

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).

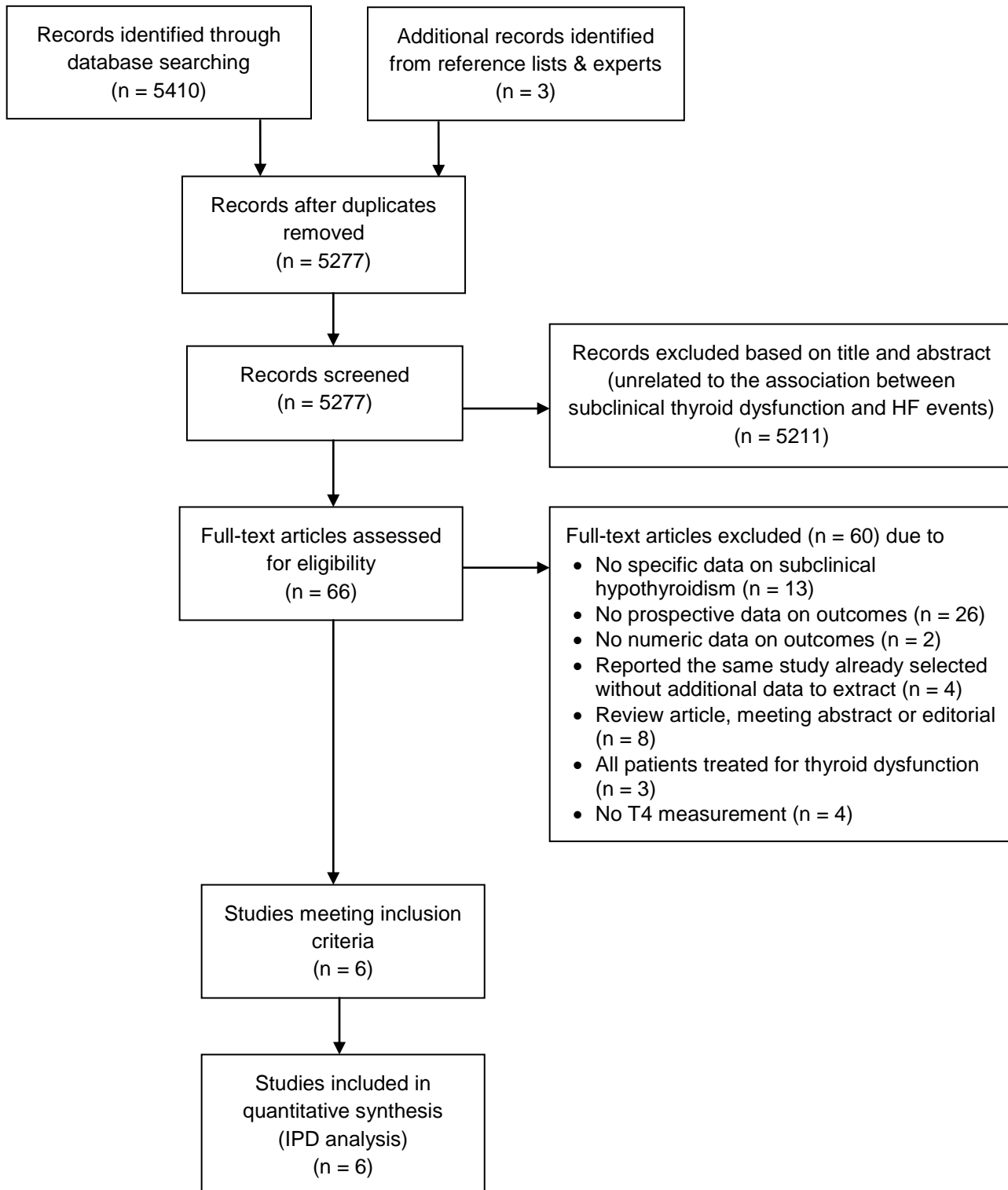
⁴ Formal adjudication procedures with experts adjudicating each case were performed only in CHS, Health ABC and PROSPER. Other cohorts relied on hospital discharge and General Practitioner's medical records.

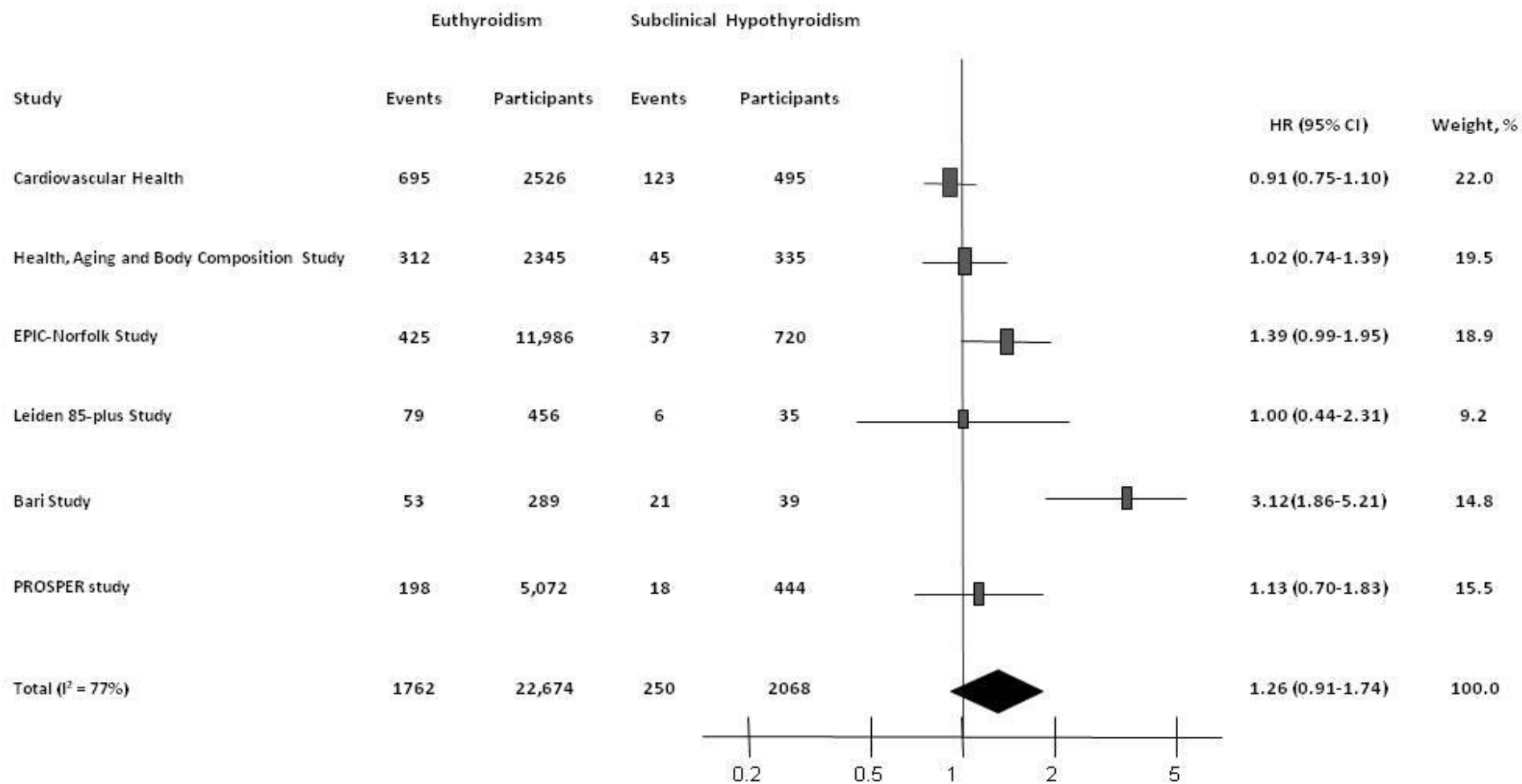
⁵ Data on creatinine and atrial fibrillation were not available for the EPIC-Norfolk study. 44 participants with missing data: 6 in CHS, 23 in Health ABC and 15 in Leiden

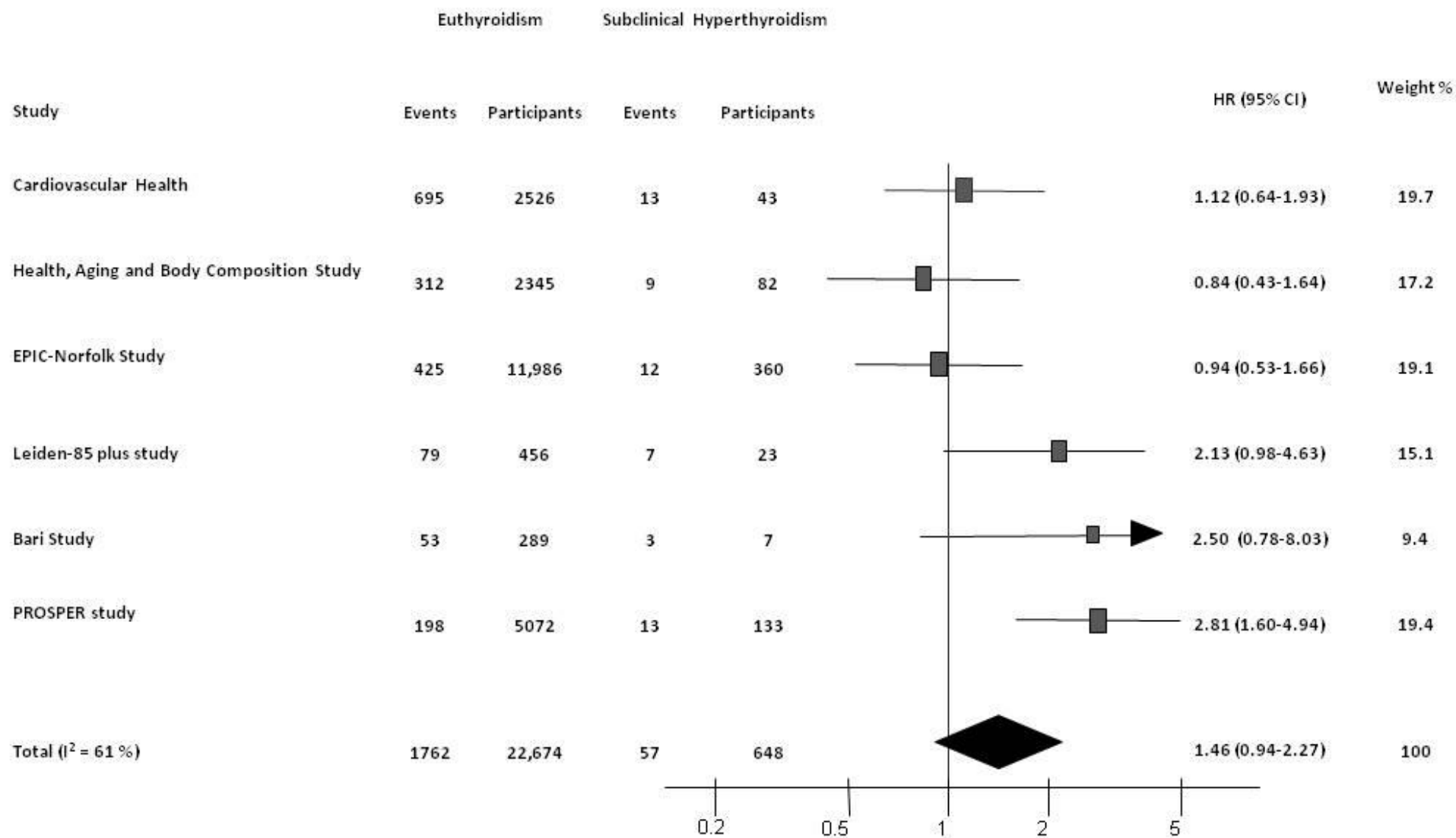
⁶ Data on lipid-lowering and antihypertensive medications were not available for the EPIC-Norfolk study. 8 participants with missing data in Health ABC.

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.

Supplemental References

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