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Subclinical Thyroid Dysfunction and the Risk of Heart Failure Events

An Individual Participant Data Analysis From 6 Prospective Cohorts

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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 \geq 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

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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 review¹³ 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 1 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 $\leq 5\%$, 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 records²⁷ (Table 1 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

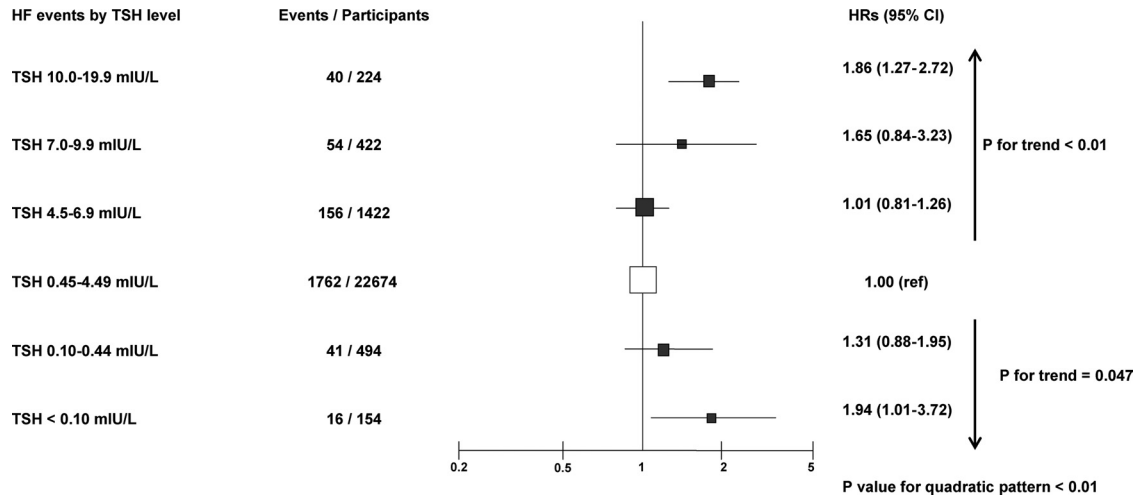


Figure. Hazard ratios (HRs) for heart failure (HF) events according to thyroid-stimulating hormone (TSH) levels. Age- and sex-adjusted HRs and their 95% confidence intervals (CIs) are represented by squares. Squares to the right of the solid lines indicate increased risk of HF events. Sizes of data markers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

	Subclinical Hypothyroidism							
	Euthyroidism, n		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 \leq 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 \geq 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 \geq 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 Study¹⁶ reported an increased risk of HF events among subjects with TSH \geq 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)
<i>P</i> 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)
<i>P</i> 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)
<i>P</i> 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)
<i>P</i> 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)
<i>P</i> 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)
<i>P</i> 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) study¹⁸ 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 HF³³ 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 hypothyroidism¹³ 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 studies⁴⁰; 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.

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Disclosures

None.

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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 Hypothyroidism 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.

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 hypothyroidism², 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 fibrillation, 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 \geq 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 \geq 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 vasodilator)	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 \geq 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 \geq 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 \geq 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 \geq 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 \geq 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					
	Events	Participants	<0.45 all			<0.10 only		
			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 Stimulating 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).

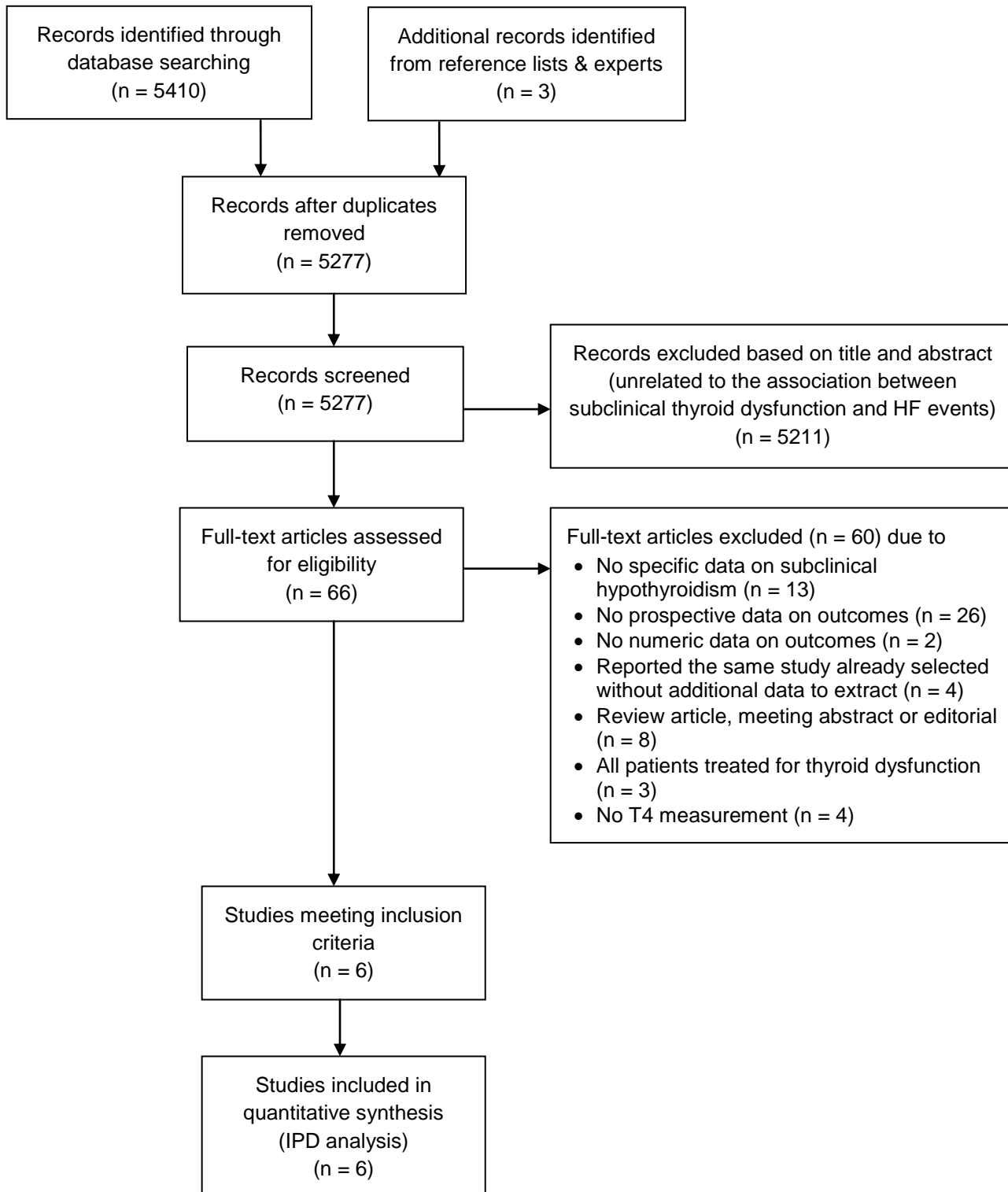
⁴ Formal adjudication procedures with experts adjudicating each case were performed only in CHS, Health ABC and PROSPER. Other cohorts relied on hospital discharge and General Practitioner's medical records.

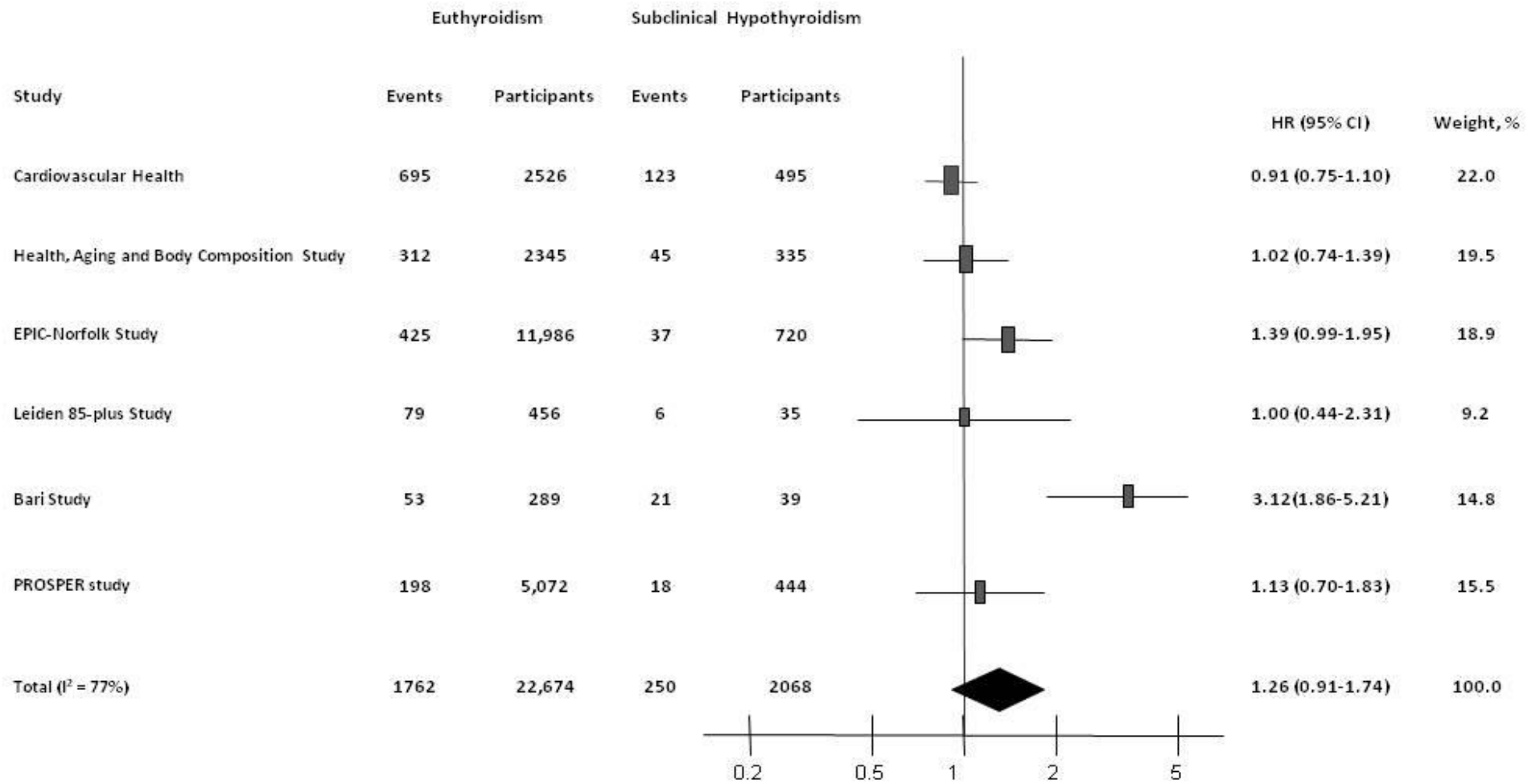
⁵ Data on creatinine and atrial fibrillation were not available for the EPIC-Norfolk study. 44 participants with missing data: 6 in CHS, 23 in Health ABC and 15 in Leiden

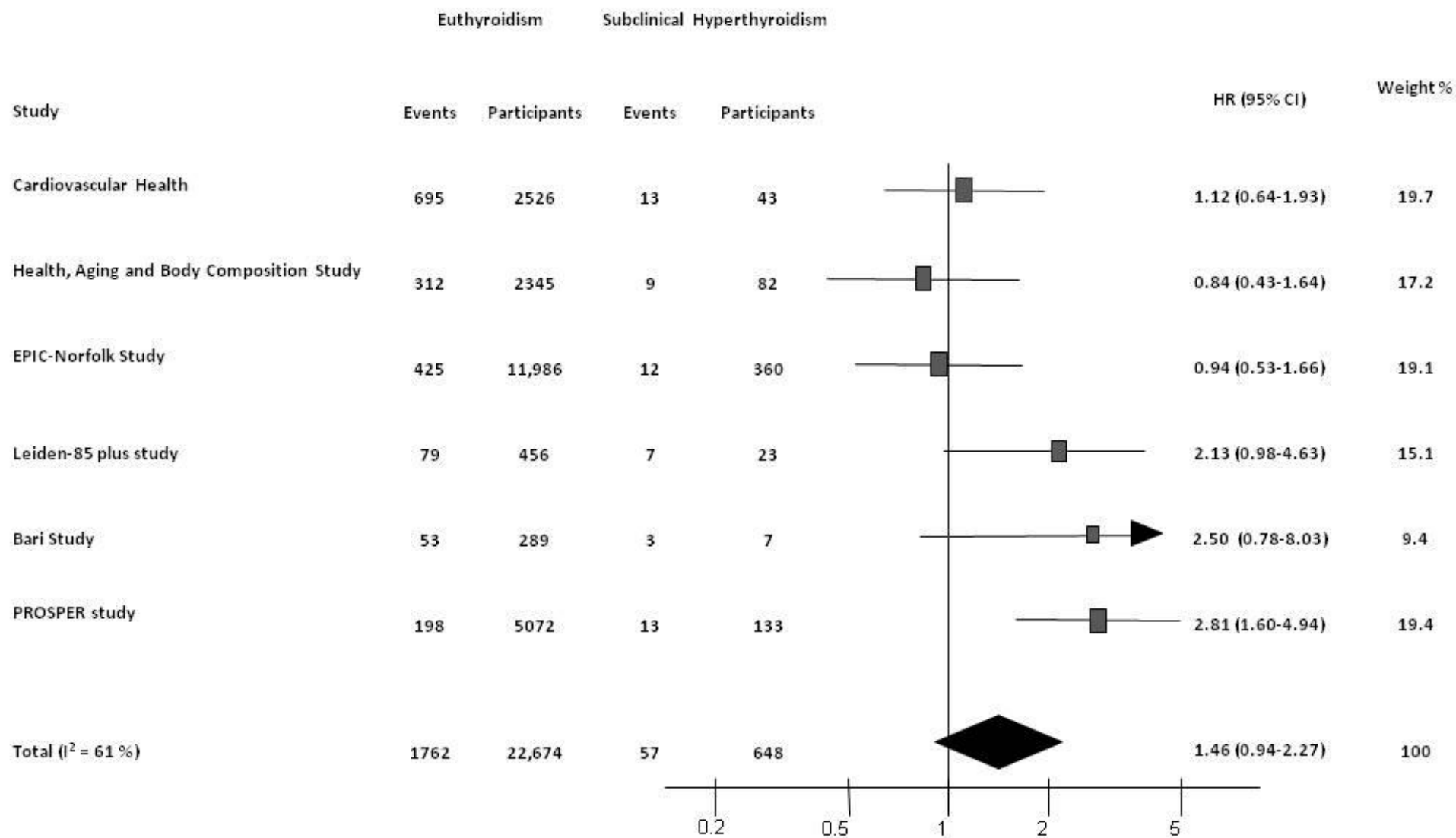
⁶ Data on lipid-lowering and antihypertensive medications were not available for the EPIC-Norfolk study. 8 participants with missing data in Health ABC.

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.







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 Diagram¹ (Page R5)

Supplemental Figure 2. Forest plots of Heart Failure (HF) events in Subclinical Hypothyroidism vs. Euthyroidism (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.

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