# Subclinical Thyroid Dysfunction and the Risk of Heart Failure Events

## An Individual Participant Data Analysis From 6 Prospective Cohorts

Baris Gencer, MD; Tinh-Hai Collet, MD; Vanessa Virgini, MD; Douglas C. Bauer, MD; Jacobijn Gussekloo, MD, PhD; Anne R. Cappola, MD, ScM; David Nanchen, MD; Wendy P.J. den Elzen, PhD; Philippe Balmer, BSc; Robert N. Luben, PhD; Massimo Iacoviello, MD; Vincenzo Triggiani, MD; Jacques Cornuz, MD, MPH; Anne B. Newman, MD, MPH; Kay-Tee Khaw, MD; J. Wouter Jukema, MD, PhD; Rudi G.J. Westendorp, MD, PhD; Eric Vittinghoff, PhD; Drahomir Aujesky, MD, MSc; Nicolas Rodondi, MD, MAS; for the Thyroid Studies Collaboration

***Background***—American College of Cardiology/American Heart Association guidelines for the diagnosis and management of heart failure recommend investigating exacerbating conditions such as thyroid dysfunction, but without specifying the impact of different thyroid-stimulation hormone (TSH) levels. Limited prospective data exist on the association between subclinical thyroid dysfunction and heart failure 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 heart failure 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 of 0.45 to 4.49 mIU/L, subclinical hypothyroidism as TSH of 4.5 to 19.9 mIU/L, and subclinical hyperthyroidism as TSH <0.45 mIU/L, the last two with normal free thyroxine levels. Among 25 390 participants, 2068 (8.1%) had subclinical hypothyroidism and 648 (2.6%) had subclinical hyperthyroidism. In age- and sex-adjusted analyses, risks of heart failure events were increased with both higher and lower TSH levels (*P* for quadratic pattern <0.01); the hazard ratio was 1.01 (95% confidence interval, 0.81–1.26) for TSH of 4.5 to 6.9 mIU/L, 1.65 (95% confidence interval, 0.84–3.23) for TSH of 7.0 to 9.9 mIU/L, 1.86 (95% confidence interval, 1.27–2.72) for TSH of 10.0 to 19.9 mIU/L (*P* for trend <0.01) and 1.31 (95% confidence interval, 0.88–1.95) for TSH of 0.10 to 0.44 mIU/L and 1.94 (95% confidence interval, 1.01–3.72) for TSH <0.10 mIU/L (*P* for trend=0.047). Risks remained similar after adjustment for cardiovascular risk factors.

***Conclusion***—Risks of heart failure events were increased with both higher and lower TSH levels, particularly for TSH ≥10 and <0.10 mIU/L. **(*Circulation*. 2012;126:1040-1049.)**

**Key Words:** cohort studies ■ epidemiology ■ heart failure ■ meta-analysis ■ thyroid



Heart failure (HF) is a frequent cause of hospitalization in people >65 years of age, with an increasing trend in the number of patients living with HF.[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 American College of Cardiology/American Heart Association 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

Received February 7, 2012; accepted June 29, 2012.

From the Department of Ambulatory Care and Community Medicine, University of Lausanne, Lausanne, Switzerland (B.G., T.-H.C., D.N., P.B., J.C.); Department of General Internal Medicine, Bern University Hospital, Bern, Switzerland (V.V., D.A., N.R.); Departments of Epidemiology and Biostatistics (D.C.B., E.V.) and Medicine (D.C.B.), University of California San Francisco; Departments of Public Health and Primary Care (J.G., W.P.J.d.E.), Cardiology (J.W.J.), and Gerontology and Geriatrics (R.G.J.W.), Leiden University Medical Center Leiden, Leiden, the Netherlands; Division of Endocrinology, Diabetes, and Metabolism, Department of Medicine, University of Pennsylvania School of Medicine, Philadelphia (A.R.C.); Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK (R.N.L., K.-T.K.); Cardiology Unit (M.I.) and Endocrinology and Metabolic Diseases (V.T.), University of Bari, Bari, Italy; Department of Epidemiology, University of Pittsburgh, Pittsburgh, PA (A.B.N.); and Netherlands Consortium for Health Ageing, Leiden, the Netherlands (R.G.J.W.).

**The online-only Data Supplement is available with this article at http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIRCULATIONAHA.112.096024/-/DC1.**

Correspondence to Nicolas Rodondi, MD, MAS, Department of General Internal Medicine, Inselspital, University of Bern, 3010 Bern, Switzerland. E-mail Nicolas.Rodondi@insel.ch



*Circulation* **is available at http://circ.ahajournals.org** **DOI: 10.1161/CIRCULATIONAHA.112.096024**

specifying the potential impact of different thyroid-stimulating hormone (TSH) levels.[8]

## Clinical Perspective on p 1049

Subclinical thyroid dysfunction is common, particularly in older individuals, with a prevalence of subclinical hypothyroidism up to 10% and of subclinical hyperthyroidism between 0.7% and 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 triiodothyronine (FT3) concentrations within their reference ranges.[10,11] Subclinical hypothyroidism and subclinical hyperthyroidism have been associated with an increased risk of coronary heart disease 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 subgroup 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 the 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 (see Methods in the online-only Data Supplement). 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 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 considered only persons taking thyroid medications (antithyroid drug or thyroxine replacement) or those with overt thyroid dysfunction (defined by abnormal TSH and FT4 levels). The updated search for additional studies until June 30, 2011, was independently assessed by 2 authors (B.G. and P.B.); any discrepancy between the authors was resolved by discussion with a third author (N.R.). The agreement rate between the 2 reviewers was 99.9% for the first screen (titles and abstracts; $\kappa$=0.66; 95% 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 (N.R. and J.G.) rated all studies for quality: methods of outcome adjudication, evaluation of confounders, and 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, sex, race), cardiovascular risk factors (total cholesterol, diabetes mellitus, blood pressure, cigarette smoking), preexisting CVD, preexisting HF, medication (lipid-lowering drugs, antihypertensive drugs, thyroxine replacement, and antithyroid medication), and other potential confounding variables for HF such as body mass index, creatinine, and atrial fibrillation (AF).

## Definition of Subclinical Thyroid Dysfunction

To maximize the comparability of the studies, we used a common definition of subclinical thyroid dysfunction based on expert reviews,[10,21] the 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 to 4.49 mIU/L, subclinical hypothyroidism as a TSH level of 4.5 to 19.9 mIU/L, and subclinical hyperthyroidism as a TSH level <0.45 mIU/L, the last two with normal FT4 levels. On the basis of previously described TSH cutoffs[13,16] and expert reviews,[10,21] subclinical hypothyroidism was subdivided into 3 groups: TSH of 4.5 to 6.9, 7.0 to 9.9, and 10.0 to 19.9 mIU/L; subclinical hyperthyroidism was subdivided into 2 groups: TSH of 0.10 to 0.44 and <0.10 mIU/L. For FT4, we used study-specific cutoffs (Table I in the online-only Data Supplement)[13] because FT4 measurements show greater intermethod 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 because the vast majority of adults with an abnormal TSH have subclinical and not overt thyroid dysfunction.[26] FT3 was measured in 2 studies (Table I in the online-only Data Supplement)[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 on the basis of all available documents (symptoms, signs, therapy, chest radiographs) within each cohort (Table I in the online-only Data Supplement). 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 coronary heart disease outcome,[12,13] and were separately analyzed in stratified analyses to explore the association between subclinical thyroid dysfunction and incident HF events and recurrent HF events.

## Potential Confounders

Primary analyses were adjusted for age and sex and then for traditional cardiovascular risk factors (systolic blood pressure, total cholesterol, smoking status, diabetes mellitus) 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, sex, 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.

**Table 1. Baseline Characteristics of Individuals in Included Studies (n=25 390)**

| Study | Description of Study Sample | n | Median Age (Range), y | Women, n (%) | Subclinical Hypothyroidism, n (%)* | Subclinical Hyperthyroidism, n (%)* | Thyroid Medication Users, n (%)† | | | Follow-Up‡ | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | At Baseline | During Follow-Up | At Any Time | Start | Median Duration (Q1-Q3), y | Person-years |
| United States | | | | | | | | | | | | |
| Cardiovascular 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 |
| Health, Aging and Body Composition 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 |
| Europe | | | | | | | | | | | | |
| European Prospective Investigation of Cancer–Norfolk 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 |
| Leiden 85-Plus Study | All adults 85 y of age 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) | 1861 |
| Bari cohort | Outpatients with HF followed up 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 |
| Prospective Study of Pravastatin in the Elderly at Risk | 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 |
| Overall | 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 |

Q1 indicates first quartile; Q3, third quartile; and HF, heart failure.

*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 the Cardiovascular Health Study and 8 participants in the Health, Aging and Body Composition Study at baseline and for all participants during follow-up in European Prospective Investigation of Cancer–Norfolk.

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

## 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 from 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 sex, 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 with graphical methods and Schoenfeld tests (all $P>0.05$). We used age- and sex-adjusted funnel plots to assess for publication bias and the Egger test.[30] In some subgroups analyses, some strata had participants with no HF events, and we used penalized likelihood methods to obtain hazard ratios (HRs) and 95% CIs,[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 (Figure I in the online-only Data Supplement); 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 had 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 of ≤5%, and all outcome adjudicators were blinded for thyroid status. A formal adjudication was done in 3 studies[15,16,18]; the other cohorts relied on hospital discharge[17,32] or general practitioners' medical records[27] (Table I in the online-only Data Supplement).

In age- and sex-adjusted analyses, the risk of HF increased in participants with both higher and lower TSH levels (the Figure) with a significant test for parabolic function across TSH categories ($P$ for quadratic pattern $<0.01$). For subclinical hypothyroidism compared with euthyroidism, the HR was 1.01 (95% CI, 0.81–1.26) for TSH of 4.5 to 6.9 mIU/L, 1.65 (95% CI, 0.84–3.23) for TSH of 7.0 to 9.9 mIU/L, and

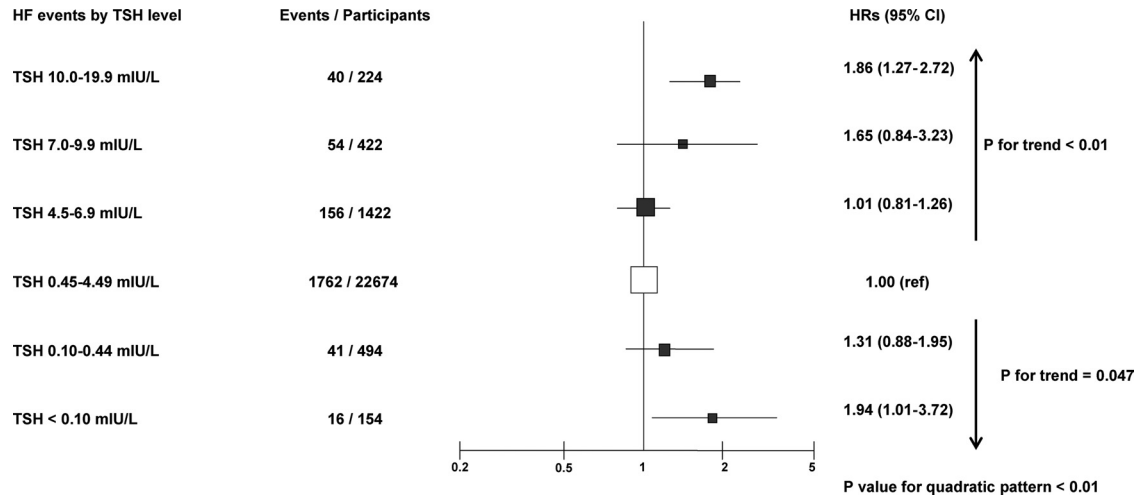



**Figure.** Hazard ratios (HRs) for heart failure (HF) events according to thyroid-stimulating hormone (TSH) levels. Age- and sex-adjusted HRs and their 95% confidence intervals (CIs) are represented by squares. Squares to the right of the solid lines indicate increased risk of HF events. Sizes of data markers are proportional to the inverse of the variance of the HRs.



1.86 (95% CI, 1.27–2.72) for TSH of 10.0 to 19.9 mIU/L (*P* for trend across higher TSH categories <0.01). For subclinical hyperthyroidism compared with euthyroidism, the HR was 1.31 (95% CI, 0.88–1.95) for TSH of 0.1 to 0.44 mIU/L and 1.94 (95% 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), the HR for HF events was 1.26 (95% CI, 0.91–1.74) in age- and sex-adjusted analyses with heterogeneity ($I^2$=77%) across studies (Figure II in the online-only Data Supplement). 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 of age), HF events were not increased, and the interaction test across age categories was not significant (*P*>0.10). We found slightly higher risks in men and whites but without significant interaction test (*P*>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 the HR remaining significant among those with TSH levels ≥10.0 mIU/L (HR, 1.59; 95% CI, 1.15–2.19). Sensitivity analyses (Table 3) yielded similar results. After the exclusion of 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; 95% CI, 1.59–3.54). Risks remained elevated among those with TSH ≥10.0 mIU/L after the exclusion of those with missing FT4 values, after further adjustment for additional HF risk factors (creatinine, body mass index, and preexisting AF), and after exclusion of those with preexisting AF. After exclusion of the Bari study (all with preexisting HF),[17] the HR decreased to 1.62 (95% CI, 1.15–2.29) with a low heterogeneity ($I^2$=0%).[29] Risks were lower after the analyses were limited to cohorts with formal adjudication procedures by experts; this analysis was possible for only 3 studies of older adults (Table I in the online-only Data Supplement).

Among all participants with subclinical hyperthyroidism (Table 4), the HR for HF events in age- and sex-adjusted analyses was 1.46 (95% CI, 0.94–2.27) compared with euthyroidism with heterogeneity ($I^2$=61%) across studies (Figure III in the online-only Data Supplement). In contrast to subclinical hypothyroidism, the risk was significantly increased among participants ≥80 years of age (HR, 2.34; 95% CI, 1.27–4.31), but there was not a significant trend across age categories (*P*=0.98). We found higher risks among women and whites, but the interaction test was not significant (*P*>0.30), and for preexisting CVD or preexisting HF. Risks were similar after further adjustment for cardiovascular risk factors.

Among participants with TSH <0.10 mIU/L, the HR for HF events was 1.94 (95% CI, 1.01–3.72) in age- and sex-adjusted analyses. In sensitivity analyses (Table II in the online-only Data Supplement), with those using thyroid medication at baseline excluded, the HR was 1.80 mIU/L (95% CI, 1.04–3.13). Risks were similar after further adjustments for HF potential confounding risk factors (body mass index, creatinine, and AF), after the exclusion of those with missing FT4 or abnormal FT3, and after the exclusion of those with preexisting HF or preexisting AF.

We found limited evidence of publication bias with visual assessment of age- and sex-adjusted funnel plots, although the Bari study might be an outlier with no corresponding negative study of similar size, and with the Egger test for subclinical hypothyroidism (*P*=0.23) and 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 TSH levels in the normal range, with statistically significant increased risks among those with TSH ≥10.0 mIU/L (HR, 1.86; 95% CI, 1.27–2.72) and those with TSH <0.10 mIU/L (HR, 1.94; 95% CI, 1.01–3.72). The HF risks were explained mainly by the degree of thyroid dysfunction, with an observed parabolic

**Table 2. Stratified Analyses for the Association Between Subclinical Hypothyroidism and Heart Failure Events**

| | HF Events | | | | | |
|---|---|---|---|---|---|---|
| | Euthyroidism | | Subclinical Hypothyroidism | | HR (95% CI), Age/Sex-Adjusted | HR (95% CI), Multivariate Model* |
| | Events | Participants | Events | Participants | | |
| Total population | 1762 | 22 674 | 250 | 2068 | 1.26 (0.91–1.74) | 1.22 (0.93–1.59) |
| Sex† | | | | | | |
| Male | 977 | 10 793 | 120 | 730 | 1.33 (0.91–1.94) | 1.28 (0.93–1.76) |
| Female | 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, y‡ | | | | | | |
| 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 | | | | | | |
| White | 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 (Referent) | 1 (Referent) |
| 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 |
| 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 |

HF indicates heart failure; HR, hazard ratio; CI, confidence interval; TSH, thyroid-stimulating hormone; and CVD, cardiovascular disease.

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

†These HRs were not adjusted for sex.

‡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 only 1 participant with subclinical hypothyroidism leading to unstable estimates.

‖The Cardiovascular Health Study (CHS) was excluded from this stratum because of no participants with subclinical hypothyroidism.

¶Data on previous CVD were not available for 11 participants in the European Prospective Investigation of Cancer (EPIC)–Norfolk and for 2 participants in the Leiden 85-Plus Study.

#No data were available in the EPIC–Norfolk (only preexisting overall CVD assessed); there was 1 missing value in Leiden 85-Plus Study, and by inclusion criteria, all participants had HF at baseline in Bari study. No participants in the Prospective Study of Pravastatin in the Elderly at Risk had preexisting HF. The CHS was not included for the multivariable in those with preexisting HF because the model was unstable (1 event/2 participants).

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 the exclusion of those with preexisting HF or preexisting AF. Further adjustment for cardiovascular risk factors and other available HF confounding risk factors did not significantly change the association with HF events, although part of the risk seemed to be mediated by cardiovascular risk factors because 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.

**Table 3. Sensitivity Analyses of the Effect of Subclinical Hypothyroidism on the Risk of Heart Failure Events**

| | Euthyroidism, n | | Subclinical Hypothyroidism | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | TSH 4.5–19.9 mIU/L | | | TSH 10.0–19.9 mIU/L | | |
| | Events | Participants | Events, n | Participants, n | HR (95% CI) | Events, n | Participants, n | HR (95% CI) |
| All eligible studies | | | | | | | | |
| Random-effects model | 1762 | 22 674 | 250 | 2068 | 1.26 (0.91–1.74) | 40 | 224 | 1.86 (1.27–2.72) |
| Fixed-effects model | 1762 | 22 674 | 250 | 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 | 237 | 1937 | 1.28 (0.88–1.87) | 33 | 192 | 1.36 (0.92–1.99) |
| At baseline and during follow-up† | 1696 | 22 238 | 197 | 1732 | 1.26 (0.93–1.69) | 24 | 146 | 2.37 (1.59–3.54) |
| Excluding those with missing FT4‡ | 1762 | 22 674 | 208 | 1575 | 1.34 (0.93–1.95) | 39 | 220 | 1.91 (1.26–2.88) |
| Outcomes | | | | | | | | |
| 3 Studies with formal adjudication procedures§ | 1205 | 9943 | 186 | 1274 | 0.96 (0.82–1.12) | 27 | 129 | 1.66 (0.95–2.91) |
| Further adjustments of multivariate models | | | | | | | | |
| Plus body mass index, creatinine, and atrial fibrillation at baseline‖ | 1326 | 10 644 | 213 | 1342 | 1.13 (0.86–1.48) | 36 | 144 | 1.51 (1.06–2.15) |
| Plus lipid-lowering and antihypertensive medications¶ | 1336 | 10 681 | 212 | 1347 | 1.14 (0.85–1.53) | 35 | 143 | 1.55 (1.09–2.19) |
| Excluding study of cardiac patients (Bari) | 1709 | 22 385 | 229 | 2029 | 1.04 (0.88–1.22) | 33 | 214 | 1.62 (1.15–2.29) |
| Excluding preexisting HF# | 1630 | 22 234 | 217 | 2005 | 1.04 (0.87–1.26) | 31 | 211 | 1.67 (1.12–2.49) |
| Excluding baseline atrial fibrillation** | 1698 | 22 500 | 238 | 2043 | 1.26 (0.92–1.72) | 37 | 220 | 1.81 (1.27–2.58) |

TSH indicates thyroid-stimulating hormone; HR, hazard ratio; CI, confidence interval; FT4, free thyroxine; and HF, heart failure. HRs 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 0 participants with subclinical hypothyroidism.

‡A total of 493 participants with subclinical hypothyroidism and missing FT4 were excluded: 21 participants excluded from the Cardiovascular Health Study (CHS), 230 from the Health, Aging and Body Composition Study (HABC; FT4 was not measured in HABC when TSH ≤7.0 mIU/L), 241 from the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER), and 1 from Leiden 85-Plus Study.

§Formal adjudication procedures with experts adjudicating each case were performed only in CHS, HABC, and PROSPER. See Table I in the online-only Data Supplement.

‖Data on creatinine and atrial fibrillation were not available at baseline for the European Prospective Investigation of Cancer (EPIC)–Norfolk study. 50 participants with missing data for body mass index, creatinine, and atrial fibrillation: 9 in CHS, 24 in HABC, and 17 in Leiden.

¶Data on lipid-lowering and antihypertensive medications were not available for the EPIC-Norfolk study. Eight participants had missing data for hypertensive and lipid-lowering treatment: 1 in CHS and 7 in HABC.

#A total of 503 were excluded because of HF at baseline: 11 in CHS, 106 in HABC, 58 in Leiden 85-Plus Study (1 missing value), 328 in Bari (all participants with preexisting HF), and 0 in PROSPER. Data on preexisting HF were not available for EPIC-Norfolk (only preexisting overall CVD assessed); after the exclusion of those with preexisting CVD from EPIC-Norfolk, the HR was 1.62 (95% CI, 1.02–2.58) for TSH of 10.0 to 19.9 mIU/L.

**A total of 199 participants were excluded because of AF at baseline: 58 in CHS, 49 in HABC, 45 in Leiden 85-Plus Study, and 43 in Bari. Data were not available for EPIC-Norfolk. Baseline AF was an exclusion criteria from PROSPER trial (4 participants had AF at baseline); 1 was missing in HABC and 2 were missing in Leiden. After exclusion of EPIC-Norfolk, the HR was 1.92 (95% CI, 1.24–2.96) for TSH of 10.0 to 19.9 mIU/L. Prevalence of baseline AF across TSH categories: 170 of 5615 (3.0%) for TSH of 0.45 to 4.49 mIU/L, 20 of 628 (3.2%) for TSH of 4.5 to 6.9 mIU/L, 1 of 174 (0.6%) for TSH of 7.0 to 9.9 mIU/L, and 4 of 102 (3.9%) for TSH of 10.0 to 19.9 mIU/L.

To the best of 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 compared 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; 95% CI, 1.19–5.60 for TSH of 7.0–9.9 mIU/L; and HR, 3.26; 95% CI, 1.37–7.77 for TSH ≥10.0 mIU/L) over a 4-year follow-up, with a higher risk for recurrent HF events among those with preexisting HF (HR, 7.62; 95% CI, 2.25–25.77)[15]; these data were updated with 8-year follow-up in the present analysis. The Cardiovascular Health Study[16] reported an increased risk of HF events among subjects with TSH ≥10.0

**Table 4. Stratified Analyses for the Association Between Subclinical Hyperthyroidism and Heart Failure Events**

| | HF Events | | | | | |
|---|---|---|---|---|---|---|
| | Euthyroidism, n | | Subclinical Hyperthyroidism, n | | HR (95% CI), Age/Sex-Adjusted | HR (95% CI), Multivariate Model* |
| | Events | Participants | Events | Participants | | |
| Total population | 1762 | 22 674 | 57 | 648 | 1.46 (0.94–2.27) | 1.51 (0.93–2.44) |
| Sex† | | | | | | |
| Male | 977 | 10 793 | 20 | 219 | 1.22 (0.77–1.94) | 1.21 (0.77–1.89) |
| Female | 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, y‡ | | | | | | |
| 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 | | | | | | |
| White | 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 (Referent) | 1 (Referent) |
| 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) |
| Yes | 132 | 440 | 7 | 15 | 1.64 (0.56–4.86) | 1.48 (0.45–4.91) |
| *P* for interaction | | | | | 0.88 | 0.99 |

HF indicates heart failure; HR, hazard ratio; CI, confidence interval; TSH, thyroid-stimulating hormone; and CVD, cardiovascular disease.

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

†These HRs were not adjusted for sex.

‡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 the subclinical hyperthyroidism group.

‖Data on previous CVD were not available for 10 participants in European Prospective Investigation of Cancer (EPIC)–Norfolk and for 2 participants in the Leiden 85-Plus Study.

¶No data were available in EPIC-Norfolk (only preexisting overall CVD assessed); 1 value was missing in Leiden 85-Plus Study. No participants in Prospective Study of Pravastatin in the Elderly at Risk had preexisting HF, and all participants had HF at baseline in the Bari study (inclusion criteria).

mIU/L (HR, 1.88; 95% CI, 1.05–3.34) over a 12-year follow-up; these data were updated with 14-year follow-up in the present analysis. 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; 95% CI, 1.12–8.11) and among those with suppressed TSH <0.10 mIU/L (HR, 4.61; 95% CI, 1.71–12.47). The Bari study, which examined only patients with preexisting HF,[17] reported an increased risk of recurrent HF events among participants with subclinical hypothyroidism (HR, 2.03; 95% CI, 1.16–3.55) but without a categorization of TSH levels. We previously found a similar pattern with an increased risk of coronary heart disease 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 levels and that 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 decreased left ventricular stroke volume, a decrease in 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 explain the associated risk of HF events with higher TSH levels in subclinical hypothyroidism reported in our study. The increased risk of coronary heart disease events with subclinical hypothyroidism[13] might also contribute to the development of HF because coronary heart disease is a common cause of HF.[34,35] Restoration of a euthyroid state in patients with subclinical hypothyroidism has been associated with normalization of some structural cardiac parameters,[9,36] and 1 randomized controlled trial found that thyroxine therapy in patients with subclinical hypothyroidism reduced the ratio of pre-ejection period to left ventricular ejection time,[37] but no large randomized controlled trial of the impact of thyroxine therapy on HF events has been conducted yet. In contrast to overt hyperthyroidism, only a few studies 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 AF with subclinical hyperthyroidism,[25,38] which might predispose to the development of HF. Recently, an individual participant analysis has reported an increased risk of AF 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 to 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 2 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 related mainly to hospitalizations, which might lower the rates of HF events. Because some patients might develop HF without hospitalization, the rate of recorded HF events is likely underestimated.[15,39] 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[40]; such misclassification was probably nondifferential because all HF outcome adjudications were blinded to thyroid status, and nondifferential misclassification would lower any potential associations. Even with the large number of individual participants, some subgroup analyses, particularly among those <50 years of age 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 because of a lack of power. In particular, a possible effect of sex and race might be explored in future larger studies. Finally, the studied population had limited data on young adults and nonwhite populations, which limits the generalization of our results to the entire population.

## Conclusions

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 and 6.99 mIU/L and TSH levels between 0.10 and 0.44 mIU/L), the risk of HF was not increased compared with euthyroid participants. Similar to previous studies,[13] we found that subclinical thyroid dysfunction is a heterogeneous entity with varying risks of CVD according to TSH levels. The American College of Cardiology/American Heart Association guidelines for the diagnosis and management of HF in adults recommend measuring the thyroid function to investigate conditions that might exacerbate HF but without specifying the potential impact of different TSH levels.[8] Our findings contribute to a better interpretation of TSH levels in the prevention and investigation of HF. Pending results from randomized controlled trials, the findings of our study might be useful to define the TSH threshold for thyroid medication among participants with subclinical thyroid dysfunction, although clinical decisions based only on observational studies should be made with great caution because 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.

## Sources of Funding

This study was supported by a grant from the Swiss National Science Foundation (SNSF 320030-138267; principal investigator, Dr Rodondi). Dr Gencer's research on cardiovascular prevention is supported by a grant from the Swiss National Science Foundation (SNSF SPUM 33CM30-124112). The Cardiovascular Health Study and the research reported in this article were supported by contracts N01-HC-80007, N01-HC-85079 through N01-HC-85086, N01-HC-35129, N01 HC-15103, N01 HC-55222, N01-HC-75150, and N01-HC-45133 and grant U01 HL080295 from the National Heart, Lung, and Blood Institute, with additional funding from the National Institute of Neurological Disorders and Stroke. Additional support was provided through grants R01 AG-15928, R01 AG-20098,

AG-027058, and AG-032317 from the National Institute on Aging; grant R01 HL-075366 from the National Heart, Lung, and Blood Institute; and grant P30-AG-024827 from the University of Pittsburgh Claude D. Pepper Older Americans Independence Center. A full list of principal investigators and institutions of the Cardiovascular Health can be found at http://www.chs-nhlbi.org. The thyroid measurements in the Cardiovascular Health Study were supported by an American Heart Association Grant-in-Aid (to Dr Fried). The Health, Aging, and Body Composition Study was supported by National Institute on Aging contracts N01-AG-6-2101, N01-AG-6-2103, and N01-AG-6-2106; National Institutes of Health grant R01-AG028050; and National Institute of Nursing Research grant R01-NR012459. The National Institute on Aging funded the Health Aging, and Body Composition study. The Netherlands Genomics Initiative/Netherlands Organization for Scientific Research (NGI/NWO; 05040202 and 050-060-810 Netherlands Consortium for Health Aging to Drs Westendorp and Jukema). The original PROSPER study was supported by an unrestricted, investigator-initiated grant from Bristol-Myers Squibb. The Leiden-85 plus Study was partly funded by the Dutch Ministry of Health, Welfare, and Sports. The European Prospective Investigation of Cancer–Norfolk Study was supported by research grants from the UK Medical Research Council and the UK Cancer Research. Dr Newman was supported by grant AG-023629 from the National Institute on Aging. The majority of the sponsors had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; or preparation, review, or approval of the manuscript, except the National Institute on Aging, which funded the Health, Aging, and Body Composition study, reviewed the manuscript and approved its publication.

## Disclosures

None.

## References

1. Curtis LH, Whellan DJ, Hammill BG, Hernandez AF, Anstrom KJ, Shea AM, Schulman KA. Incidence and prevalence of heart failure in elderly persons, 1994–2003. *Arch Intern Med*. 2008;168:418–424.
2. Roger VL, Weston SA, Redfield MM, Hellermann-Homan JP, Killian J, Yawn BP, Jacobsen SJ. Trends in heart failure incidence and survival in a community-based population. *JAMA*. 2004;292:344–350.
3. Kalogeropoulos A, Georgiopoulou V, Kritchevsky SB, Psaty BM, Smith NL, Newman AB, Rodondi N, Satterfield S, Bauer DC, Bibbins-Domingo K, Smith AL, Wilson PW, Vasan RS, Harris TB, Butler J. Epidemiology of incident heart failure in a contemporary elderly cohort: the Health, Aging, and Body Composition Study. *Arch Intern Med*. 2009;169:708–715.
4. Haldeman GA, Croft JB, Giles WH, Rashidee A. Hospitalization of patients with heart failure: National Hospital Discharge Survey, 1985 to 1995. *Am Heart J*. 1999;137:352–360.
5. Bleumink GS, Knetsch AM, Sturkenboom MC, Straus SM, Hofman A, Deckers JW, Witteman JC, Stricker BH. Quantifying the heart failure epidemic: prevalence, incidence rate, lifetime risk and prognosis of heart failure: the Rotterdam Study. *Eur Heart J*. 2004;25:1614–1619.
6. Butler J, Kalogeropoulos A, Georgiopoulou V, Belue R, Rodondi N, Garcia M, Bauer DC, Satterfield S, Smith AL, Vaccarino V, Newman AB, Harris TB, Wilson PW, Kritchevsky SB. Incident heart failure prediction in the elderly: the Health ABC Heart Failure Score. *Circ Heart Fail*. 2008;1:125–133.
7. Butler J, Kalogeropoulos A. Worsening heart failure hospitalization epidemic: we do not know how to prevent and we do not know how to treat! *J Am Coll Cardiol*. 2008;52:435–437.
8. Jessup M, Abraham WT, Casey DE, Feldman AM, Francis GS, Ganiats TG, Konstam MA, Mancini DM, Rahko PS, Silver MA, Stevenson LW, Yancy CW. 2009 Focused update: ACCF/AHA guidelines for the diagnosis and management of heart failure in adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. *Circulation*. 2009;119:1977–2016.
9. Biondi B, Cooper DS. The clinical significance of subclinical thyroid dysfunction. *Endocr Rev*. 2008;29:76–131.
10. Surks MI, Ortiz E, Daniels GH, Sawin CT, Col NF, Cobin RH, Franklyn JA, Hershman JM, Burman KD, Denke MA, Gorman C, Cooper RS, Weissman NJ. Subclinical thyroid disease: scientific review and guidelines for diagnosis and management. *JAMA*. 2004;291:228–238.
11. Cooper DS, Biondi B. Subclinical thyroid disease. *Lancet*. 2012;379:1142–1154.
12. Collet TH, Gussekloo J, Bauer DC, den Elzen WP, Cappola AR, Balmer P, Iervasi G, Asvold BO, Sgarbi JA, Volzke H, Gencer B, Maciel RM, Molinaro S, Bremner A, Luben RN, Maisonneuve P, Cornuz J, Newman AB, Khaw KT, Westendorp RG, Franklyn JA, Vittinghoff E, Walsh JP, Rodondi N; Thyroid Studies Collaboration. Subclinical hyperthyroidism and the risk of coronary heart disease and mortality. *Arch Intern Med*. 2012;172:799–809.
13. Rodondi N, den Elzen WP, Bauer DC, Cappola AR, Razvi S, Walsh JP, Asvold BO, Iervasi G, Imaizumi M, Collet TH, Bremner A, Maisonneuve P, Sgarbi JA, Khaw KT, Vanderpump MP, Newman AB, Cornuz J, Franklyn JA, Westendorp RG, Vittinghoff E, Gussekloo J. Subclinical hypothyroidism and the risk of coronary heart disease and mortality. *JAMA*. 2010;304:1365–1374.
14. Ochs N, Auer R, Bauer DC, Nanchen D, Gussekloo J, Cornuz J, Rodondi N. Meta-analysis: subclinical thyroid dysfunction and the risk for coronary heart disease and mortality. *Ann Intern Med*. 2008;148:832–845.
15. Rodondi N, Newman AB, Vittinghoff E, de Rekeneire N, Satterfield S, Harris TB, Bauer DC. Subclinical hypothyroidism and the risk of heart failure, other cardiovascular events, and death. *Arch Intern Med*. 2005;165:2460–2466.
16. Rodondi N, Bauer DC, Cappola AR, Cornuz J, Robbins J, Fried LP, Ladenson PW, Vittinghoff E, Gottdiener JS, Newman AB. Subclinical thyroid dysfunction, cardiac function, and the risk of heart failure: the Cardiovascular Health Study. *J Am Coll Cardiol*. 2008;52:1152–1159.
17. Iacoviello M, Guida P, Guastamacchia E, Triggiani V, Forleo C, Catanzaro R, Cicala M, Basile M, Sorrentino S, Favale S. Prognostic role of sub-clinical hypothyroidism in chronic heart failure outpatients. *Curr Pharm Des*. 2008;14:2686–2692.
18. Nanchen D, Gussekloo J, Westendorp RG, Stott DJ, Jukema JW, Trompet S, Ford I, Welsh P, Sattar N, Macfarlane PW, Mooijaart SP, Rodondi N, de Craen AJ. Subclinical thyroid dysfunction and the risk of heart failure in older persons at high cardiovascular risk. *J Clin Endocrinol Metab*. 2012;97:852–861.
19. Galli E, Pingitore A, Iervasi G. The role of thyroid hormone in the pathophysiology of heart failure: clinical evidence. *Heart Fail Rev*. 2010;15:155–169.
20. Biondi B, Palmieri EA, Lombardi G, Fazio S. Effects of subclinical thyroid dysfunction on the heart. *Ann Intern Med*. 2002;137:904–914.
21. Helfand M. Screening for subclinical thyroid dysfunction in nonpregnant adults: a summary of the evidence for the U.S. Preventive Services Task Force. *Ann Intern Medicine*. 2004;140:128–141.
22. Gharib H, Tuttle RM, Baskin HJ, Fish LH, Singer PA, McDermott MT. Subclinical thyroid dysfunction: a joint statement on management from the American Association of Clinical Endocrinologists, the American Thyroid Association, and the Endocrine Society. *J Clin Endocrinol Metab*. 2005;90:581–585; discussion 586–587.
23. Sterne JA, Egger M, Smith GD. Systematic reviews in health care: Investigating and dealing with publication and other biases in meta-analysis. *BMJ*. 2001;323:101–105.
24. Simmonds MC, Higgins JP, Stewart LA, Tierney JF, Clarke MJ, Thompson SG. Meta-analysis of individual patient data from randomized trials: a review of methods used in practice. *Clin Trials*. 2005;2:209–217.
25. Cappola AR, Fried LP, Arnold AM, Danese MD, Kuller LH, Burke GL, Tracy RP, Ladenson PW. Thyroid status, cardiovascular risk, and mortality in older adults. *JAMA*. 2006;295:1033–1041.
26. Hollowell JG, Staehling NW, Flanders WD, Hannon WH, Gunter EW, Spencer CA, Braverman LE. Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). *J Clin Endocrinol Metab*. 2002;87:489–499.
27. Gussekloo J, van Exel E, de Craen AJ, Meinders AE, Frolich M, Westendorp RG. Thyroid status, disability and cognitive function, and survival in old age. *JAMA*. 2004;292:2591–2599.
28. Stewart LA, Clarke MJ. Practical methodology of meta-analyses (overviews) using updated individual patient data. Cochrane Working Group. *Stat Med*. 1995;14:2057–2079.
29. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327:557–560.

30. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315:629–634.
31. Heinze G, Schemper M. A solution to the problem of monotone likelihood in Cox regression. *Biometrics*. 2001;57:114–119.
32. Boekholdt SM, Titan SM, Wiersinga WM, Chatterjee K, Basart DC, Luben R, Wareham NJ, Khaw KT. Initial thyroid status and cardiovascular risk factors: the EPIC-Norfolk prospective population study. *Clin Endocrinol*. 2010;72:404–410.
33. Redfield MM, Jacobsen SJ, Burnett JC Jr, Mahoney DW, Bailey KR, Rodeheffer RJ. Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. *JAMA*. 2003;289:194–202.
34. Wilhelmsen L, Rosengren A, Eriksson H, Lappas G. Heart failure in the general population of men: morbidity, risk factors and prognosis. *J Intern Med*. 2001;249:253–261.
35. Lloyd-Jones DM, Larson MG, Leip EP, Beiser A, D'Agostino RB, Kannel WB, Murabito JM, Vasan RS, Benjamin EJ, Levy D. Lifetime risk for developing congestive heart failure: the Framingham Heart Study. *Circulation*. 2002;106:3068–3072.
36. Biondi B. Cardiovascular effects of mild hypothyroidism. *Thyroid*. 2007;17:625–630.
37. Monzani F, Di Bello V, Caraccio N, Bertini A, Giorgi D, Giusti C, Ferrannini E. Effect of levothyroxine on cardiac function and structure in subclinical hypothyroidism: a double blind, placebo-controlled study. *J Clin Endocrinol Metab*. 2001;86:1110–1115.
38. Sawin CT, Geller A, Wolf PA, Belanger AJ, Baker E, Bacharach P, Wilson PW, Benjamin EJ, D'Agostino RB. Low serum thyrotropin concentrations as a risk factor for atrial fibrillation in older persons. *N Engl J Med*. 1994;331:1249–1252.
39. Schellenbaum GD, Heckbert SR, Smith NL, Rea TD, Lumley T, Kitzman DW, Roger VL, Taylor HA, Psaty BM. Congestive heart failure incidence and prognosis: case identification using central adjudication versus hospital discharge diagnoses. *Ann Epidemiol*. 2006;16:115–122.
40. Schellenbaum GD, Rea TD, Heckbert SR, Smith NL, Lumley T, Roger VL, Kitzman DW, Taylor HA, Levy D, Psaty BM. Survival associated with two sets of diagnostic criteria for congestive heart failure. *Am J Epidemiol*. 2004;160:628–635.

## CLINICAL PERSPECTIVE

Analysis of individual participant data from all available prospective cohorts suggests that the risk of heart failure is increased with both higher and lower levels of thyroid-stimulating hormone compared with the normal range, particularly in those with thyroid-stimulating hormone levels ≥10.0 or <0.10 mIU/L. These findings might lead to a better interpretation of thyroid-stimulating hormone levels; the latest American College of Cardiology/American Heart Association guidelines for the diagnosis and management of heart failure in adults recommend measurement of thyroid function to investigate conditions that might exacerbate heart failure without specifying the clinical impact of different thyroid-stimulating hormone levels. In the absence of randomized controlled trials that would give definitive evidence about the impact of treatment on heart failure, our findings might be useful for defining thyroid-stimulating hormone threshold for thyroid medication, although clinical decisions based only on observational studies should be made with great caution. To definitively clarify this issue, a randomized controlled trial (Thyroid Hormone Replacement for Subclinical Hypo-Thyroidism Trial ([TRUST] trial; www.trustthyroidtrial.com) has just been started in Europe among elderly individuals with subclinical hypothyroidism to assess the impact of thyroxine replacement therapy on cardiovascular outcomes, including heart failure events.

# Subclinical Thyroid Dysfunction and the Risk of Heart Failure Events: An Individual Participant Data Analysis From 6 Prospective Cohorts

Baris Gencer, Tinh-Hai Collet, Vanessa Virgini, Douglas C. Bauer, Jacobijn Gussekloo, Anne R. Cappola, David Nanchen, Wendy P.J. den Elzen, Philippe Balmer, Robert N. Luben, Massimo Iacoviello, Vincenzo Triggiani, Jacques Cornuz, Anne B. Newman, Kay-Tee Khaw, J. Wouter Jukema, Rudi G.J. Westendorp, Eric Vittinghoff, Drahomir Aujesky and Nicolas Rodondi

*Circulation.* 2012;126:1040-1049; originally published online July 19, 2012;
doi: 10.1161/CIRCULATIONAHA.112.096024
*Circulation* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7322. Online ISSN: 1524-4539

**Supplemental Material**

## Supplemental Methods

### Data Sources and Search Strategies

We updated the systematic literature search done for our recent analysis on the risks associated with subclinical hypothyroidism[2], in MEDLINE and EMBASE databases, from 1950 to June 30, 2011, without language restriction, on the association between subclinical thyroid dysfunction and mortality (cardiovascular and total), non-fatal coronary heart disease, atrial fibrillation or heart failure. We did our search on an Ovid (MEDLINE) server by using broadly defined Medical Subject Headings: *thyroid diseases*, *hypothyroidism*, *hyperthyroidism*, *thyroid hormones, thyrotropin, heart failure, atrial fribrillation, mortality*, *myocardial ischemia*, *survival*, and *cardiovascular diseases*; and the following keywords: *subclinical hypothyroidism*, *subclinical hyperthyroidism*, *subclinical dysthyroidism*, and *subclinical thyroid*; combined with the filter designed by knowledge information specialists from *BMJ* to select prospective studies (MEDLINE cohort-study filter)[3] but without their year limitation. We did our search in EMBASE using similar terms. We also searched bibliography of key articles and those articles included in this review.

## Supplemental Table 1. Definitions of Subclinical Thyroid Dysfunction and HF Events

| Study | Subclinical hypothyroidism | Subclinical hyperthyroidism | HF events: definition | Methods for HF ascertainment |
|---|---|---|---|---|
| Cardiovascular Health Study[4] | TSH ≥4.5 mU/L & TSH <20 mU/L, normal FT4 0.7-1.7 ng/dl (9-22 pmol/l) or missing FT4 (21/492, 4.3%) | TSH < 0.45 mU/L & normal FT4 0.7-1.7 ng/dl (9-22 pmol/l) or missing FT4 (33/43, 76.7%). FT3 value not available for SA. | Based on diagnosis from a physician and consideration of symptoms, signs, chest radiographs, and treatment of HF (current prescription for a diuretic agent and digitalis or as vasodilator) | Based on interview, review of medical records, and other support documents. Adjudication by a panel of experts without physician knowledge of thyroid status. |
| Health Age, Body, Composition (Health ABC) Study[5] | TSH ≥4.5 mU/L & TSH <20 mU/L, normal FT4 0.8-1.8 ng/dl (10.3-23.2 pmol/l) or missing FT4 (230/335, 68.7%) [a] | TSH < 0.45 mU/L & normal FT4 0.8-1.8 ng/dl (10.3-23.2 pmol/l) or missing FT4 (57/82, 69.5%) [a]. FT3 value not available for SA. | The HF criteria required at least this diagnosis from a physician and treatment for HF (current prescription for a diuretic agent and either digitalis or a vasodilatator) | Based on symptoms, signs, chest x-ray film results, and echocardiography findings. Adjudication by a panel of experts without physician knowledge of thyroid status. |
| EPIC-Norfolk Study[6] | TSH ≥4.5 mU/L & TSH <20 mU/L, normal FT4 0.7-1.6 ng/dl (9-20 pmol/L) or missing FT4 (0/720) | TSH < 0.45 mU/L & normal FT4 0.7-1.6 ng/dl (9-20 pmol/L) or missing FT4 (0/360). FT3 value not available for SA. | HF events were defined by an hospitalization due to HF. | Hospital discharge coding by data linkage with NHS central-register. |
| Leiden 85-plus Study[7] | TSH ≥4.5 mU/L & TSH <20 mU/L, normal FT4 1.0-1.8 ng/dl (13-23 pmol/L) or missing FT4 (1/35, 2.9%) | TSH < 0.45 mU/L & normal FT4 1.0-1.8 ng/dl (13-23 pmol/L) or missing FT4 (0/7), & normal FT3 305-532 pg/dL (only in SA) | HF was defined on the basis of a clinical diagnosis of acute HF events from a physician, who considered symptoms, signs, chest radiographs, including hospitalisation. | Annual interview of treating general practitioner and review of overall medical records of general practitioners |
| Bari Study[8] | TSH ≥4.5 mU/L & TSH <20 mU/L, normal FT4 0.7-1.8 ng/dl (9-23.2 pmol/l) or missing FT4 (0/39) | TSH <0.45 mU/L & normal FT4 0.7-1.8 ng/dL (9-23.2 pmol/l) or missing FT4 (0/39), & normal FT3 230-420 pg/dL (only in SA) | Progression of HF: death, urgent heart transplantation or hospitalization due to worsening HF. | Hospital discharge records, ECG, echocardiography findings |
| Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) [9] | TSH ≥4.5 mU/L & TSH <20 mU/L, normal FT4 0.9-1.4 ng/dl (12-18 pmol/l) or missing FT4 (241/444, 54.3%) | TSH < 0.45 mU/L & normal FT4 0.9-1.4 ng/dl (12-18 pmol/L) or missing FT4 (62/133, 46.6%). FT3 value not available for SA. | HF events were defined by an hospitalization due to HF. | A panel of experts adjudicated HF hospitalization, based on hospital discharge records, symptoms, signs, chest x-ray film results, and echocardiography findings. |

Abbreviations: HF: Heart Failure; TSH: Thyroid-Stimulating Hormone; T4: Thyroxine; FT4: Free Thyroxine; FT3 Free Triiodothyronine: SA: Sensitivity Analysis

[a] fT4 measured only in participants with TSH ≥ 7mU/L in this cohort, as overt hypothyroidism is very uncommon in participants with TSH < 7.0 mU/L.

**Supplemental Table 2. Sensitivity analyses of the effect of subclinical hyperthyroidism on the risk of Heart Failure (HF) events**

| | Euthyroidism | | Subclinical Hyperthyroidism | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | <0.45 all | | | <0.10 only | | |
| | Events | Participants | Events | Participants | HR (95% CI) | Events | Participants | HR (95% CI) |
| ***All eligible studies*** | | | | | | | | |
| Random-effects model | 1762 | 22,674 | 57 | 648 | 1.46 (0.94, 2.27) | 16 | 154 | 1.94 (1.01, 3.72) |
| Fixed-effects model | 1762 | 22,674 | 57 | 648 | 1.42 (1.09, 1.85) | 16 | 154 | 2.07 (1.26, 3.41) |
| ***Excluding those with thyroid medication use*** [1] | | | | | | | | |
| At baseline | 1730 | 22,351 | 51 | 589 | 1.48 (1.02, 2.13) | 13 | 140 | 1.80 (1.04, 3.13) |
| At baseline and during follow-up | 1696 | 22,238 | 47 | 576 | 1.45 (1.00, 2.09) | 10 | 134 | 1.56 (0.86, 2.82) |
| ***Definition of subclinical hyperthyroidism*** | | | | | | | | |
| Excluding those with missing FT4 [2] | 1762 | 22,674 | 34 | 496 | 1.53 (0.95, 2.48) | 15 | 149 | 1.89 [1.03, 3.47] |
| Excluding those with abnormal FT3 [3] | 1762 | 22,674 | 51 | 627 | 1.47 (0.89, 2.40) | 14 | 146 | 2.02 (0.95, 4.28) |
| ***Outcomes*** | | | | | | | | |
| Three studies with formal adjudication procedures [4] | 1205 | 9943 | 35 | 258 | 1.40 (0.69, 2.85) | 9 | 63 | 1.81 (0.53, 6.24) |
| ***Further adjustments of multivariate models*** | | | | | | | | |
| Plus body mass index, creatinin and atrial fibrillation at baseline [5] | 1326 | 10,644 | 45 | 288 | 1.60 (0.88, 2.90) | 12 | 73 | 1.92 (0.63, 5.84) |
| Plus lipid-lowering and antihypertensive medications [6] | 1336 | 10,681 | 45 | 287 | 1.58 (0.93, 2.70) | 12 | 72 | 1.92 (0.76, 4.88) |
| ***Excluding study of cardiac patients (Bari)*** | 1709 | 22,385 | 54 | 641 | 1.38 (0.86, 2.22) | 16 | 154 | 1.94 (1.01, 3.72) |
| ***Excluding preexisting HF*** [7] | 1630 | 22,234 | 50 | 633 | 1.35 (0.86, 2.12) | 13 | 148 | 1.64 (0.71-3.80) |
| ***Excluding baseline Atrial Fibrillation*** [8] | 1698 | 22,500 | 51 | 635 | 1.32 (0.86, 2.04) | 14 | 149 | 1.82 (0.91, 3.63) |

Abbreviations: AF, Atrial Fibrillation; CI,Confidence Interval; FT3, Free tri-iodothyronine; FT4, Free thyroxine; HF, Heart Failure; HR, Hazard Ratio; NA, data not applicable; TSH, Thyroid Stimulatiing Hormone. HR are all age and sex-adjusted unless stated otherwise

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

[2] 152 participants with subclinical hyperthyroidism and missing T4 were excluded : 33 excluded from CHS, 57 from Health ABC and 62 from PROSPER,

[3] 21 participants with subclinical hyperthyroidism and abnormal T3 were excluded : Leiden 21, Bari 0 (not measured in other studies).

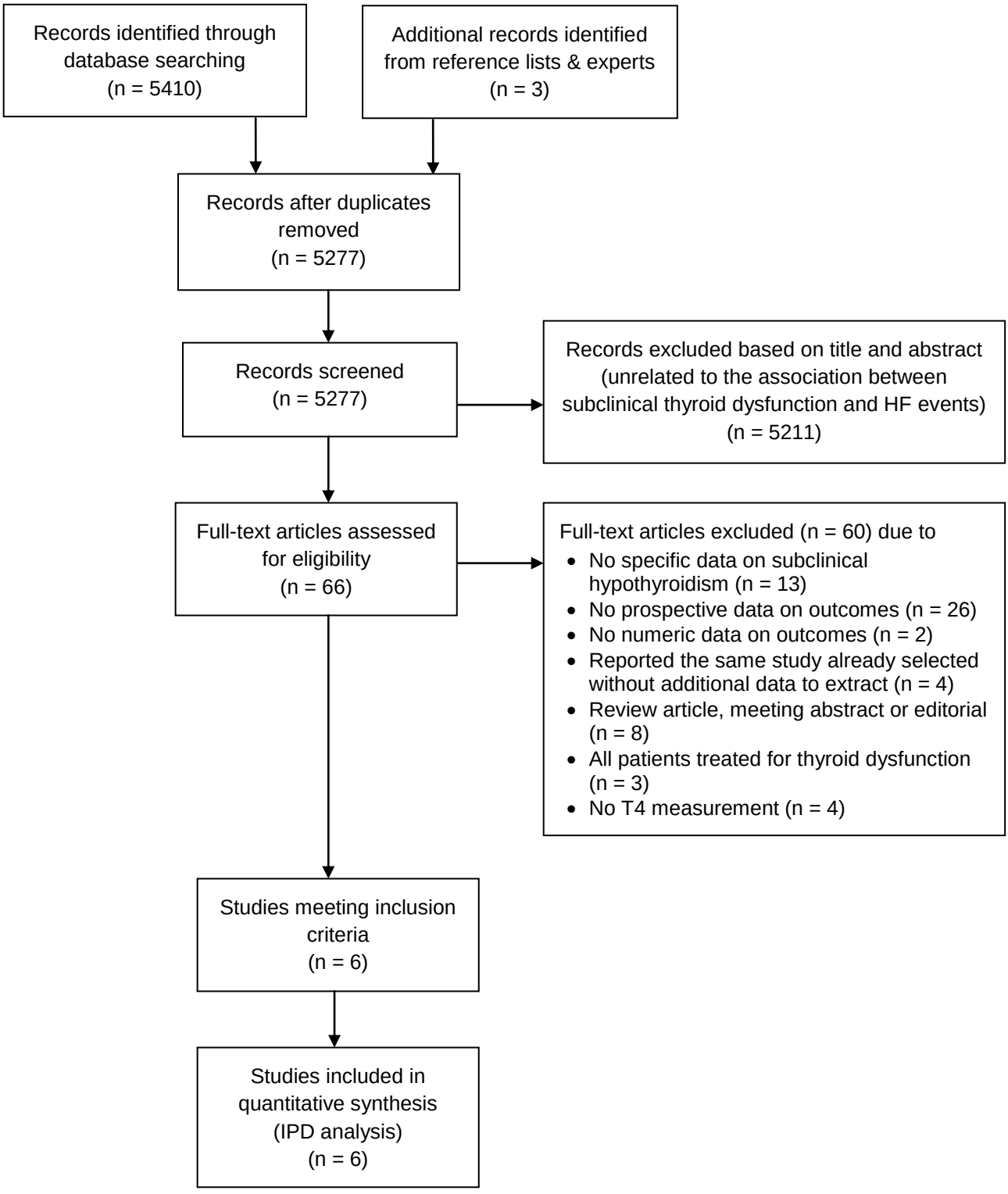
[4] Formal adjudication procedures with experts adjudicating each case were performed only in CHS, Health ABC and PROSPER. Other cohorts relied on hospital discharge and General Practitioner's medical records.

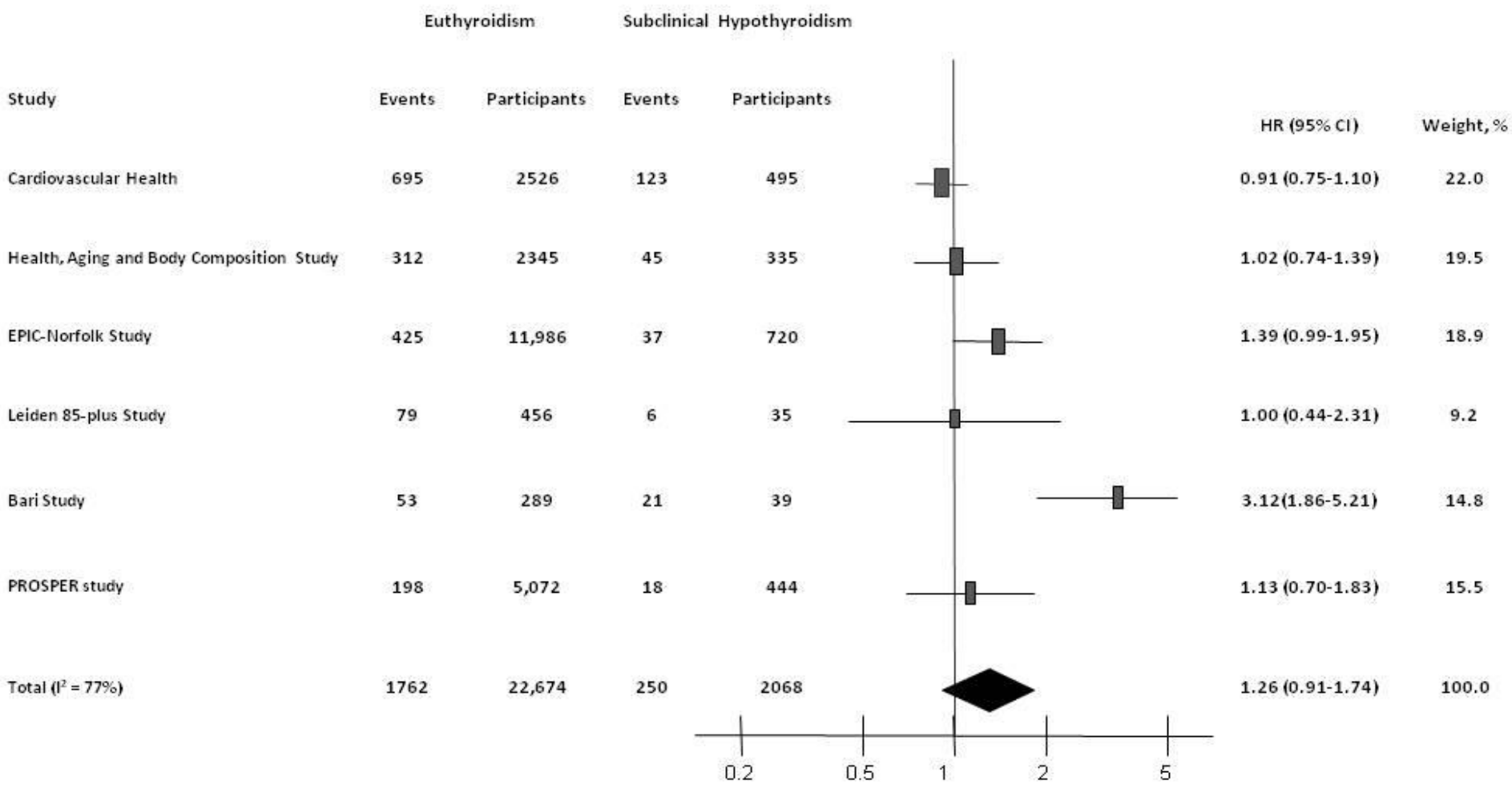
[5] Data on creatinine and atrial fibrillation were not available for the EPIC-Norfolk study. 44 participants with missing data: 6 in CHS, 23 in Health ABC and 15 in Leiden

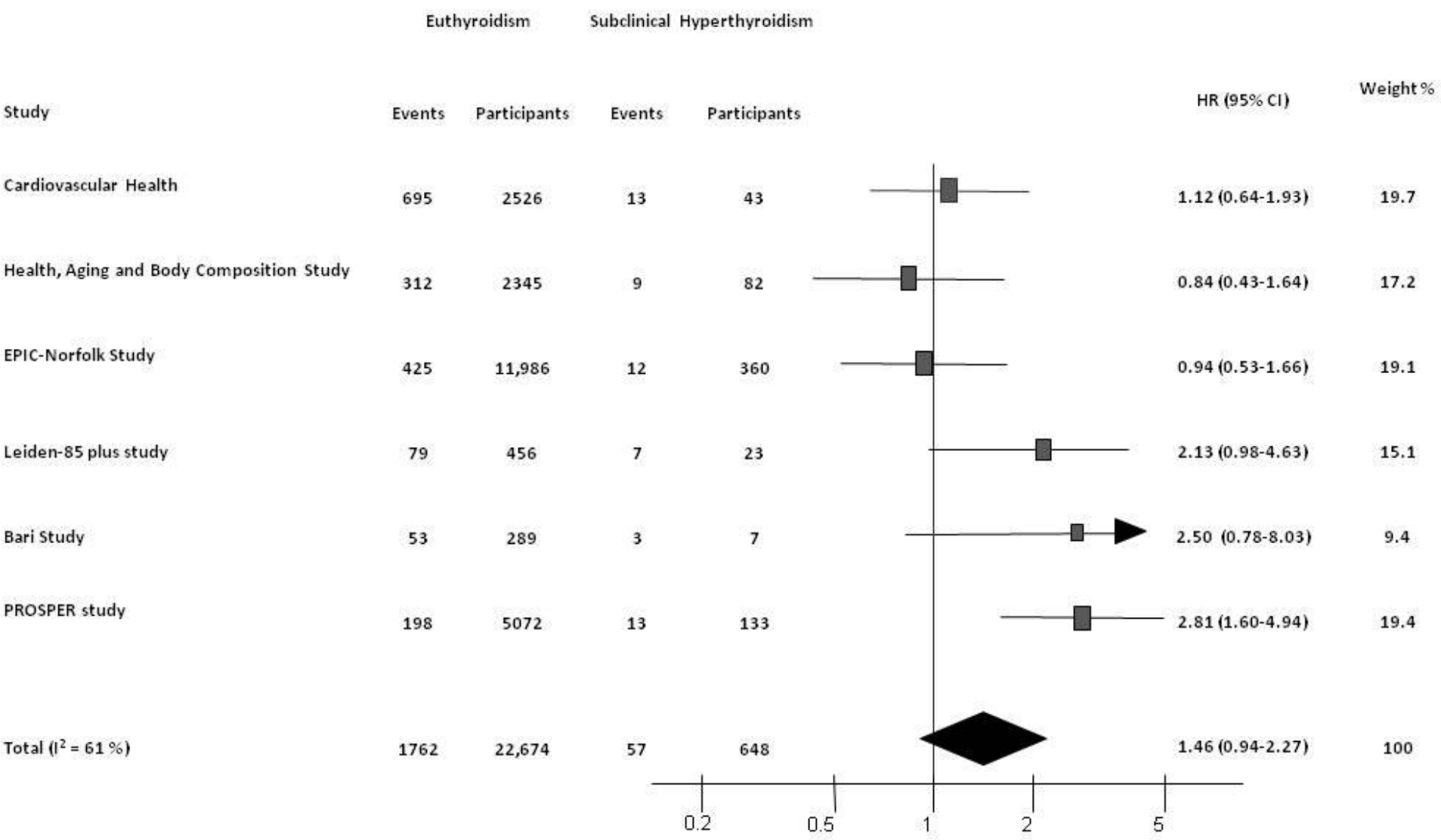
[6] Data on lipid-lowering and antihypertensive medications were not available for the EPIC-Norfolk study. 8 participants with missing data in Health ABC.

[7] 455 excluded because of HF at baseline: 9 in CHS, 95 in Health ABC, 55 in Leiden, 296 in Bari (all participants with preexisting 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 1.43 (0.59, 3.48) for TSH < 0.10 mIU/L

[8] 187 participants were excluded because of AF at baseline: 50 in CHS, 48 in Health ABC, 49 in Leiden and 36 in Bari. Data were not available for EPIC-Norfolk study. Baseline AF was an exclusion criteria from PROSPER study (4 participants had AF at baseline). 1 missing in HABC, 2 missing in Leiden. Prevalence of baseline AF across TSH ranges: 170/5615 (3.0%) for TSH 0.45-4.49 mIU/L, 8/115 (7.0%) for TSH 0.10-0.44 mIU/L and 5/40 (12.5%) for TSH <0.10 mIU/L.


Records identified through database searching (n = 5410)
Additional records identified from reference lists & experts (n = 3)
Records after duplicates removed (n = 5277)
Records screened (n = 5277)
Records excluded based on title and abstract (unrelated to the association between subclinical thyroid dysfunction and HF events) (n = 5211)
Full-text articles assessed for eligibility (n = 66)
Full-text articles excluded (n = 60) due to
No specific data on subclinical hypothyroidism (n = 13)
No prospective data on outcomes (n = 26)
No numeric data on outcomes (n = 2)
Reported the same study already selected without additional data to extract (n = 4)
Review article, meeting abstract or editorial (n = 8)
All patients treated for thyroid dysfunction (n = 3)
No T4 measurement (n = 4)
Studies meeting inclusion criteria (n = 6)
Studies included in quantitative synthesis (IPD analysis) (n = 6)


Euthyroidism
Subclinical Hypothyroidism
Study
Events
Participants
Events
Participants
HR (95% CI)
Weight, %
Cardiovascular Health
695
2526
123
495
0.91 (0.75-1.10)
22.0
Health, Aging and Body Composition Study
312
2345
45
335
1.02 (0.74-1.39)
19.5
EPIC-Norfolk Study
425
11,986
37
720
1.39 (0.99-1.95)
18.9
Leiden 85-plus Study
79
456
6
35
1.00 (0.44-2.31)
9.2
Bari Study
53
289
21
39
3.12(1.86-5.21)
14.8
PROSPER study
198
5,072
18
444
1.13 (0.70-1.83)
15.5
Total ($I^2$ = 77%)
1762
22,674
250
2068
1.26 (0.91-1.74)
100.0
0.2
0.5
1
2
5


Euthyroidism
Subclinical Hyperthyroidism
Study
Events
Participants
Events
Participants
HR (95% CI)
Weight %
Cardiovascular Health
695
2526
13
43
1.12 (0.64-1.93)
19.7
Health, Aging and Body Composition Study
312
2345
9
82
0.84 (0.43-1.64)
17.2
EPIC-Norfolk Study
425
11,986
12
360
0.94 (0.53-1.66)
19.1
Leiden-85 plus study
79
456
7
23
2.13 (0.98-4.63)
15.1
Bari Study
53
289
3
7
2.50 (0.78-8.03)
9.4
PROSPER study
198
5072
13
133
2.81 (1.60-4.94)
19.4
Total ($I^2$ = 61 %)
1762
22,674
57
648
1.46 (0.94-2.27)
100
0.2
0.5
1
2
5

## Supplemental Figure Legends

**Supplemental Figure 1**. Flow Chart: Studies Evaluated for Inclusion in the Individual Participant Data Analysis for the association between Subclinical Thyroid Dysfunction and Heart Failure events, Adapted from PRISMA Statement Flow Diagram[1] (Page R5)

**Supplemental Figure 2**. Forest plots of Heart Failure (HF) events in Subclinical Hypothyroidism vs. Euthyrodism (Page R6)

Abbreviations: CI: Confidence Interval; HR: Hazard Ratio

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.

**Supplemental Figure 3**. Forest plots of Heart Failure (HF) and in Subclinical Hyperthyroidism vs. Euthyroidism (Page R7)

Abbreviations: CI: Confidence Interval; HR: Hazard Ratio

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.

## Supplemental References


1. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: The prisma statement. *PLoS Med*. 2009;6:e1000097
2. Ochs N, Auer R, Bauer DC, Nanchen D, Gussekloo J, Cornuz J, Rodondi N. Meta-analysis: Subclinical thyroid dysfunction and the risk for coronary heart disease and mortality. *Ann Intern Med*. 2008;148:832-845
3. Search filters (medline cohort study filter). *ClinicalEvidence website*. 2010
4. Cappola AR, Fried LP, Arnold AM, Danese MD, Kuller LH, Burke GL, Tracy RP, Ladenson PW. Thyroid status, cardiovascular risk, and mortality in older adults. *JAMA*. 2006;295:1033-1041
5. Rodondi N, Newman AB, Vittinghoff E, de Rekeneire N, Satterfield S, Harris TB, Bauer DC. Subclinical hypothyroidism and the risk of heart failure, other cardiovascular events, and death. *Arch Intern Med*. 2005;165:2460-2466
6. Boekholdt SM, Titan SM, Wiersinga WM, Chatterjee K, Basart DC, Luben R, Wareham NJ, Khaw KT. Initial thyroid status and cardiovascular risk factors: The epic-norfolk prospective population study. *Clin Endocrinol (Oxf)*. 2010;72:404-410
7. Gussekloo J, van Exel E, de Craen AJ, Meinders AE, Frolich M, Westendorp RG. Thyroid status, disability and cognitive function, and survival in old age. *JAMA*. 2004;292:2591-2599
8. Iacoviello M, Guida P, Guastamacchia E, Triggiani V, Forleo C, Catanzaro R, Cicala M, Basile M, Sorrentino S, Favale S. Prognostic role of sub-clinical hypothyroidism in chronic heart failure outpatients. *Curr Pharm Des.* 2008;14:2686-2692.
9. Nanchen D, Gussekloo J, Westendorp RG, Stott DJ, Jukema JW, Trompet S, Ford I, Welsh P, Sattar N, Macfarlane PW, Mooijaart SP, Rodondi N, de Craen AJ. Subclinical Thyroid Dysfunction and the Risk of Heart Failure in Older Persons at High Cardiovascular Risk. *The Journal of Clinical Endocrinolgy and Metabolism.* 2012;97.