Supplementary Online Content

Rodondi N, den Elzen WPJ, Bauer DC, et al, for the Thyroid Studies Collaboration. Subclinical hypothyroidism and the risk of coronary heart disease and mortality. *JAMA*. 2010;304(12):1365-1374.

This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods. Data Sources and Search Strategies

Identification of potential studies was based upon protocols developed for our previous study-level meta-analysis of prospective cohort studies.[2] We conducted a systematic literature search of articles in any language on the association between subclinical thyroid dysfunction and mortality (cardiovascular and total) or non-fatal coronary heart disease published from 1950 to May 31st, 2010 in MEDLINE and EMBASE. We did our search on an Ovid (MEDLINE) server by using broadly defined Medical Subject Headings: *thyroid diseases*, *hypothyroidism*, *hyperthyroidism*, *thyroid hormones*, *thyrotropin*, *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[3] (MEDLINE cohort-study filter) but without their year limitation. We did our search in EMBASE using similar terms. We also searched bibliographies of key articles and those articles included in this review.

eTable. Definitions of Subclinical Hypothyroidism, CHD Mortality, and CHD Events

Study – Year of publication	Subclinical hypothyroidism	Hypothyroid symptom assessment	CHD mortality / Methods for ascertainment	Incident fatal and non-fatal CHD events	Methods for CHD ascertainment	Separate data for "Hard" CHD events [a]
Cardiovascular Health Study[4] – 2006	TSH ≥4.5 mU/L & TSH <20 mU/L, normal fT4 0.7-1.7 ng/dL [b] or missing fT4 (21/492, 4.3%)	Not assessed	CHD mortality / Medical records, death certificates, autopsy reports, and coroners' reports reviewed by experts	Coronary heart disease (MI, angina, coronary angioplasty, coronary artery surgery, atherosclerotic CHD mortality)	Interview and hospital records reviewed by experts	Available
Health ABC Study[5] – 2005	TSH ≥4.5 mU/L & TSH <20 mU/L, normal fT4 0.8-1.8 ng/dL [b] (no missing fT4 [c])	Not assessed	CHD mortality / Hospital records, death certificates, and other support documents reviewed by a panel of clinicians	Incident CHD (fatal or non-fatal acute MI, angina pectoris, angioplasty of coronary arteries, coronary artery surgery (definite & possible)	Interview, hospital records, and other support documents reviewed by a panel of clinicians	Available
Birmingham Study[6] – 2001	TSH ≥4.5 mU/L & TSH <20 mU/L, normal fT4 9-24 pmol/L [b] or missing fT4 (20/92, 21.7%)	Not assessed	CHD mortality / Death certificates; causes of death coded with ICD9-CM 410-414	Not available	NA	Not available
EPIC-Norfolk Study[7] – 2010	TSH ≥4.5 mU/L & TSH <20 mU/L, normal fT4 9-20 pmol/L [b] (no missing fT4)	Not assessed	CHD mortality / Death certificates and hospital coding: causes of death coded with ICD9-CM 410-414	CHD mortality + hospital coding with diagnosis of CHD (ICD9-CM 410-414)	Hospital discharge coding by data linkage with NHS central register	Not available

eTable. Definitions of Subclinical Hypothyroidism, CHD Mortality and CHD Events (*continued*)

Study – Year of publication	Subclinical hypothyroidism	Hypothyroid symptom assessment	CHD mortality / Methods for ascertainment	Incident fatal and non-fatal CHD events	Methods for CHD ascertainment	Separate data for "Hard" CHD events [a]
HUNT study[8] – 2008	TSH ≥4.5 mU/L & TSH <20 mU/L, normal fT4 8-20 pmol/L [b] (no missing fT4)	Not assessed	CHD mortality / Death certificates; causes of death coded with ICD9 410-414; ICD10 I20-I25	Not available	NA	Not available
Leiden 85-plus Study[9] – 2004	TSH ≥4.5 mU/L & TSH <20 mU/L, normal fT4 13-23 pmol/L [b] or missing fT4 (1/35, 2.9%)	Not assessed	CHD mortality / Causes of death obtained from Statistics Netherlands, where all national death certificates are coded by experts; ICD10 I20-I25	Incident fatal and non-fatal MI, angina pectoris	Interview, ECG and records of general practitioners	Available
Pisa cohort[10] – 2007	TSH ≥4.5 mU/L & TSH <20 mU/L, normal fT4 0.71-1.85 ng/dL [b] (no missing fT4)	Symptomatic participants were excluded after evaluation by an endocrinologist	CHD mortality, sudden death / Death certificates, hospital records, general practitioner and patient interviews (if living)	CHD mortality + non-fatal MI	Hospital records, general practitioner and patient interviews (if living)	Available
Whickham Survey[11, 12] – 1996, 2010	TSH ≥6 mU/L & TSH <21.5 mU/L [d], normal serum total T4 3.6-13.6 μg/dL [b] or missing T4 (2/124, 1.6%) [e]	Symptomatic participants excluded if judged as having clinical overt hypothyroidism after evaluation by an endocrinologist	CHD mortality / Death certificates, postmortem reports, hospital or general practitioners' reports, ECG during the final illness coded (36%): causes of death coded with ICD9 410-414	Incident CHD = (fatal + non-fatal) MI or angina pectoris diagnosis by GPs, MI on ECG, death certificates	Self-reported history of angina or MI confirmed by general practitioners or hospital records	Not available

eTable. Definitions of Subclinical Hypothyroidism, CHD Mortality and CHD Events (*continued*)

Study – Year of publication	Subclinical hypothyroidism	Hypothyroid symptom assessment	CHD mortality / Methods for ascertainment	Incident fatal and non-fatal CHD events	Methods for CHD ascertainment	Separate data for "Hard" CHD events [a]
Busselton Health Study[13] – 2005	TSH ≥4.5 mU/L & TSH <20 mU/L, normal fT4 9-23 pmol/L [b] or missing fT4 (1/89, 1.1%)	Not assessed	CHD mortality / Registrar General's list of deaths: coded with ICD9-CM 410-414	CHD mortality + hospital coding with a diagnosis of CHD	Hospital records: diagnoses coded with ICD-9 and ICD-10	Not available
Nagasaki Adult Health Study[14] – 2004	TSH ≥4.5 mU/L & TSH <20 mU/L, normal fT4 0.8-2.5 ng/dL [b] (no missing fT4)	Not assessed	CHD mortality / Death certificates; causes of death coded with ICD9-CM 410-414	Not available	NA	Not available
Brazilian Thyroid Study[15] – 2010	TSH ≥4.5 mU/L & TSH <20 mU/L, normal fT4 0.7-1.5 ng/dL [b] (no missing fT4)	Symptoms and signs of thyroid dysfunction assessed. Participants with history of thyroid disease excluded.	NA [f]	NA [f]	NA	Not available

Abbreviations: CHD: coronary heart disease; TSH: thyroid-stimulating hormone; T4: thyroxine; fT4: free thyroxine; NA: not applicable; MI: myocardial infarction.

[a] "Hard" events were defined as nonfatal myocardial infarction or CHD death, as in the Framingham Risk Score.[16]

[b] To convert free T4 from pmol/L to ng/dL, divide by 12.87. To convert total T4 from nmol/L to μg/dL, divide by 12.87.

[c] 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.[17]

[d] Since the Whickham Survey used a first generation TSH radioimmunoassay, which gives higher measured TSH values than current assays[18], a TSH range of ≥ 6.0-21.5 mU/L was used for this IPD analysis, as in the original analysis of this study[11]. A serum TSH of 6.0 mU/L corresponded to the 97.5th centile of the "thyroid negative" group, close to the modern level of 4.5 mU/l for the current generation of assays.

[e] All studies measured free thyroxine (fT4), except the older Whickham Survey[11, 12] that measured total serum T4.

[f] Not included in analyses of CHD mortality, because of unreliable estimates given the low number of CHD deaths (n=10).

References

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eFigure. Flow Chart: Studies Evaluated for Inclusion in the Individual Participant Data (IPD) Analysis, Adapted from PRISMA Statement Flow Diagram[1]