At baseline	1730	22,351	33	1937	1.28 (0.88, 1.87)	33	192	1.36 (0.92, 1.99)
At baseline and during follow-up†	1696	22,238	24	1732	1.26 (0.93, 1.69)	24	146	2.37 (1.59, 3.54)
Excluding those with missing FT4 ‡	1762	22,674	39	1575	1.34 (0.93, 1.95)	39	220	1.91 (1.26, 2.88)
Outcomes								
Three studies with formal adjudication procedures§	1205	9943	27	1274	0.96 (0.82, 1.12)	27	129	1.66 (0.95, 2.91)
Further adjustments of multivariate models								
Plus body mass index, creatinin and atrial fibrillation at baseline//	1326	10,644	36	1342	1.13 (0.86, 1.48)	36	144	1.51 (1.06, 2.15)
Plus lipid-lowering and antihypertensive medications#	1336	10,681	35	1347	1.14 (0.85, 1.53)	35	143	1.55 (1.09, 2.19)
Excluding study of cardiac patients (Bari)	1709	22,385	33	2029	1.04 (0.88, 1.22)	33	214	1.62 (1.15, 2.29)
Excluding preexisting HF **	1630	22,234	31	2005	1.04 (0.87, 1.26)	31	211	1.67 (1.12, 2.49)
Excluding baseline Atrial Fibrillation ***	1698	22,500	37	2043	1.26 (0.92, 1.72)	37	220	1.81 (1.27, 2.58)

Abbreviations: CI, Confidence Interval; FT4, Free Thyroxine; HF, Heart Failure; HR, Hazard Ratio; NA, data not applicable; TSH, Thyroid-Stimulating Hormone. HR are all age and sex-adjusted unless stated otherwise.

*
The numbers of participants with thyroid medication appear in Table 1.

†
Leiden was excluded from this stratum because of zero participant with subclinical hypothyroidism.

‡
493 participants with subclinical hypothyroidism and missing t4 were excluded: 21 participants excluded from CHS, 230 from Health ABC (T4 not measured in Health ABC when TSH 7.0), 241 from PROSPER and 1 from Leiden

§
Formal adjudication procedures with experts adjudicating each case were only performed in CHS, HABC and PROSPER. See eTable 1.

//
Data on creatinin and atrial fibrillation were not available at baseline for the EPIC-Norfolk study. 50 participants with missing data for body mass index, creatinine and atrial fibrillation: 9 in CHS, 24 in Health ABC and 17 in Leiden.

Data on lipid-lowering and antihypertensive medications were not available for the EPIC-Norfolk study. 8 participants with missing data for hypertensive and lipid-lowering treatment: 1 in CHS, and 7 in Health ABC.

** 503 excluded because of HF at baseline: 11 in CHS, 106 in Health ABC, 58 in Leiden (1missing value), 328 in Bari (all participants with pre-existing HF), 0 in PROSPER. Data on preexisting HF were not available for EPIC study (only preexisting overall CVD assessed); after excluding those with preexisting CVD from EPIC, HR was 1.62 (1.02, 2.58) for TSH 10–19.9 mIU/L.

*** 199 participants were excluded because of AF at baseline. 58 in CHS, 49 in Health ABC, 45 in Leiden 43 in Bari. Data were not available for EPIC-Norfolk study. Baseline AF was an exclusion criteria from PROSPER trial (4 participants had AF at baseline) 1 missing in HABC, 2 missing in Leiden. After excluding EPIC-Norfolk study, HR was 1.92 (1.24, 2.96) for TSH 10.0–19.9 mIU/L. Prevalence of baseline AF across TSH categories: 170/5615 (3.0%) for TSH 0.45–4.49 mIU/L, 20/628 (3.2%) for TSH 4.5–6.9 mIU/L, 1/174 for TSH 7.0-9.9 mIU/L (0.6%) and 4/102 (3.9%) for TSH 10.0–19.9 mIU/L.

Table 4

Stratified analyses for the association between subclinical hyperthyroidism and Heart Failure (HF) Events

	Euthyroidism		Subclinical Hyperthyroidism		HF Events	
	Events	Participants	Events	Participants	HR (95% CI) age/gender-adjusted	HR (95% CI) multivariate model*
Total population	1762	22,674	57	648	1.46 (0.94, 2.27)	1.51 (0.93, 2.44)
Gender†						
Men	977	10,793	20	219	1.22 (0.77, 1.94)	1.21 (0.77, 1.89)
Women	785	11,881	37	429	1.72 (1.02, 2.91)	1.56 (0.97, 2.50)
P for interaction					0.33	0.45
Age‡ (years)						
18–49§	15	2756	0	71	1.95 (0.10, 39.59)	2.61 (0.14, 49.09)
50–64	128	5798	4	151	1.79 (0.26, 12.34)	1.63 (0.26, 10.02)
65–79	1370	12,666	37	375	1.20 (0.82, 1.77)	1.20 (0.81, 1.76)
80	249	1454	16	51	2.34 (1.27, 4.31)	2.40 (1.19, 4.85)
P for trend					0.98	0.91
Race						
Caucasian	1573	21,541	52	615	1.49 (0.95, 2.35)	1.50 (0.95, 2.35)
Black	189	1133	5	33	1.07 (0.46, 2.51)	1.07 (0.45, 2.53)
P for interaction					0.50	0.50
TSH (mIU/L)						
0.45–4.49	1762	22,674			1 (ref)	1 (ref)
0.10–0.44			41	494	1.31 (0.88, 1.95)	1.31 (0.88, 1.94)
<0.10			16	154	1.94 (1.01, 3.72)	1.92 (0.99, 3.71)
P for trend					0.047	0.054
Preexisting CVD‖						
None	1091	18,448	33	532	1.50 (0.92, 2.44)	1.37 (0.92, 2.03)
Yes	669	4214	24	116	1.46 (0.84, 2.55)	1.44 (0.83, 2.50)
P for interaction					0.94	0.89
Preexisting HF#						
None	1205	10,247	38	273	1.49 (0.87, 2.56)	1.47 (0.84, 2.59)

	Euthyroidism		Subclinical Hyperthyroidism			HF Events	
	Events	Participants	Events	Participants	HR (95% CI) age/gender-adjusted	HR (95% CI) multivariate model [*]	
Yes	132	440	7	15	1.64 (0.56, 4.86)	1.48 (0.45, 4.91)
P for interaction					0.88	0.99

Abbreviations: CI, Confidence Interval; CVD, Cardiovascular Disease; HF, Heart Failure; HR, Hazard Ratio; NA, data not applicable; TSH, Thyroid-Stimulating Hormone.

[*] Adjusted for age, gender, systolic blood pressure, current and former smoking, total cholesterol and prevalent diabetes at baseline.

[†] These HRs were not adjusted for gender.

[‡] These HRs were adjusted for sex and age as a continuous variable to avoid residual confounding within age strata.

[§] Bari was excluded from this stratum because of no participants in subclinical hyperthyroidism group.

[||] Data on previous CVD were not available for 10 participants in EPIC and for 2 participants in Leiden-study

[#] No data available in EPIC (only preexisting overall CVD assessed), 1 missing value in Leiden. No participants in PROSPER had preexisting HF and all participants had HF at baseline in Bari study (inclusion criteria)